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(54) **Title:** EXTENDED RELEASE ORAL PHARMACEUTICAL COMPOSITIONS OF 3-HYDROXY-N-METHYLMORPHINAN AND METHOD OF USE

(57) **Abstract:** The present invention is directed to oral, therapeutically effective extended release pharmaceutical compositions of 3-hydroxy-N-methylmorphinan, including delayed onset, extended release dosage forms and the use thereof.

EXTENDED RELEASE ORAL PHARMACEUTICAL COMPOSITIONS OF 3-HYDROXY-N-METHYLMORPHINAN AND METHOD OF USE

[01] This application is entitled to priority to the applicant's U.S. patent application No. 12/223,987, which is the U.S. national phase application of PCT/US2006/042962, filed November 2, 2006 and claiming the benefit of U.S. Provisional Application No 60/732,121, filed November 2, 2005; to the applicant's U.S. patent application No. 12/216,645, which is the a continuation-in-part of PCT/US2006/042962, filed November 2, 2006 and claiming the benefit of both PCT/US2006/042962 and US Provisional Application No. 60/929,611, filed July 5, 2007; to the applicant's U.S. patent application No. 12/223,327, which is the U.S. national phase application of PCT/US2007/002378, filed January 29, 2007 and claiming the benefit of U.S. Provisional Application No. 60/762,489, filed January 27, 2006; to the applicant's U.S. patent application No. 12/223,327, which is the U.S. national phase application of PCT US2008/005541, filed 26 April 2008 and claiming the benefit of U.S. Provisional Application No. 60/907,987, filed 26/04/2007; to the applicant's U.S. provisional application No. 61/202,447, filed on February 26, 2009; to the applicant's U.S. provisional application No. 61/272,650 2009, filed October 14, 2009; and to the applicant's U.S. provisional application No. 61/265,884, filed December 2, 2009, all of which are herein incorporated in their entirety for all purposes.

FIELD OF THE INVENTION

[02] The present invention is directed to extended release oral pharmaceutical compositions and to delayed onset, extended release oral pharmaceutical compositions of *d,l* 3-hydroxy-N-methylmorphinan and *l* 3-hydroxy-N-methylmorphinan and their pharmaceutically acceptable salts, and the use thereof.

BACKGROUND OF THE INVENTION

[03] This application concerns therapeutically effective dosage forms of extended release levorphanol and delayed onset, extended release levorphanol, their manufacture and their use in subjects in need of levorphanol.

[04] Extended release opioid formulations have now become the standard of care for the management of chronic pain and a number of extended release opioids have been commercialized. Despite this, chronic pain continues to be a major therapeutic challenge for both patients and their caregivers. There is therefore a need for new therapeutic alternatives for the management of pain, including alternative extended release opioids that are bioavailable, therapeutically effective and pharmacologically differentiated from existing extended release opioids

[05] Levorphanol (or *l* 3-hydroxy-N-methylmorphinan) is a potent opioid analgesic. It is the

mirror image of dextrophan, which is the primary metabolite of the cough suppressant dextromethorphan. Dextrophan (*l* 3-hydroxy-N-methylmorphinan) is devoid of significant opioid agonist activity. Instead, substantially all the opioid agonist activity resides in the levo isomer, levorphanol.

[06] Levorphanol is differentiated from morphine, hydromorphone, oxycodone, oxycodone, hydrocodone and other commonly used opioids, by virtue of its different structural class and pharmacology, which confer significant advantages over currently available extended release opioids. For example, levorphanol has significant binding at the kappa and delta opioid receptors as an agonist, and to the NMDA receptor as an antagonist, in addition to its mu [morphine like] opioid agonism. When adjusted for their potencies at the mu opioid receptor, levorphanol has significant greater activity than morphine at the kappa and delta opioid receptor, and robust activity as an NMDA antagonist, the latter being important in modulating pain and opioid tolerance. Levorphanol has also been shown to substantially reverse analgesic tolerance to morphine.

[07] Additionally, levorphanol is purported to have a long half life and a long duration of analgesic action. It would therefore be reasonable to expect widespread use of levorphanol, particularly given expert and consensus opinion about the need for additional (and preferably pharmacologically differentiated) alternatives to “morphine-like” opioids for “opioid rotation”. Despite this, compared to other opioids, levorphanol has been a commercial failure. It is hardly ever prescribed and its U.S. unit sales are negligible. Furthermore, levorphanol is not actively promoted by any pharmaceutical company.

[08] Levorphanol is commercially available only in the United States, and only in one (2 mg) strength, providing little dosing flexibility for the treating physician and for the patient with pain. For example, using the purported 5:1 potency ratio of levorphanol to morphine, 2 mg or levorphanol would be approximately equal to 10 mg of morphine and approximately equal to 2 mg of hydromorphone. However, oral immediate release morphine is available in tablet form at an equianalgesic dose to levorphanol which is 3 times higher and in an almost unlimited dose as a 20 mg/mL concentrate. Hydromorphone is available in tablet form at an equianalgesic dose to levorphanol which is 4 times higher and in an almost unlimited dose as a 1 mg/mL concentrate.

[09] To the applicant’s knowledge, no extended release dosage forms of levorphanol have been developed or commercialized in any country. There is therefore a need for a therapeutically effective extended release dosage form of levorphanol: (i) as first line opioid therapy in chronic pain; (ii) as an alternative to extended release dosage forms of morphine and morphine-like opioids (e.g., hydromorphone, oxycodone and oxycodone); (iii) for use in patients who have a suboptimal efficacy or safety response to currently available extended release dosage forms of opioids; and (iv) in the setting of pharmacologic tolerance to morphine-like drugs.

[10] Commercially available levorphanol tartrate tablets (from Roxane Laboratories, Columbus,

Ohio) must be stored in the narrow range of 20 °C to 25 °C (USP Controlled Room Temperature) and dispensed in a Tight Container as defined by United States Pharmacopeia, USP/NF. Storage specifications which are restrictive can add to the economic cost of the product, reduce its shelf life, and inconvenience the patients. Another aspect of the invention provides for improved storage conditions for once-daily extended release levorphanol.

[11] In view of the foregoing, it is immediately apparent that a serious need exists for an improvement in the dosage form of oral levorphanol for optimal therapeutic effect. There are other product performance issues associated with commercially available oral levorphanol tartrate IR tablets.

[12] According to the FDA approved U.S. prescribing information for commercially available levorphanol tartrate tablets, (i) the onset of analgesia following administration of levorphanol is similar to morphine; (ii) the peak analgesic effect following administration of levorphanol is similar to morphine; and (iii) levorphanol is well absorbed after oral administration with peak plasma concentrations occurring approximately 1 hour after dosing. The applicant has determined that the foregoing statements are substantially incorrect when applied to the commercially available oral IR levorphanol tartrate tablets.

[13] Commercially available IR levorphanol tablets have an in-vitro release rate of more than about 85% at about 10 minutes and more than about 95% at about 20 minutes when tested by the USP Paddle Method at 50 rpm. Despite this, the onset and peak analgesia of commercially available levorphanol tartrate tablets can be demonstrated to be significantly slower than commercially other commercially available opioids.

[14] In view of the foregoing, it is immediately apparent that a serious that a serious need exists for an improvement in the dosage forms of oral levorphanol for the treatment of pain. In view of the shift in standard of care for chronic pain, there is a need for robust extended release dosage forms of oral levorphanol.

[15] Commercially available immediate-release dosage of levorphanol are available only as the tartrate salt in about a 1:1 molar ratio and comprising, in addition to levorphanol tartrate dihydrate, lactose, corn starch, stearic acid, magnesium stearate and talc. These excipients account for about 98% of the tablet weight. These pharmaceutical excipients are ubiquitous in modern pharmaceutical dosage forms. However, in the case of the commercially available dosage form of levorphanol tartrate, these excipients may provide an inefficient dosage form.

[16] There is therefore a need for therapeutically effective dosage forms of levorphanol which are devoid of the excipients found in commercially available oral levorphanol tablets and which provide more rapid and consistent in vivo performance.

[17] There is therefore a need for therapeutically effective dosage forms of levorphanol which provide a robust therapeutic response, suitable for up to once-a-day administration and up to 24

hours of therapeutic effect.

- [18] Continuous suppression of pain through the use of around the clock opioid analgesics is now recommended in numerous guidelines for pain management. Extended release opioids can result in fewer interruptions in sleep, reduced dependence on caregivers, improved compliance, enhanced quality of life outcomes, and increased control over the management of their pain. In addition, such formulations can provide more constant plasma concentrations and clinical effects, less frequent peak to trough fluctuations and fewer side effects, compared with short acting opioids.
- [19] A number of oral extended release formulations of opioid analgesics have been developed or commercialized, including morphine, hydromorphone, oxycodone, hydrocodone and oxymorphone. However, these opioid analgesics have very similar pharmacologic profiles and do not provide adequate clinical differentiation.
- [20] To the applicant's knowledge, there are no marketed extended release formulations of levorphanol.
- [21] In addition to the pharmacologic differences with existing extended release opioids, the effect of levorphanol on monoaminergic reuptake inhibition has previously been underestimated. Monoamines play an important role in modulating analgesia. This finding provides an important additional impetus for the development of an extended release dosage form, since it has been shown that extended release dosage forms of monoaminergic reuptake inhibitors produce fewer adverse effects.
- [22] There are important additional reasons for the development of therapeutically effective and efficient dosage forms of extended release levorphanol. For example, pain clinicians frequently report that patients with poor analgesic efficacy or safety outcomes on one opioid do well on alternate opioids. Many opioid side effects are sufficiently bothersome as to require: (i) use of additional medications to treat the iatrogenic symptoms; (ii) more intensive patient management; (iii) use of lower doses that leave patients in continued pain; or (iv) in other cases, complete discontinuation of analgesic therapy. Patients receiving chronic opioid therapy also frequently report a reduction in efficacy over time, presumably due to the development of pharmacologic tolerance. As a consequence of this wide variability in efficacy and safety, current guidelines recommend that patients with poor outcomes on one opioid should be tried on another opioid. This concept is referred to as "opioid rotation". (see for example, Agency for Health Care Policy and Research Clinical Practice Guidelines for Cancer Pain Management, Guideline No. 9, AHCPR Publication No. 94-0592, March 1994; American Pain Society Guideline for the Management of Cancer Pain in Adults, 2005; Hagen and Babul, *Cancer* 1997;79:1428-37).
- [23] Oral extended release formulations of levorphanol with their differential opioid receptor binding and clinical effects have the potential to be a drug of choice in opioid rotation regimens in patients who don't respond well to other available extended release opioids (e.g., oxycodone,

morphine, oxymorphone, hydromorphone).

[24] There are several purported challenges to the wide spread use of oral levorphanol which have until this application, provided a significant counter-argument to the development of an extended release dosage forms. These include its purported long half-life, complex dose titration, risk of significant accumulation with repeated dosing, and a long time to steady state. Such counter-arguments have heretofore proved to be a deterrent to the development and commercialization of extended release levorphanol. Long-half life drugs are considered by some to be unsuitable for extended release formulations for a number of reasons, including: (i) the lack of justification for an extended release formulation, since the drug may be administered in immediate release form with the purported benefit of an extended duration of therapeutic effect; (ii) the considerably longer time to reach steady state, which means that patients may wait an extended period of time before achieving adequate, optimum or maximum therapeutic benefit; (iii) the risk of drug accumulation and associated toxicity over time; (iv) the difficulty with dose titration, especially rapid dose titration, which leaves the patient vulnerable to accumulation and drug intoxication; (v) the need to wait until steady state before further dose titration; (vi) the risk of unexpected late onset opioid toxicity due to drug accumulation, after the clinician and patient have been “lulled” into an expectation of tolerability. Under the long half-life scenario, it has been argued by some that the use of drugs with long half-lives in extended release formulations may put patients at risk for increased nausea, vomiting, sedation, constipation, fatigue, obtundation and more seriously, respiratory depression. This in turn could require greater medical management (e.g., more frequent medical monitoring, more frequent clinic visits, slow titration and more frequent dose adjustments) and the concurrent use of drugs to manage the side effects (e.g., antiemetics, laxatives, etc). Below is a review of the purported challenges and some of the findings of the invention which provide further support the development of extended release levorphanol.

[25] Applicant has surprisingly discovered that the mean apparent elimination half-life, pharmacokinetic variability and accumulation kinetics of oral extended release levorphanol tested of the invention are about the same or less than for commonly used extended release opioids such as morphine, hydromorphone, oxycodone and oxymorphone.

[26] Therefore, there is now an even more compelling rationale for developing extended release dosage forms of levorphanol which provide efficacy and safety at least comparable to extended release dosage forms of morphine, hydromorphone, oxycodone and oxymorphone.

[27] A challenge in developing opioids for once-daily administration is the documented poor bioavailability of unitary, monolithic, matrix or non-multiparticulate drug extended release opioid delivery systems. Another aspect of the invention provides for improved oral bioavailability of once-daily extended release levorphanol.

- [28] To the applicant's knowledge, there are no commercially available non-multiparticulate once-daily extended release compositions of any opioid analgesics in the USA.
- [29] Another aspect of the invention provides for resistance of the dosage forms of extended release levorphanol to alcohol induced dose dumping. This problem has been documented with several extended release opioid analgesics and can have serious adverse consequences. (Sloan and Babul, Expert Opinion on Drug Delivery 2006;3:489-97)
- [30] There is therefore a need for extended release opioids which do not evidence dose dumping in relation to alcohol intake, which do not evidence clinically significant changes in rate or extent of absorption in relation to alcohol intake, which do not evidence clinically significant pharmacodynamic variability in relation to alcohol intake, and which do not evidence bio-inequivalence of the dosage form when given with or without alcohol.
- [31] Many commercialized extended release opioids have been shown to have a significant food effect. Another aspect of the invention provides for reduced fed fasted pharmacokinetic variability. An important issue with oral extended release products is its potential for "dose dumping" in relation to food, where the active drug, intended for slow release, is instead released rapidly, resulting in toxicity on the one hand and a decreased duration of effect on the other.
- [32] There is therefore a need for extended release opioids which do not evidence dose dumping in relation to food intake, which do not evidence clinically significant changes in rate or extent of absorption in relation to food intake, which do not evidence clinically significant pharmacodynamic variability in relation to food intake, and which do not evidence bio-inequivalence of the dosage form when given in a fed or fasted state.
- [33] A pharmaceutically acceptable dosage form of oral levorphanol for the treatment of levorphanol responsive conditions beyond its short duration of action at a controlled rate over an extended period of time appears to be lacking in the pharmaceutical and medical arts.
- [34] There is therefore a need for new pharmaceutical compositions and methods for subjects in need of levorphanol which provide a prolonged duration of therapeutic effect when given orally.
- [35] An important drawback with the use of opioid analgesics is the risk of addiction, diversion and abuse. Tampering extended release opioid formulations can deliver a significant dose in immediate release form and produce a variety of potentially serious or life threatening side effects. The focus of virtually all abuse resistant technology for extended release opioid formulations has been predicated on abuse through tampering of the extended release dosage form by the recreational drug user or drug addicts. In the applicants view, the foregoing technologies are not an adequate solution to the problem of opioid abuse and fail to take into account the full spectrum of misuse, overuse and abuse of opioids. The invention also provides extended release dosage forms of levorphanol which provide a novel composition and method of deterring abuse by patients, recreational drug users and individuals with an addiction disorder.

- [36] A major issue with pharmacologic management of chronic conditions is compliance with therapy. Compliance with extended releases dosage opioid analgesics is still not adequate, which defeats the now widely recommended concept of continuous suppression of pain. Another aspect of the invention provides for improved compliance with treatment.
- [37] An additional reason for the lack of commercial success of levorphanol may relate to incorrect equianalgesic and potency conversion tables in the literature for levorphanol relative to morphine. Another aspect of the invention provides for appropriate potency ratios relative to morphine.
- [38] In view of the foregoing presentation, it is immediately apparent that a serious need exists for an improvement in the delivery of oral levorphanol for its therapeutic effect. The need exists to provide a novel therapeutic composition comprising oral levorphanol, the need exists to provide a novel dosage form comprising oral levorphanol, and the need exists to provide a novel method of administering levorphanol to a patient in need of levorphanol therapy.
- [39] Therefore, the present invention has been made with a view towards solving the above problems of the prior art.
- [40] The invention provides an oral, relatively easy mode and manner of levorphanol administration.

SUMMARY OF THE INVENTION

- [41] It is apparent from the foregoing description that levorphanol has had little commercial success and has heretofore been viewed as unsuitable for therapeutic use in an extended release dosage form for a variety of reasons.
- [42] The present invention is therefore directed at extended release pharmaceutical compositions of oral levorphanol, its manufacture and use for the treatment for patients in need of levorphanol.
- [43] The present invention is also directed at extended release oral pharmaceutical compositions of levorphanol and methods of treatment for patients with pain, dyspnea, cough, addiction disorders and other levorphanol or opioid responsive medical conditions.
- [44] Applicant has developed an extended release dosage form of levorphanol based on numerous in vitro and in vivo findings. There are several aspects to this invention, including: (1) robust, therapeutically effective oral extended release dosage forms of levorphanol for dosing up to once-a-day (e.g., twice-a-day (BID), once-a-day (QD), Q12H or Q24H); (ii) highly bioavailable non-multiparticulate oral extended release dosage forms of levorphanol for dosing once-a-day (e.g., QD or Q24H); (3) extended release dosage forms of levorphanol which provide a substantially greater temperature range of stability than claimed by the only commercially marketed oral dosage form of levorphanol; (4) extended release dosage forms of levorphanol which provide a comparable onset and peak analgesic effect to other extended release opioids, unlike commercially marketed oral

dosage form of immediate release levorphanol, when compared with other immediate release opioids; (5) extended release dosage forms of levorphanol that can reduce side effects from the heretofore unknown substantially greater selectivity for serotonin reuptake inhibition over norepinephrine reuptake inhibition for levorphanol; (6) the heretofore unknown apparent elimination half-life for extended release levorphanol substantially less than suggested in the published literature from oral immediate release levorphanol data; (7) the heretofore unknown apparent elimination half-life for extended release levorphanol which is about the same or less than the apparent elimination half-life of other extended release opioids; (8) the heretofore unknown apparent time to steady state and accumulation on repeated dosing for extended release levorphanol which is about the same or less than for other extended release opioids; (9) a surprisingly slow in vitro dissolution rate corresponding to optimal (faster) in vivo release than predicted by other extended release opioids; (10) a higher therapeutic dose and wider therapeutic dose range for extended release levorphanol based on the heretofore overestimation of levorphanol potency; (11) abuse resistance of the dosage form; (12) a method of achieving abuse resistance based on the development and use of delayed onset, extended release dosage forms of levorphanol for duodenal, jejunal, ileal and colonic delivery and release of the dose; (13) extended release dosage forms of levorphanol which are resistant to alcohol associated dose dumping; (14) extended release dosage forms of levorphanol which are resistant to dose dumping and pharmacokinetic variability in relation to the co-ingestion with or without food; (15) delayed onset, extended release dosage forms of levorphanol which provide for improved compliance with treatment by making the formulation less effective when taken on an as needed (PRN) basis, rather than on a scheduled (around the clock); and (16) methods to achieve efficient dose titration and therapeutic effect with reduced side effects.

[45] Applicant has developed a robust extended release dosage form of levorphanol which is highly stable when tested under a variety of temperature and relative humidity conditions for a prolonged period of time (e.g., without a significant increase in levorphanol degradation products or deterioration of product performance). According to the U.S. prescribing information for the only commercially available levorphanol tartrate (conventional, immediate release or IR) tablets (from Roxane Laboratories, Columbus Ohio), the tablets in their original packaging must be stored in the narrow range of 20 °C to 25 °C (USP Controlled Room Temperature) and dispensed in a Tight Container as defined by United States Pharmacopeia, USP/NF. According to the USP, a Tight Container “protects the contents from contamination by extraneous liquids, solids, or vapors; from loss of the article; and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution; and is capable of tight reclosure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of an article.”

[46] The required conditions of storage can significantly affect the manufacture, storage,

transportation, distribution, dispensing and patient use of a dosage form. Storage specifications which are restrictive can add to the economic cost of the product, reduce its shelf life, inconvenience the pharmacist, discourage pharmacies from stocking a product and adversely affect product performance once it is in the patient's home. Furthermore, as a Schedule II controlled substance, levorphanol must be stored in pharmacy safe, under lock and key, where control of temperature is even more problematic. Restrictive storage and packaging specifications present a substantial burden in Climatic Zone III (hot, dry climate), Zone IVa (hot, humid climate) and the Zone IVb (hot, very humid climate), where, according to the WHO, access to prescription opioids is already severely limited. These climatic zones involve over 80 countries in the Americas, Africa, Asia and Oceanic region.

[47] Despite the rapid release of substantially all of the levorphanol from the dosage form, applicant has surprisingly determined that commercially available IR levorphanol tablets provide a suboptimal in vivo response by the oral route.

[48] The onset of analgesia of commercially available levorphanol tartrate tablets can be demonstrated to be significantly slower than commercially available oral IR morphine, commercially available oral IR hydromorphone, commercially available oral IR oxymorphone and commercially available oral IR oxycodone. The peak analgesic effects of commercially available levorphanol tartrate tablets can be demonstrated to be significantly less than commercially available oral IR morphine, commercially available oral IR hydromorphone, commercially available oral IR oxymorphone and commercially available oral IR oxycodone. The time to peak concentration of commercially available oral IR levorphanol tartrate tablets can be demonstrated to be significantly less than commercially available oral IR morphine, commercially available oral IR hydromorphone, commercially available oral IR oxymorphone and commercially available oral IR oxycodone.

[49] Without being bound by theory, the applicant asserts that the commercially available dosage form of levorphanol tartrate in combination with its excipients adversely interacts in the gastrointestinal environment to provide an inefficient dosage form.

[50] In addition, the applicant has determined that commercially available oral IR levorphanol tartrate tablets have: (i) a very small gastrointestinal absorption rate constant, providing slow and highly variable absorption; (ii) an mean absorption time (MAT) that is incompatible with robust analgesic efficacy at recommended doses; and (iii) a fraction of dose absorbed immediately after administration (e.g. 0.5, 0.75, 1, 1.25 and 1.5 hours) that is substantially less than for commercially available oral IR morphine, commercially available oral IR hydromorphone, commercially available oral IR oxymorphone and commercially available oral IR oxycodone.

[51] Without being bound by theory, the applicant asserts that the lack of commercial success of the marketed oral levorphanol tablets despite an attractive pharmacologic profile, is in part due to

one or more of the following: (i) its failure to provide a robust therapeutic effect; (ii) a slow onset of pain relief; (iii) suboptimal maximal relief from pain; (iv) suboptimal total relief from pain; [each of (i) to (v) readily demonstrable in established models of single dose analgesic evaluation]; (v) the constituents of the dosage form, which may adversely impact the in vivo efficiency and efficacy of the dosage form; and (vii) the particle size of the levorphanol tartrate active pharmaceutical ingredient (API) in the dosage form.

[52] In addition to the pharmacologic differences with existing extended release opioids, applicant has now surprisingly discovered that the effect of levorphanol on monoaminergic reuptake inhibition has previously been underestimated. Monoamines play an important role in modulating analgesia. For example, applicant has now surprisingly discovered that in addition to potently inhibiting norepinephrine and serotonin reuptake in rat brain synaptosomes, levorphanol shows approximately 40 fold greater selectivity for serotonin reuptake inhibition over norepinephrine reuptake inhibition. This is substantially greater than previously understood. This finding provides an important additional impetus for the development of an extended release dosage form, since it has been shown that extended release dosage forms of monoaminergic reuptake inhibitors produce fewer adverse effects.

[53] Half-life is one of the most misunderstood and misused biological parameters. The most accurate assessment of the elimination half-life (terminal elimination half-life) of a drug which exhibits pharmacokinetic linearity and stationarity is following intravascular administration (e.g., intravenous, intra-arterial or intracardiac) by bolus (“instantaneous”) administration, followed by its “instantaneous” absorption and distribution. In this setting, the data can be described by single exponential expression using a one-compartment open model. However, even with bolus IV administration or short term IV infusions, a variety of processes, including absorption, distribution, intercompartmental transfer, equilibration, sequestration, enterohepatic recycling and metabolism are going on in parallel, even if one process may predominate at any given time. In the case of oral IR administration, additional processes, such as disintegration, dissolution, gastric emptying, site specific absorption and metabolism, and first pass metabolism come into play. Even though efforts are made to characterize the oral (elimination) half-life using data from the purported “postabsorptive, post distributive phase” of plasma concentration-time data, the calculated half-life after oral administration is often longer than that reported after IV bolus administration. Applicant maintains that for this reason, the term “elimination half-life” at least when applied to oral dosing, should be modified by a descriptor, e.g., “apparent elimination half-life”. The situation is even more complicated with oral, extended release dosage forms where liberation, absorption and distribution may be ongoing 6, 12, 24, and 36 hours following dosing. Practically, this means application of half-lives obtained from an IV bolus or IV infusion to fully explain the behavior of an orally administered drug is not appropriate.

- [54] The apparent elimination half-life of orally levorphanol is purportedly very long. According to the American Pain Society, levorphanol has along “plasma half life (12-16 but may be as long as 90-120 hours after 1 week of dosing)” [Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, Sixth Ed., American, Pain Society (2008)]. Similarly, the half life of oral levorphanol has been reported in two patients by Dixon et al [Res Commun Chem Pathol Pharmacol, 1983;41:3-17]. In this study, the half-life of oral levorphanol was approximately 16 hours in one patient and nearly double that at 30 hours, in a second patient.
- [55] Drugs with long half-lives purportedly lack a scientific justification for development into an extended release dosage form, since the drug may be administered in immediate release form with the benefit of an extended duration of therapeutic effect. In addition, concern has been expressed about the systemic accumulation drugs with long apparent elimination half-lives upon repeated dosing, particularly when given in extended release dosage forms.
- [56] The purported 16 hour apparent elimination half-life reported in one patient and the 30 hour apparent elimination half-life reported in a second patient would suggest wide and unacceptable interindividual variability. Using the lower reported 16 hour oral apparent elimination half-life of levorphanol, it would take 80 hours to reach steady state therapeutic concentration upon repeated dosing. Using the higher reported 30 hour oral apparent elimination half-life in the second patient in the study by Dixon, it would take 150 hours to reach steady state therapeutic concentration upon repeated dosing. The mean time to steady state using the average of the two reported values would provide a time to steady-state of 115 hours.
- [57] Applicant has now surprisingly discovered that the mean apparent elimination half-life of oral extended release levorphanol tested for four different dosage forms (each tested in 14 to 15 subjects) was 10.9 hours, 13.6 hours, 14.1 hour and 14.4 hours. This half life is about the same or less than the apparent elimination half-life of commonly used extended release opioids such as morphine, hydromorphone, oxycodone and oxymorphone. For example, (i) the mean apparent elimination half-lives of once-daily extended release oral hydromorphone multiparticulate dosage form (Palladone™) is purportedly about 15 hours [Vashi et al., J Clin Pharmacol, 2005;45;547-554]; (ii) the mean apparent elimination half-life of once-daily extended release oral hydromorphone in a push pull osmotic pump (Jurnista™ and Exalgo™) is purportedly about 16.8 to 18.1 hours (various doses) [Exalgo™ Briefing Document, FDA Advisory Committee Meeting, September 23, 2009]; (iii) the mean apparent elimination half-life of once-daily extended release oral morphine in multiparticulate dosage form (Kadian™) is purportedly about 11 to 14 hours (various doses) [Johnson et al, Journal of Pain., 2008;9:330-336]; (iv) the mean apparent elimination half-life of once-daily extended release oral morphine in multiparticulate form (Avinza™) is purportedly about 23 to 25 hours [Avinza™ NDA 21-260 FDA Summary Basis for Approval, Freedom of Information Request]; (v) the mean apparent elimination half-life of once-daily extended release twice-daily oral

morphine (MS ContinTM) is purportedly about 17 to 22 hours (various doses) [Kaiko et al., J Clin Pharmacol 1995;35:499-504]; and the mean apparent elimination half-life of twice-daily extended release oral oxymorphone (OpanaTM) is purportedly about 9 to 12 hours (various doses) [Adams MP et al, Pharmacotherapy, 2004;24:468-76].

[58] Applicant has also surprisingly discovered that extended release levorphanol is no more prone to accumulation than other commercially marketed and well accepted extended release opioids. Using elimination rate constants (Method 1), the mean accumulation index for four different extended release levorphanol dosage forms (each tested in 14 to 15 subjects) was 1.3, 1.4, 1.8 and 2.3. Using individual calculations (Method 2), the mean accumulation index for four different extended release levorphanol dosage forms (each tested in 14 to 15 subjects) was 1.6, 2.0, 2.0 and 2.6. This accumulation index is about the same or less than the purported mean accumulation index of commonly used extended release opioids such as morphine, hydromorphone, oxycodone and oxymorphone. For example, (i) the mean accumulation index of once-daily extended release oral hydromorphone multiparticulate dosage form (PalladoneTM) is purportedly about 1.83 hours [Vashi et al., J Clin Pharmacol, 2005;45:547-554]; (ii) the mean accumulation index of once-daily extended release oral hydromorphone in a push pull osmotic pump (JurnistaTM and ExalgoTM) calculated from published mean data is 2.2 (Method 1) and 2.7 (Method 2) [Sathyan et al., BMC Clinical Pharmacology, 2007 Feb 27:2]; (iii) the mean accumulation index of once-daily extended release oral morphine in multiparticulate dosage form (EmbedaTM) calculated from published mean data is about 2.7 (Method 1) and about 2.37 (Method 2); (iv) the mean accumulation index of twice-daily extended release oral oxymorphone (OpanaTM) is purportedly about 3.43, 2.29, 2.39 and 2.13 for 5 mg, 10 mg, 20 mg and 40 mg tablets, respectively [NDA 21-610 FDA Summary Basis for Approval for OpanaTM ER].

[59] Applicant has also determined that oral immediate release levorphanol dosed according to its recommended every 6 or 8 hour frequency accumulates to a substantially greater extent than extended release levorphanol dosage forms of the invention. The mean accumulation index of oral immediate release levorphanol dosed by the applicant is about 3.6 (Method 1) and 3.1 (Method 2), using a Q6H dosing frequency and about 2.8 (Method 1) and 2.4 (Method 2), using a Q8H dosing frequency. This is in contrast to the mean accumulation index for four different extended release levorphanol dosage forms of about 1.3, 1.4, 1.8 and 2.3 (Method 1) and about 1.6, 2.0, 2.0 and 2.6 (Method 2).

[60] Applicant has also surprisingly discovered that the time to achieve steady state with extended release levorphanol is substantially similar to or less than the time to achieve steady state with other commercially marketed and well accepted extended release opioids. Levorphanol ER dosage forms of the invention are at about 90% of steady state concentrations by the second dose or third dose (about 48 to 60 hours after first administration). By comparison, once-daily

extended release oral hydromorphone multiparticulate dosage form (Palladone™) purportedly achieves steady state in about “3 to 4 days in most subjects” respectively [NDA 21-044, FDA Summary Basis for Approval for Palladone™], twice-daily extended release oral oxycodone (OxyContin™) purportedly achieves steady state in six days [NDA 20-553, FDA Summary Basis for Approval for OxyContin™], once-daily extended release oral morphine in multiparticulate dosage form (Avinza™) purportedly achieves steady state in about in about five days [Avinza™ NDA 21-260 FDA Summary Basis for Approval, Freedom of Information Request], and once-daily extended release oral hydromorphone in a push pull osmotic pump (Jurnista™ and Exalgo™) purportedly achieves steady state in about 4 days [Exalgo™ Briefing Document, FDA Advisory Committee Meeting, September 23, 2009].

[61] Applicant has now also surprisingly discovered that the variability in apparent elimination half-life of extended release levorphanol is not significantly different from that with other extended release opioids, contrary to the findings of Dixon.

[62] Another aspect of the invention provides for improved oral bioavailability of once-daily extended release levorphanol. A challenge in developing opioids for once-daily administration is the documented poor bioavailability of unitary, monolithic, matrix or non-multiparticulate drug extended release opioid delivery systems. Matrix extended release dosage forms are a commonly used technology for development of extended release formulations. The popularity of matrix extended release drug delivery systems can be attributed to a number of factors. Such delivery systems (i) may be developed, manufactured using conventional processing and equipment; (ii) require no further capital expenditures; and (iii) have the capability to handle a wide range drug loads and drugs. However, in the case of opioids, extended release non-multiparticulate systems for once-daily administration purportedly provide poor oral bioavailability despite providing in vitro evidence (e.g., dissolution) suggestive of once-daily delivery in vivo. Without being bound by theory, this reduced bioavailability may be due to uneven or incomplete liberation or absorption of the opioid from matrix dosage forms in the distal gastrointestinal tract (necessary for once-daily extended release dosage forms) due the local environment and its interaction with the dosage form (e.g., level of hydration, pH, levels of surfactant, presystemic biotransformation).

[63] For example, US Patent Application Nos. 5,968,551, 6,572,885, and 7,270,831, and pending US Patent Application Nos. 20080181941, 20080044482, and 20090068269 to Oshlack notes that “in order to provide a 24 hour dosage form of an opioid analgesic, it is necessary to do so via a sustained multiparticulate system” and that “while sustained-release tablets and sustained-release multiparticulate systems of opioid analgesics may be prepared with in-vitro dissolution indicative of a 24 hour formulations, only sustained-release multiparticulate systems of opioid analgesics are bioavailable. This is true even when the sustained-release tablets have an in-vitro dissolution profile which is virtually equivalent to that provided by the multiparticulate system.”

Among the limitations of multiparticulate matrices of this type are the need for two or more coating steps and particle blending steps for subsequent release and content control, the large overall volume of particulates in cases where there is a need for high drug content, the poor controlled release properties of the pellets due to the large surface area, the need for specialized manufacturing and coating equipment, and the higher susceptibility to alcohol induced dose dumping.

- [64] In support of the foregoing patents and patent applications for fully bioavailable extended release once-a-day multiparticulate system for opioids, Oshlack et al. provide data purporting to show that while both matrix and multiparticulate formulations have in vitro dissolution which should allow for once-a-day dosing (Q24H), only the bead formulations of morphine intended for once-daily administration provided a mean bioavailability comparable to twice-a-day extended release matrix formulations of morphine (MS Contin™). In contrast, the matrix tablet formulation of morphine intended for once-daily administration provided a mean bioavailability of only 66%, when compared with twice-a-day extended release matrix formulations of morphine (MS Contin™). The T_{max} of the experimental matrix tablet formulation was only 3.38 hours.
- [65] Similar results have also been observed for experimental hydromorphone matrix tablet formulation, where the mean bioavailability was only 91%, when compared with oral immediate release hydromorphone (Grandy R et al. J Clin Pharmacol 1991; 125:871).
- [66] The problem of low bioavailability for extended release opioid formulations extends beyond monolithic matrix formulations. For example, a variety of extended release dosage forms of the opioid tramadol have been developed. When compared with oral immediate release tramadol, Zamadol™ SR capsules, developed by Temmler Pharma (ASTA Medica Group) and available in 50, 100, 150 and 200 mg strengths for Q12H administration from Meda Pharmaceuticals have a relative bioavailability of 89% (Schulz et al, *Arzneim-Forsch/Drug Res* 1999;49:582-87; Raber et al, *Arzneim-Forsch/Drug Res* 1999;49:588-89; Keating GM. *Drugs* 2006;66:223-230; and U.K. Summary of Product Characteristics for Zamadol™ SR capsules); Zamadol™ SR tablets, developed by Purdue Pharma/Napp Napp Pharmaceuticals Ltd and available in 100/200/300 mg strengths for Q24H administration from Meda Pharmaceuticals have a relative mean AUC of 89 to 91% at steady-state (Bodalia et al, *J Pain Symptom Manage* 2003;25:142-9); Ryzolt™ tablets developed by Labopharm and available in 100, 200 and 300 mg strengths for Q24H administration from Purdue Pharma have a relative mean AUC of about 93 to 95% after single doses (Ryzolt U.S. prescribing information, 2010 and Labopharm patent application No. WO2004/038428); Zydol™ SR Tablets, developed by Grunenthal and available in 20, 100, 150 and 200 mg strengths for Q12H administration have a relative mean AUC of about 91% (U.K. Summary of Product Characteristics for Zydol™ SR tablets); Zydol™ XL Tablets, containing the same excipients as Zamadol™ SR tablets and developed by Purdue Pharma/Napp are available in 150, 200 mg, 300 mg and 400 mg strengths for Q24H administration from Grunenthal, and have a relative mean AUC of about 91% (U.K.

Summary of Product Characteristics for Zydol™ SR tablets and Bodalia et al, J Pain Symptom Manage 2003;25:142-9); Zeridame™ SR (Minular™) Prolonged Release Tablets are available in 100, 150 and 200 mg strengths for Q12H administration from Actavis LTD have a relative mean AUC of about 91% (U.K. Summary of Product Characteristics for Zeridame™ SR Prolonged Release Tablets); and Ultram™ ER tablets, developed by Biovail and available in 100/200/300 mg strengths for Q24H administration from Ortho-McNeil have a relative mean AUC of 85 to 90% (Ultram™ ER U.S. prescribing information, 2010).

- [67] Applicant has surprisingly discovered that extended release dosage forms of levorphanol suitable for up to once-a-day administration including non-multiparticulate dosage forms can provide surprisingly good bioavailability.
- [68] Applicant has also surprisingly discovered that certain hydrogenated vegetable oil compositions can provide a preferred bioavailability and extended release pharmacokinetic profile for levorphanol, making them suitable for up to once-a-day administration (e.g, Q12H or Q24H).
- [69] For oral extended release dosage forms, the in vitro dissolution rate and bioavailability are the two most salient properties that require consideration when assessing the performance of a dosage form. The applicant has surprisingly discovered that to provide therapeutically effective dosage forms of levorphanol suitable for dosing every 12 or 24 hours or suitable for therapeutic effects for about 12 or about 24 hours, certain extended release dosage form of the invention require an unexpectedly slow in vitro release rate of levorphanol, for example 85%, or 90%, or 95% release at about 25, 30, 35, 40, 45, 50, or 55 hours, when measured by the USP Paddle Method with a sinker at 75 rpm in 600 mL of simulated intestinal fluid (SIF) USP, pH 6.8 (without enzymes) at 37 °C.
- [70] Another aspect of the invention provides for dosage forms of extended release levorphanol which are resistant to alcohol induced dose dumping. Extended release opioids which do not evidence dose dumping in relation to alcohol intake, which do not evidence clinically significant changes in rate or extent of absorption in relation to alcohol intake, which do not evidence clinically significant pharmacodynamic variability in relation to alcohol intake, and which do not evidence bio-inequivalence of the dosage form when given with or without alcohol provide a significant therapeutic advantage.
- [71] In 2005, a serious new clinical problem arose with the therapeutic use of extended release opioids, particularly extended release multiparticulate capsule dosage forms, when co-ingested with alcohol. Although subjects with chronic pain are discouraged from using opioids with alcohol, such co-ingestion in the setting of intractable pain is rather widespread. In addition, when used for non-medical purposes (e.g., to obtain a euphoric effect by recreational drug users), opioids are often used concomitantly with alcohol. This co-ingestion provides additional mood altering effects desired by the non-medical user. Regardless of whether the concomitant use of opioids and alcohol

is for medical or non-medical purposes, any impact of alcohol on the integrity of an extended release dosage form of an opioid can produce additional toxicity from alcohol induced dose dumping.

[72] The problem of alcohol induced dose dumping for extended release opioids was discovered with a once-a-day extended release multiparticulate formulation of hydromorphone HCL (Palladone™ capsules). Palladone™ was introduced in the United States and Canada in 2004. In 2005, Palladone™ was withdrawn from the market in both countries due to dose-dumping when co-ingested with alcohol. Patients consuming Palladone™ with 240 mL of 40% ethanol had a 6-fold mean increase in peak plasma hydromorphone concentration compared with co-ingestion with water. One subject experienced a 16-fold increase. Patients consuming 240 mL of 20% ethanol had a 2-fold mean increase in peak plasma hydromorphone concentration. One subject experienced a 6-fold increase. In some subjects, 8 ounces of 4% alcohol (equivalent to 2/3 of a typical serving of beer) resulted in almost twice the peak plasma hydromorphone concentration. In requesting the withdrawal of Palladone™, FDA noted that the manufacturer of “drinking alcohol while taking Palladone™ capsules may cause rapid release of hydromorphone, leading to high drug levels in the body, with potentially fatal effects. High drug levels of hydromorphone may depress or stop breathing, cause coma, and even cause death. The Agency has concluded that the overall risk versus benefit profile of Palladone™ is unfavorable due to a potentially fatal interaction with alcohol. Pharmacokinetic data indicate that the co-ingestion of Palladone™ and alcohol results in dangerous increases in the peak plasma concentrations of hydromorphone. These elevated levels may be lethal, even in opioid tolerant patients.” (Sloan and Babul, Expert Opinion on Drug Delivery 2006;3:489-97)

[73] FDA has since noted that a number of other controlled release opioids may be similarly vulnerable to dose dumping when co-ingested with alcohol. In vitro studies of alcohol dose dumping studies performed by the FDA demonstrated that Avinza™ (once-daily extended release morphine) release was alcohol concentration-dependent, leading to a more rapid release of morphine. FDA the mandated a “Black Box” warning which states “consumption of alcohol while taking Avinza may result in the rapid release and absorption of a potentially fatal dose of morphine” (Sloan and Babul, Expert Opinion on Drug Delivery 2006;3:489-97; Avinza™ U.S. Prescribing Information, April, 2008). Similarly, when evaluated with alcohol, Opana™ ER (twice-daily extended release oxymorphone) demonstrates significant dose dumping. The mean oxymorphone peak plasma concentration increase was 70% and 31%, after concomitant administration of 240 mL of 40% and 20% ethanol, respectively. In individual subjects, oxymorphone peak plasma concentrations increased by up to about 260%. Similarly, the mean extent of absorption was numerically higher by 13% after co-administration of 240 mL of 40% alcohol (U.S. Prescribing Information for Opana™ ER).

- [74] Another aspect of the invention provides for dosage forms of extended release levorphanol which are resistant to fed fasted pharmacokinetic variability. Extended release opioids which do not evidence dose dumping in relation to food intake, which do not evidence clinically significant changes in rate or extent of absorption in relation to food intake, which do not evidence clinically significant pharmacodynamic variability in relation to food intake, and which do not evidence bioequivalence of the dosage form when given in a fed or fasted state provide a significant therapeutic advantage.
- [75] An important issue with oral extended release products is its potential for “dose dumping” in relation to food, where the active drug, intended for slow release, is instead released rapidly, resulting in toxicity on the one hand and a decreased duration of effect on the other. Concurrent intake of food may increase, decrease or have no effect on the bioavailability of pharmaceutical products. The ability to resist food related changes in bioavailability is both a therapeutic benefit and a competitive marketing advantage.
- [76] Many commercialized extended release opioids have been shown to have a significant food effect. For example, the U.S. prescribing information for OxyContin™ (oxycodone ER) states “Food has no significant effect on the extent of absorption of oxycodone from OxyContin. However, the peak plasma concentration of oxycodone increased by 25% when an OxyContin 160 mg Tablet was administered with a high-fat meal”.
- [77] The U.S. prescribing information for Avinza™ (morphine ER) states “When a 60 mg dose of AVINZA was administered immediately following a high fat meal, peak morphine concentrations and AUC values were similar to those observed when the dose of AVINZA was administered in a fasting state, although achievement of initial concentrations was delayed by approximately 1 hour under fed conditions.”
- [78] According to the FDA “food caused a 16.9% increase in C_{max} shifting t_{max} from 21.06 hour to 8.54 hour” with Palladone™ (hydromorphone ER), (Palladone™ New Drug Application No. 21-044, FDA Summary Basis for Approval).
- [79] The U.S. prescribing information for Kadian™ (morphine ER) states “While concurrent administration of food slows the rate of absorption of KADIAN™, the extent of absorption is not affected and KADIAN™ can be administered without regard to meals”.
- [80] The U.S. prescribing information for Opana™ ER (oxymorphone ER) states “two studies examined the effect of food on the bioavailability of single doses of 20 and 40 mg of OPANA ER in healthy volunteers. In both studies, after the administration of OPANA ER, the C_{max} was increased by approximately 50% in fed subjects compared to fasted subjects. A similar increase in C_{max} was also observed with oxymorphone solution.”
- [81] Fed-fasted effects on oral bioavailability of extended release opioids are not limited to dose dumping in the presence of food or a high fat meal. For example, an extended release abuse

deterrent dosage form of oxycodone (Remoxy™) which is currently under FDA review for marketing authorization purportedly has adequate bioavailability when taken with food but also purportedly has reduced bioavailability in the fasted state. The manufacturer of Remoxy™ states that “a food effect study indicated that administration with food has a significant effect on the rate and extent of absorption of oxycodone. The rate of absorption is slower and the extent of absorption is higher; REMOXY should therefore be taken with food” (NDA 22-324, REMOXY XRT™, FDA Advisory Committee Briefing Materials for the Anesthetic Life Support Drugs Advisory Committee Meeting of November 13, 2008). A poster presentation on Remoxy™ at scientific meeting suggests more than a doubling of its extent of absorption (AUC₀₋₄₈) in relation to food status (Friedmann et al, Remoxy™, A Novel Drug Candidate, Deters Oxycodone Abuse in Humans, World Institute of Pain Meeting, Barcelona, 2004).

[82] Another aspect of the invention provides for extended release dosage forms of levorphanol which resist abuse by patients, recreational drug users and individuals with an addiction disorder. Extended release opioids which do not require the incorporation of aversive and potentially unsafe excipients into the formulation, which do not require the incorporation of sequestered or unsequestered opioid antagonists, which involve multiple mechanism of abuse deterrence and/or complement other safe and effective methods of abuse deterrence provide a significant therapeutic advantage. The abuse deterrent pharmaceutical dosage forms of the invention are achieved in part through delayed onset, extended release dosage forms which provide duodenal release, jejunal release, ileal release, ileo-colonic release or colonic release of the extended release levorphanol from the dosage form.

[83] An important drawback with the use of opioid analgesics is the risk of addiction, diversion and abuse. Tampering extended release opioid formulations can deliver a significant dose in immediate release form and produce a variety of potentially serious or life threatening side effects. The focus of virtually all abuse resistant technology for extended release opioid formulations has been predicated on abuse through tampering of the extended release dosage form by the recreational drug user or drug addicts. Such technologies purport to (i) frustrate attempts at dosage form tampering to extract the drug; (ii) nullify the effects of the drug if tampered, and/or (iii) produce an unpleasant or unwanted effect when consumed in tampered form.

[84] In the applicants view, the foregoing technologies are not an adequate solution to the problem of opioid abuse and fail to take into account the full spectrum of misuse, overuse and abuse of opioids. Such technologies show an overreliance on the experience of addiction disorder clinics and emergency rooms which treat a very small minority of non-medical opioid users, primarily “hard core” abusers who consume the dosage form after tampering to maximize the delivered dose. In contrast to this skewed observation derived from a minority of non-medical “hard core” opioid abusers, in a vast majority of cases, the abuse of opioid analgesics is with the intact dosage form

(i.e., the dosage form has not been physically manipulated or tampered with to alter its absorption profile) and the opioid is taken by the usual (oral) route of administration. For example, a vast majority of recreational drug users and patients with an addiction disorder, including iatrogenic addiction disorders will seldom or never use an opioid intended to be taken orally by any other route (e.g., intravenously after extraction and filtration, or by inhalation), nor will they physically manipulate or tamper the dosage form prior to oral ingestion. This population has a different self-image of their non-medical opioid use and attempts to distinguish or differentiate themselves and their use (abuse) from what they sometimes perceive as “reckless” and “irresponsible” use by “junkies”, “addicts”, “hard core addicts” or “real addicts”. In addition, a considerable amount of abuse of opioids is the intact ingestion at a dose which is simply higher than the medically prescribed dose. A majority of technologies described in the art do little or nothing to deal with the abuse of intact dosage forms of opioids.

[85] Another aspect of the invention provides for improved compliance with treatment. A major issue with pharmacologic management of chronic conditions is compliance with therapy. While extended release dosage forms assist this effort, compliance with extended release dosage forms is still not adequate, which defeats the now widely accepted concept of continuous suppression of pain. Many erroneously assume that medication compliance is not a problem in chronic pain (unlike, an asymptomatic condition such as hypertension), since the patient will be reminded when to take their medication by the recurrence of pain. We have previously demonstrated that patients given unlimited access to PRN or as needed opioids consume lower doses of opioids but have worse analgesic outcomes than patients who are placed on schedule around the clock therapy (Arkinstall et al, *Pain*, 2005;62:169-78). The present invention provides a novel method to improve compliance by making the dosage form substantially ineffective when taken on a PRN basis but effective when taken regularly.

[86] The lack of commercial success of levorphanol may also relate to incorrect equianalgesic and potency conversion tables in the literature for levorphanol relative to morphine. Applicant has surprisingly discovered that under certain conditions, the potency of levorphanol is far less than suggested in the literature and in expert guidelines. This means that higher doses of levorphanol are required than are suggested in the literature. For example, two guidelines for cancer pain management indicate that the daily dose of oral levorphanol tartrate equianalgesic to oral morphine sulfate 180 to 240 mg per day is 12 to 16 mg (Agency for Health Care Policy and Research Clinical Practice Guidelines for Cancer Pain Management, Guideline No. 9, AHCPR Publication No. 94-0592, March 1994 and Evidence Based Report of the U.S. Agency for Healthcare Research and Quality (AHRQ) on the Management of Cancer Pain, Report No. 35, AHRQ Publication No. 02-E002, October 2001). Another cancer pain management guideline indicates that the daily dose of oral levorphanol tartrate equianalgesic to oral morphine sulfate 120 to 240 mg per day is 8 to 16 mg

[Guideline for the Management of Cancer Pain in Adults and Children, American Pain Society, 2005). Yet another guideline indicates that the dose of oral levorphanol tartrate equianalgesic to oral morphine sulfate 30 mg is 4 mg for acute pain and 1 mg for chronic pain (Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, Sixth Ed., American, Pain Society (2008)].

BRIEF DESCRIPTION OF THE DRAWINGS

[87] The included drawings are illustrative but not limiting of the methods and composition of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention. Figures 1 to 53 are fully described within the specifications, within Example 6 to Example 40, inclusive; Figure 54 shows the mean Levorphanol ER release rate obtained with a prototype over about 48 hours when measured by the USP Paddle Method with a sinker at 75 rpm in 600 mL of simulated intestinal fluid (SIF) USP, pH 6.8 (without enzymes) at 37 °C; Figure 55 shows the mean Levorphanol ER release rate for obtained with a prototype over about 48 hours when measured by the USP Paddle Method with a sinker at 75 rpm in 600 mL of simulated intestinal fluid (SIF) USP, pH 6.8 (without enzymes) at 37 °C; Figure 56 shows the mean Levorphanol ER release rate obtained with a prototype over about 48 hours when measured by the USP Paddle Method with a sinker at 75 rpm in 600 mL of simulated intestinal fluid (SIF) USP, pH 6.8 (without enzymes) at 37 °C; Figure 57 shows the mean Levorphanol ER release rate obtained with a prototype over about 48 hours when measured by the USP Paddle Method with a sinker at 75 rpm in 600 mL of simulated intestinal fluid (SIF) USP, pH 6.8 (without enzymes) at 37 °C; Figure 70 shows the of resistance of four Levorphanol ER dosage forms of the invention to dose dumping in a high ethanol concentration gastric environment, in comparison with a commercially available extended release dosage form of oxycodone (reference). To simulate this, representative dosage forms were put through an extreme stress test: (i) the intact dosage form was placed in 18 mL of 0.1N HCl in a 60 mL bottle; (ii) the contents were agitated at 240 rpm on an orbital shaker for 30 min; (iii) after 30 min, 12 mL of 95% ethanol was added and the contents swirled and a 1 mL aliquot obtained; (iv) agitation was continued at 240 rpm and additional aliquots obtained at 10, 20, 30, 40, 60 and 180 minutes. In this Figure, Time "0" is after 30 minutes of prior agitation in acid at 240 RPM x 30 Minutes. All four tested Levorphanol ER formulations demonstrated excellent resistance to dose dumping in the presence of ethanol. Formulation VE2470 which comprises hydrogenated palm kernel oil showed the greatest level of resistance to dose dumping in the in a high ethanol concentration gastric environment. In contrast, the reference dosage form was significantly more susceptible to the effects of ethanol and produced release rates that may be associated with toxicity, particularly in opioid naïve subjects; Figure 71 shows the of resistance of four Levorphanol ER dosage forms of the invention to dose dumping even in a tampered form in a high ethanol concentration gastric environment in comparison with a tampered commercially

available extended release dosage form of oxycodone (reference). To simulate this, representative dosage forms were put through an extreme stress test: (i) a tampered dosage form was placed in 18 mL of 0.1N HCl in a 60 mL bottle; (ii) the contents were agitated at 240 rpm on an orbital shaker for 30 min; (iii) after 30 min, 12 mL of 95% ethanol was added and the contents swirled and a 1 mL aliquot obtained; (iv) agitation was continued at 240 rpm and additional aliquots obtained at 10, 20, 30, 40, 60 and 180 minutes. In this Figure, Time "0" is after 30 minutes of prior agitation in acid at 240 RPM x 30 Minutes. All four tested Levorphanol ER formulations demonstrated significant resistance to dose dumping in the presence of ethanol. Formulation VE2470 which comprises hydrogenated palm kernel oil showed the greatest level of resistance to dose dumping in the in a high ethanol concentration gastric environment. In contrast, the reference dosage form was significantly more susceptible to the effects of ethanol and produced release rates that may be associated with toxicity, particularly in opioid naïve subjects; Figure 72 shows resistance of four Levorphanol ER formulation batches (A, B, C and D) to dose dumping in a simulated high ethanol concentration gastric environment, when compared with a commercially available extended release dosage form of oxycodone (E), each tested in a tampered state after continuous agitation in acidic media comprising 0.1N HCl (pH 1.2) at 240 rpm for 30 minutes (Panel A), and after agitation in acidic media (0.1N HCl) for 30 minutes, followed by the addition of 95% ethanol and further agitation for 30 min at 240 rpm (Panel B). All Levorphanol ER formulations demonstrated significant resistance to dose dumping in the presence of ethanol, while the extended release oxycodone was highly susceptible to the dose dumping in simulated high ethanol gastric environment and produced active drug release rates that may be associated with significant toxicity. Formulation VE2470 which comprises hydrogenated palm kernel oil showed the greatest level of resistance to dose dumping in the in a high ethanol concentration gastric environment; Figure 73, Figure 74, Figure 75, Figure 76, Figure 77, Figure 78, Figure 79, Figure 80, Figure 81, and Figure 82 primarily address the delayed onset, extended release dosage Levorphanol ER dosage forms of the invention which are therapeutically effective and which also provide abuse deterrence and improved compliance as further described in the specifications; Figure 73 illustrates the average pH for dissolution of many pH sensitive polymers in the various segments of the gastrointestinal tract; Figure 74 illustrates the average gastrointestinal transit times for various segments of the gastrointestinal tract; Figure 75 illustrates the cross sectional view of an oral capsule or tablet dosage form of delayed onset, extended release oral levorphanol, where (A) is a dissolution, diffusion and/or pH sensitive material to render the dosage form delayed onset, optionally further overcoated with a film coat or an immediate release active; (B) is the outer shell of the capsule, optionally sealed in the overlapping region of capsule body and cap, or the usual outer margin of the core tablet, each optionally coated with additional excipients prior to coating with said material; and (C) is a monolithic solid, or a compressed multiparticulate plug, or one or more populations of

multiparticulates (e.g. beads, spheroids, pellets) comprising the active drug and controlled release material to render the dosage form extended release, and optionally, also delayed onset. The dosage form resists release of the active drug in the stomach, and optionally, also in the duodenum, jejunum and ileum, or until it reaches the desired GI pH, or until a specified amount of time has elapsed after ingestion; Figure 76 illustrates the cross sectional view of an oral tablet dosage form of delayed onset, extended release oral Levorphanol, where (A) is a dissolution, diffusion or pH sensitive material to render the dosage form delayed onset, optionally further overcoated with a film coat or an immediate release active; (B) is the usual outer margin of the core tablet, optionally coated with controlled release material or additional excipients prior to coating with dissolution, diffusion or pH sensitive material; and (C) is the tablet core comprising the active drug and controlled release material to render the dosage form extended release (said controlled release material optional in the event the core tablet in "B" is coated with controlled release material), and optionally, also delayed onset. The dosage form resists release of the active drug in the stomach, and optionally, also in the duodenum, jejunum and ileum, or until it reaches the desired GI pH, or until a specified amount of time has elapsed after ingestion; Figure 77 illustrates a dosage form for colonic release, where (1) the outer layer which dissolves at a pH of about 7; (2) a sustained release polymer coating; (3) levorphanol which has been coated onto a nonpareil core or bead (4); Figure 78 illustrates the in vivo release of a delayed onset, extended release dosage form of Levorphanol comprising an ileo-colonic pH sensitive polymer embedded in the dosage form or coated on the dosage form. The dosage form resists release of the active drug at pH less than 5 for a prolonged period of time and gradually releases the active drug from the dosage form at a pH greater than 6.5; Figure 79 illustrates the in vivo release of a delayed onset, extended release dosage form of Levorphanol ER comprising an ileo-colonic pH sensitive polymer embedded in the dosage form or coated on the dosage form. The dosage form resists release of the active drug at pH less than 5.5 for a prolonged period of time and gradually releases the active drug from the dosage form at a pH greater than 7; Figure 80 illustrates the in vivo release of a delayed onset, extended release dosage form of oral levorphanol upon reaching or traversing the ileo-cecal junction and transiting into the colon; Figure 81 illustrates the in vivo release of a delayed onset, extended release dosage form of oral levorphanol upon reaching or traversing the ileo-cecal junction and transiting into the colon; Figure 82 illustrates a delayed onset, extended release dosage form for ileo-colonic or colonic release. Following a lag period during which little or no levorphanol is released in vivo, the dosage form upon reaching a certain GI environment (e.g., desired pH, pressure, enzymes, microbial flora) or time, or a combination of variables, gradually releases the active drug; Figure 83 shows the effects of levorphanol tartrate on the [³H]5-HT incorporation into rat brain synaptosomes; Figure 84 shows the effects of levorphanol tartrate on the [³H]NE incorporation into rat hypothalamus synaptosomes.

DETAILED DESCRIPTION OF THE INVENTION

- [88] It is an object of certain embodiments of the present invention to provide bioavailable formulations of extended release levorphanol suitable for up to twice-day or up to once-a-day administration to subjects in need of levorphanol.
- [89] It is an object of certain preferred embodiments of the present invention to provide oral formulations which provide therapeutic effects for up to about 8, 10, 12, 14, 16, 18, 20, 22, 24 or 30 hours.
- [90] It is an object of certain embodiments of the present invention to provide dosage forms of extended release levorphanol suitable for up to once-a-day administration which are fully bioavailable.
- [91] It is an object of certain embodiments of the present invention to provide dosage forms of extended release levorphanol suitable for up to once-a-day administration which have a bioavailability comparable to oral immediate-release levorphanol.
- [92] It is an object of certain embodiments of the present invention to provide dosage forms of extended release levorphanol suitable for up to once-a-day administration which are bioequivalent with regard to extent of absorption when compared to oral immediate-release levorphanol.
- [93] It is an object of certain embodiments of the present invention to provide dosage forms of extended release levorphanol suitable for up to once-a-day administration which have about the same apparent oral elimination half-life as commercially available extended release morphine, hydromorphone, oxycodone and oxymorphone.
- [94] It is an object of certain embodiments of the present invention to provide dosage forms of extended release levorphanol suitable for up to once-a-day administration which have about the same time to reach 85% or 90% of the steady state plasma concentration as commercially available extended release morphine, hydromorphone, oxycodone and oxymorphone.
- [95] It is an object of certain embodiments of the present invention to provide dosage forms of extended release levorphanol suitable for up to once-a-day administration which have about the same time to reach steady state plasma concentrations as commercially available extended release morphine, hydromorphone, oxycodone and oxymorphone.
- [96] It is an object of certain embodiments of the present invention to provide dosage forms of extended release levorphanol suitable for up to once-a-day administration which have about the same or lower time to reach steady state plasma concentrations as oral immediate-release levorphanol.
- [97] It is an object of certain embodiments of the present invention to provide dosage forms of extended release levorphanol suitable for up to once-a-day administration which have about the same accumulation index as commercially available extended release morphine, hydromorphone, oxycodone and oxymorphone.

- [98] It is an object of certain embodiments of the present invention to provide dosage forms of extended release levorphanol suitable for up to once-a-day administration which have about the same or lower accumulation index as oral immediate-release levorphanol.
- [99] It is an object of certain embodiments of the present invention to provide dosage forms of extended release levorphanol suitable for up to once-a-day administration which are not multiparticulate dosage forms but have a bioavailability comparable to oral immediate-release levorphanol.
- [100] It is an object of certain embodiments of the present invention to provide dosage forms of extended release levorphanol suitable for up to once-a-day administration which have a bioavailability comparable to multiparticulate extended release dosage forms of levorphanol suitable for up to once-a-day administration.
- [101] It is an object of certain embodiments of the present invention to provide dosage forms of extended release levorphanol suitable for up to once-a-day administration which have a bioavailability ratio versus oral immediate release levorphanol which is comparable to the bioavailability ratio of multiparticulate extended release dosage forms of other opioids versus oral immediate release dosage forms of said opioid and which are also suitable for up to once-a-day administration.
- [102] It is an object of certain preferred embodiments of the present invention to provide oral extended release levorphanol pharmaceutical compositions which have a lower particle size for the levorphanol tartrate than found in commercially available oral immediate-release levorphanol tartrate tablets.
- [103] It is an object of certain embodiments of the present invention to provide bioavailable formulations of extended release levorphanol suitable for up to twice-day or up to once-a-day administration to subjects in need of levorphanol, said dosage form having reduced abuse liability compared with oral immediate-release levorphanol.
- [104] It is an object of certain embodiments of the present invention to provide bioavailable formulations of extended release levorphanol suitable for up to twice-day or up to once-a-day administration to subjects in need of levorphanol, said dosage form having reduced abuse liability compared with other extended release opioids.
- [105] It is an object of certain embodiments of the present invention to provide bioavailable formulations of extended release levorphanol suitable for up to twice-day or up to once-a-day administration to subjects in need of levorphanol, said dosage form having reduced side effects compared with oral immediate-release levorphanol.
- [106] It is an object of certain embodiments of the present invention to provide bioavailable formulations of extended release levorphanol which have an accumulation index comparable to oral immediate release levorphanol.

- [107] It is an object of certain embodiments of the present invention to provide bioavailable formulations of extended release levorphanol which have time to reach steady state comparable to or less than oral immediate release levorphanol.
- [108] It is an object of certain embodiments of the present invention to provide bioavailable formulations of extended release levorphanol which have an accumulation index comparable to or less than other extended release opioids.
- [109] It is an object of certain embodiments of the present invention to provide bioavailable formulations of extended release levorphanol which have time to reach steady state comparable to or less than other extended release opioids.
- [110] It is an object of certain embodiments of the present invention to provide bioavailable formulations of extended release levorphanol suitable for up to twice-day or up to once-a-day administration to subjects in need of levorphanol, said dosage form producing less side effects (e.g., drowsiness, dizziness, nausea, vomiting) than after an equal amount (or dose) or lower amount (or dose) of oral immediate release levorphanol.
- [111] It is an object of certain embodiments of the present invention to provide bioavailable formulations of extended release levorphanol suitable for up to twice-day or up to once-a-day administration to subjects in need of levorphanol, said dosage form producing less abuse or abuse potential (e.g., produces lower abuse scores for “drug effects”, “drug liking”, “coasting”, “take again”, as defined herein) than after an equal amount (or dose) or lower amount (or dose) of oral immediate release levorphanol.
- [112] It is an object of certain embodiments of the present invention to provide bioavailable formulations of extended release levorphanol suitable for up to twice-day or up to once-a-day administration to subjects in need of levorphanol, said dosage form producing less neurologic, cognitive, motor and psychomotor impairment given orally (e.g., produces lower impairment scores for “critical tracking task”, “stop signal task” and “Tower of London” (TOL), as defined herein) than after an equal amount (or dose) or lower amount (or dose) of oral immediate release levorphanol.
- [113] In some embodiments, the extended release oral pharmaceutical compositions of the invention comprise some portion of the dose as immediate release levorphanol.
- [114] In some embodiments, the present invention is directed at oral pharmaceutical composition for the treatment of levorphanol responsive medical conditions comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof.
- [115] In some embodiments, the present invention relates to oral levorphanol pharmaceutical compositions and methods for the treatment of pain.
- [116] It is an object of certain preferred embodiments of the present invention to provide

bioavailable oral levorphanol formulations suitable for up to once-daily administration which improve the efficiency and quality of pain management.

[117] It is an object of some embodiments of the invention to provide extended release oral pharmaceutical compositions of levorphanol and methods for the treatment of subjects in need of levorphanol, wherein the dosage form is administered at a prespecified dosing regimen. In some embodiments, said dosing regimen is associated with reduced side effects, improved tolerability, improved efficiency of therapeutic response, reduced breakthrough symptoms (e.g., breakthrough pain) and reduced treatment discontinuation due to side effects.

[118] It is an object of certain preferred embodiments of the present invention to treat pain in patients who have a suboptimal efficacy or safety response with other orally approved opioids [e.g., opioids described in FDA's Orange Book; Goodman & Gilman's The Pharmacological Basis of Therapeutics (Brunton, Lazo and Parker, eds, 11th ed., McGraw Hill (2005); Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, Fifth Ed., American Pain Society (2003); Evidence Based Report of the U.S. Agency for Healthcare Research and Quality (AHRQ) on the Management of Cancer Pain, Report No. 35, AHRQ Publication No. 02-E002, October 2001; Carr et al. J Nat Cancer Inst Monograph 2004;32:23-31; Agency for Health Care Policy and Research Clinical Practice Guidelines for Cancer Pain Management, Guideline No. 9, AHCPR Publication No. 94-0592, March 1994; Agency for Health Care Policy and Research Clinical Practice Guideline for Acute Pain Management, Guideline No. 1, AHCPR Publication No. 92-0032, February, 1992; Guideline for the Management of Cancer Pain in Adults, American Pain Society, 2005; Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis, 2nd Ed., American Pain Society, 2002], including morphine, codeine, oxycodone, oxymorphone, hydromorphone, methadone, hydrocodone, tapentadol and nalbuphine.

[119] It is an object of certain preferred embodiments of the present invention to treat pain in patients who have a suboptimal efficacy or safety response with other orally approved extended release opioids (e.g., MS Contin[™], Kadian[™], Avinza[™], Ultram[™] ER, Opana[™] ER, Palladone[™], Journista[™]).

[120] It is an object of certain preferred embodiments of the present invention to substantially improve the efficiency and quality of pain management in human patients experiencing pain which is unresponsive or suboptimally responsive to mu-receptor agonists.

[121] It is an object of certain preferred embodiments of the present invention to provide bioavailable oral levorphanol formulations which provide a substantially increased duration of effect as compared with oral immediate release levorphanol formulations. In some embodiments, such an unexpectedly short duration of therapeutic effect provides a basis for an extended release dosage forms that provide a more extended duration of efficacy.

[122] It is an object of certain preferred embodiments of the invention to provide an oral

levorphanol formulation which provides an early onset and extended duration of therapeutic effect.

- [123] It is an object of certain preferred embodiments of the present invention to provide bioavailable formulations oral administration which provide a therapeutic effect for up to 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28 or 30 hours after administration.
- [124] It is an object of certain preferred embodiments of the present invention to provide bioavailable formulations oral administration suitable dosing every 8, 12, or 24 hours.
- [125] It is an object of certain preferred embodiments of the invention to provide a method and formulations of oral levorphanol, said formulations having a reduced intrasubject variability in C_{\max} compared with immediate release oral levorphanol.
- [126] It is an object of certain preferred embodiments of the invention to provide a method and formulations of oral levorphanol, said formulations having a reduced intrasubject variability in T_{\max} compared with immediate release oral levorphanol.
- [127] It is an object of certain preferred embodiments of the invention to provide a method and formulations of oral levorphanol, said formulations having a reduced intrasubject variability in mean absorption time (MAT), compared with immediate release oral levorphanol.
- [128] It is an object of certain preferred embodiments of the invention to provide a method and formulations of oral levorphanol, said formulations having a reduced intrasubject variability in extent of absorption (AUC), compared with immediate release oral levorphanol.
- [129] It is an object of certain preferred embodiments of the invention to provide a method and formulations of oral levorphanol for the treatment of pain in patients tolerant to other opioids (e.g, morphine, oxymorphone, buprenorphine, oxycodone, oxymorphone, hydromorphone or hydrocodone).
- [130] It is an object of certain preferred embodiments of the invention to provide a method and formulations of oral levorphanol for the treatment of pain in patients with hyperalgesia from the use of other opioids (e.g, morphine, oxymorphone, buprenorphine, oxycodone, oxymorphone, hydromorphone or hydrocodone).
- [131] It is an object of the present invention to provide a method to substantially improve the efficiency and quality of pain management in human patients experiencing moderate or severe pain.
- [132] It is an object of the present invention to provide extended release dosage forms of levorphanol which are delayed onset, extended release dosage forms, said dosage form having reduced abuse liability compared with oral immediate-release levorphanol.
- [133] It is an object of the present invention to provide delayed onset, extended release dosage forms with reduced abuse which provide duodenal release, jejunal release, ileal release, ileo-colonic release or colonic release of the extended release levorphanol from the dosage form
- [134] It is an object of certain embodiments of the present invention to provide bioavailable levorphanol formulations suitable for twice-a-day (BID), once-a-day (QD), Q12H or Q24H

administration which substantially improve the efficiency and quality of pain management.

- [135] It is an object of certain embodiments of the present invention to provide bioavailable levorphanol formulations suitable for BID or QD administration which also provides deterrence (i.e., tamper deterrence or abuse deterrence) against tampering or physical manipulation of the levorphanol from the dosage form (e.g., crushing, powdering, melting, solvent extraction, inhalation, ease of filtration or the application of mechanical, thermal or chemical energy to make the dosage form more attractive to drug addicts or drug abusers by facilitating, for example, a greater "high" or by allowing easier use by alternative routes, e.g., inhalation, insufflation, intranasal administration, intravenous administration or oral administration.
- [136] It is an object of certain embodiments of the present invention to provide bioavailable extended release levorphanol formulations which provide a substantially increased duration of effect as compared to immediate release levorphanol formulations.
- [137] It is an object of certain embodiments of the invention to provide orally administrable extended release levorphanol formulations which provide an early onset and sustained duration of therapeutic effect.
- [138] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations without a propensity of substantial drug accumulation.
- [139] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations without a significant risk of levorphanol toxicity associated with substantial drug accumulation.
- [140] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations without the need for a loading dose.
- [141] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations without the need for levorphanol efficacy and toxicity monitoring beyond that ordinarily required for short half-life opioids (e.g., morphine, hydromorphone, oxycodone, hydrocodone).
- [142] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations without the need for more dosage adjustments than ordinarily required for short half-life opioids (e.g., morphine, hydromorphone, oxycodone, oxymorphone, hydrocodone).
- [143] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations without cumbersome and resource intensive dose titration to achieve optimal pain relief.
- [144] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations wherein at least about 87.5% of the steady state therapeutic concentration is reached in less than about 40 hours or less than about 36 hours.

- [145] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations wherein at least about 87.5% of the steady state therapeutic concentration of levorphanol or levorphanol-3-glucuronide (L3G) is reached in less than about 36 hours in a patient or a population of patients, when an oral solid extended release dosage formulation having from about 2.5 mg to about 60 mg of levorphanol or 2.5 mg to about 60 mg of a pharmaceutically acceptable salt is administered to a patient.
- [146] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations wherein at least about 93.75% of the steady state therapeutic concentration of levorphanol or L3G is reached in less than about 48 hours or less than about 54 hours in a patient or a population of patients.
- [147] It is an object of certain embodiments of the present invention to provide bioavailable extended release levorphanol formulations which provide a substantially increased duration of effect as compared to immediate release levorphanol formulations.
- [148] It is an object of certain embodiments of the invention to provide orally administrable extended release levorphanol formulations which provide an early onset and sustained duration of therapeutic effect.
- [149] In certain preferred embodiments of the present invention, an effective amount of levorphanol in immediate release form is included in the extended release unit dose levorphanol formulation to be administered. The immediate release form of the levorphanol is preferably included in an amount which is effective to shorten the time to C_{max} of the levorphanol in the blood (e.g., plasma). In such embodiments, an effective amount of the levorphanol in immediate release form may be coated onto the substrates of the present invention. For example, where the extended release levorphanol from the formulation is due to a controlled release coating, the immediate release layer would be overcoated on top of the controlled release coating. On the other hand, the immediate release layer maybe coated onto the surface of substrates wherein the levorphanol is incorporated in a controlled release matrix. Where a plurality of the extended release substrates comprising an effective unit dose of the levorphanol (e.g., multiparticulate systems including pellets, spheres, beads and the like) are incorporated into a hard gelatin capsule, the immediate release portion of the levorphanol dose may be incorporated into the gelatin capsule via inclusion of the sufficient amount of immediate release levorphanol as a powder or granulate within the capsule. Alternatively, the gelatin capsule itself may be coated with an immediate release layer of the levorphanol. One skilled in the art would recognize still other alternative manners of incorporating the immediate release levorphanol into the unit dose. Such alternatives are deemed to be encompassed by the appended claims. By including such an effective amount of immediate release levorphanol in the unit dose, the experience of relatively higher levels of pain or other symptoms in patients may be significantly reduced.

- [150] In some embodiments, the present invention discloses that the analgesic potency of levorphanol relative to morphine (the usual standard for comparison with other opioids) is at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 60% or 70% less than that disclosed in the expert analgesic guidelines cited herein.
- [151] In some embodiments, the present invention discloses that the equianalgesic dose of levorphanol relative to morphine (the usual standard for comparison with other opioids) is at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 60% or 70% greater than that disclosed in the expert analgesic guidelines cited herein.
- [152] In some embodiments, the present invention discloses that the analgesic potency of levorphanol relative to oxycodone is at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 60% or 70% less than that disclosed in the approved prescribing information for extended release oxycodone (OxyContin™).
- [153] In some embodiments, the present invention discloses that the equianalgesic dose of levorphanol relative to oxycodone is at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 60% or 70% greater than that disclosed in the approved prescribing information for extended release oxycodone (OxyContin™).
- [154] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; and material which imparts abuse deterrence, abuse resistance, tamper resistance, tamper deterrence qualities or which otherwise deters the abuse, misuse, diversion or recreational use or abuse of the drug.
- [155] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition of levorphanol is a delayed onset, extended release of levorphanol.
- [156] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition of levorphanol which provides a square wave plasma concentration time profile.
- [157] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition of levorphanol which provides rapid onset, a prolonged action, followed by rapid offset of effect, i.e., a "square wave" profile.
- [158] The invention is also directed to kits of the dosage forms, including kits for titration disclosed herein.
- [159] In a preferred embodiment, the dosage form containing levorphanol is an extended release form suitable for every 12 or every 24 hour administration. Oral, extended release levorphanol has several distinct advantages over oral immediate release opioids and over intranasal opioids, including fewer interruptions in sleep, reduced dependence on caregivers, improved compliance, enhanced quality of life outcomes, and increased control over the management of their malady (e.g.,

pain). In addition, such formulations can provide more constant plasma concentrations and clinical effects, less frequent peak to trough fluctuations and fewer side effects.

[160] The above objects and others are attained by virtue of the present invention, which in certain embodiments, provides an oral extended release dosage form comprising an analgesically effective amount of levorphanol or a pharmaceutically acceptable salt thereof and a sufficient amount of controlled release material to render the dosage form suitable for up to once-a-day administration (e.g., Q12H, BID, QD, Q24H).

[161] **Pharmacokinetics of Extended Release Levorphanol**

[162] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; and a controlled release material with gastroretentive properties to render said dosage form suitable for extended release oral administration to a human patient.

[163] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; and a controlled release material with osmotic release to render said dosage form suitable for extended release oral administration to a human patient.

[164] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; and a controlled release material with zero-order or pseudo-zero-order release to render said dosage form suitable for extended release oral administration to a human patient.

[165] In some preferred embodiments, the dosage form comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol a therapeutically effective amount of levorphanol and, optionally, controlled release material to render said dosage form suitable for twice-a-day (Q12H or Q12H PRN) or once-a-day (QD, Q24H or Q24H PRN) administration to a human patient, said dosage form after administration to a human patient providing less than about 20%, 30%, 40%, 50%, 60% or 70% the total absorbed dose into systemic circulation (as measured by bioavailability) during the first half of the intended dosing frequency.

[166] In some preferred embodiments, the extended release dosage form of the invention suitable for up to once-a-day provides about the same or shorter apparent oral elimination half-life as commercially available extended release morphine, hydromorphone, oxycodone or oxymorphone.

[167] In some preferred embodiments, the extended release dosage form of the invention suitable for up to once-a-day provides an apparent oral elimination half-life which is within 5%, 10%, 15%, 20%, 25%, 30%, 35% or 40% of the mean apparent oral elimination half-life of commercially available extended release morphine, hydromorphone, oxycodone or oxymorphone.

- [168] In some preferred embodiments, the extended release dosage form of the invention suitable for up to once-a-day provides about the same or shorter time to reach 85%, or 90% or 100% of the steady state plasma concentration as commercially available extended release morphine, hydromorphone, oxycodone or oxymorphone.
- [169] In some preferred embodiments, the extended release dosage form of the invention suitable for up to once-a-day provides a time to reach 85%, or 90% or 100% of the steady state plasma concentration which is within 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40% or 50% of said time for commercially available extended release morphine, hydromorphone, oxycodone or oxymorphone.
- [170] In some preferred embodiments, the extended release dosage form of the invention suitable for up to once-a-day provides about the same or shorter time to reach 85%, or 90% or 100% of the steady state plasma concentration as oral immediate-release levorphanol.
- [171] In some preferred embodiments, the extended release dosage form of the invention suitable for up to once-a-day provides about the same or lower accumulation index as commercially available extended release morphine, hydromorphone, oxycodone and oxymorphone.
- [172] In certain embodiments of the invention, the dosage form provides a time to maximum plasma concentration (T_{max}) of levorphanol or L3G in-vivo at about 3 to about 8 hours, at about 4 to about 5 hours, at about 2 to about 15 hours or at about 4 to about 8 hours after administration of the dosage form.
- [173] It is an object of certain embodiments of the invention to provide orally administrable extended release levorphanol formulations which provide an accumulation index (AI) of levorphanol or L3G of less than about 4.0, or less than about 3.5, or less than about 3.0, or less than about 2.5, or less than about 2.0, or less than about 1.5 and which provides effective pain relief to the patient.
- [174] It is an object of certain embodiments of the invention to provide orally administrable extended release levorphanol formulations which are self-titrating from dose to dose upon first administration, e.g., do not require gradual increases or upward adjustments in the dose of the extended release levorphanol over the first few days for up to about a week, or for 2, 3 or 4 weeks as the patient improves their tolerability to the levorphanol.
- [175] It is an object of certain embodiments of the invention to provide orally administrable extended release levorphanol formulations which are self-titrating from dose to dose upon first administration, e.g., do not require gradual increases or upward adjustments in the dose of the extended release levorphanol over the first few days for up to about a week, or for 2, 3 or 4 weeks which provide effective pain relief to the patient.
- [176] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which provides a C_{max} of levorphanol or L3G which is less than about 60%, 50% or 40% of the C_{max} of an equivalent dose of an immediate release levorphanol reference

formulation.

- [177] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which provides a time to 75% mean C_{max} of levorphanol or L3G which is about 85% to about 1200% of the time to 75% mean C_{max} of an immediate release levorphanol reference formulation.
- [178] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which provides a time to 75% mean C_{max} of levorphanol or L3G from about 0.25 to 18 hours, or about 0.5 to 16 hours, or about 0.5 to 15 hours, or about 0.75 to 16 hours, or about 1 to 16 hours.
- [179] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which provides a time to 80% mean C_{max} of levorphanol or L3G which is about 125% to about 450% of the time to 80% C_{max} of an equivalent dose of an immediate release levorphanol reference formulation.
- [180] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which provides a time to 50% mean C_{max} of levorphanol or L3G from about 0.25 to 5 hours.
- [181] In other preferred embodiments of the invention, there is provided an oral extended release dosage form of which provides a time to 50% mean C_{max} of levorphanol or L3G from about 0.5 to 5 hours.
- [182] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which maintains a plasma levorphanol or L3G concentration within 60% of C_{max} for about 1 to about 9 hours during a 12 hour dosing interval, or about 2 to about 18 hours during the 24 hour dosing interval.
- [183] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which maintains a plasma levorphanol or L3G concentration within 80% of C_{max} for about 1 to about 9 hours during a 12 hour dosing interval, or about 2 to about 18 hours during the 24 hour dosing interval.
- [184] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which maintains a plasma levorphanol or L3G concentration within 75% of C_{max} for about 1 to about 9 hours during a 12 hour dosing interval, or about 2 to about 18 hours during the 24 hour dosing interval.
- [185] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which maintains a plasma levorphanol or L3G concentration within 50% of C_{max} for about 1 to about 9 hours during a 12 hour dosing interval, or about 2 to about 18 hours during the 24 hour dosing interval.
- [186] In some preferred embodiments of the invention, there is provided provided an oral

extended release levorphanol dosage form which provides a time to maximum plasma concentration (T_{max}) of levorphanol or L3G at about 2 to about 8 hours, or about 3 to about 7 hours after oral administration of the dosage form.

[187] In some preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which provides a time to maximum plasma concentration (T_{max}) of levorphanol or L3G at about 2 to about 18 hours, or about 2 to about 15 hours, or about 2 to about 14 hours, or about 4 to about 18 hours about 4 to about 16 hours, or about 4 to about 14 hours about 6 to about 18 hours, or about 6 to about 16 hours, or about 6 to about 14 hours, or about 8 to about 18 hours, or about 8 to about 16 hours, or about 8 to about 14 hours, or about 9 to about 18 hours about 9 to about 16 hours, or about 9 to about 14 hours about 9 to about 12 hours, or about 10 to about 18 hours, or about 10 to about 16 hours, or about 10 to about 14 hours after oral administration of the dosage form.

[188] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which provides a T_{max} of levorphanol or L3G at a time point 1 to 7 times later than the T_{max} provided by an equivalent dose of an immediate release levorphanol reference formulation.

[189] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which provides a mean in vivo extent of absorption of levorphanol or L3G from 0 to 4 hours which is at least about 20% or about 30%, or about 40%, or about 50% of the mean in vivo extent of absorption from to 0 to 12 hours, wherein the mean in vivo extent of absorption is the area under the plasma or serum levorphanol concentration time curve from the time of drug administration to the specified time point.

[190] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which provides a mean in vivo extent of absorption of levorphanol or L3G from 0 to 4 hours which is at least about 20% or about 30%, or about 40%, or about 50% of the mean in vivo extent of absorption from to 0 to ∞ , wherein the mean in vivo extent of absorption is the area under the plasma or serum levorphanol concentration time curve from the time of drug administration to the specified time point and where AUC infinity is the sum of AUC from time "0" to time "t" (the last quantifiable time point which has been sampled) plus the extrapolated AUC from the last quantifiable sampling time point to infinity.

[191] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which provides a mean in vivo extent of absorption of levorphanol or L3G from 0 to 8 hours which is at least about 20% or about 30%, or about 40%, or about 50% of the mean in vivo extent of absorption from to 0 to 24 hours, wherein the mean in vivo extent of absorption is the area under the plasma or serum levorphanol concentration time curve from the time of drug administration to the specified time point.

- [192] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which provides a mean in vivo extent of absorption of levorphanol or L3G from 0 to 8 hours which is at least about 20% or about 30%, or about 40%, or about 50% of the mean in vivo extent of absorption from 0 to ∞ , wherein the mean in vivo extent of absorption is the area under the plasma or serum levorphanol concentration time curve from the time of drug administration to the specified time point and where AUC infinity is the sum of AUC from time "0" to time "t" (the last quantifiable time point which has been sampled) plus the extrapolated AUC from the last quantifiable sampling time point to infinity.
- [193] In other preferred embodiments of the invention, there is provided an oral extended release levorphanol dosage form which provides levorphanol plasma levels which are suitable for 12 hourly dosing, characterized by a HVD for levorphanol or L3G of between 1.5 and 20 hours, or 1.5 to 16 hours, or 2 to 12 hours, 6 to 20 hours, or 2 to 10 hours, or 4 to 10 hours, or 6 to 10 hours (e.g., about 4, 6, 8 or 10 hours).
- [194] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations which provide a mean maximum plasma concentration (C_{max}) of levorphanol from about 1 ng/mL to about 16 ng/mL for each mg of levorphanol base administered orally as levorphanol base, the racemate of levorphanol (racemorphan) or a pharmaceutically acceptable salt of levorphanol or racemorphan. In other embodiments of the invention, said C_{max} is from about 1 ng/mL to about 12 ng/mL, from about 2 ng/mL to about 16 ng/mL from about 2 ng/mL to about 12 ng/mL, from about 3 ng/mL to about 12 ng/mL, from about 4 ng/mL to about 10 ng/mL. It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations which provides a C_{max} of levorphanol or L3G in a patient or a population of patients from a mean of about 2 to about 10 hours after first administration or at steady state. In other embodiments of the invention, the C_{max} is achieved from a mean of about 2 to about 10 hours, of about 2 hours to about 8 hours, of about 2 hours to about 6 hours, of about 2.5 hours to about 5 hours, of about 2.5 hours to about 10 hours; said C_{max} determined after first administration or at steady state.
- [195] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations which provide pain control in substantially all patients by administering an oral solid extended release dosage formulation comprising up to about 60 mg of levorphanol or up to about 60 mg of a pharmaceutically acceptable salt thereof, such that a mean C_{max} of levorphanol up to about 700 ng/mL after first administration or at steady state. In some embodiments, the mean C_{max} of levorphanol is up to about 650 ng/mL, or about 600 ng/mL, or about 550 ng/mL, or about 500 ng/mL after first administration or at steady state.
- [196] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations which provide a mean minimum plasma concentration

(C_{\min}) of levorphanol from about 0.25 ng/mL to about 8 ng/mL for each mg of levorphanol base administered orally as levorphanol base, the racemate of levorphanol (racemorphan) or a pharmaceutically acceptable salt of levorphanol or racemorphan. In other embodiments of the invention, said C_{\min} is from about 0.25 ng/mL to about 6 ng/mL, from about 0.5 ng/mL to about 8 ng/mL, from about 0.5 ng/mL to about 6 ng/mL, from about 0.75 ng/mL to about 6 ng/mL, from about 0.8 ng/mL to about 5 ng/mL.

[197] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations which provide pain control in substantially all patients by administering an oral solid extended release dosage formulation comprising up to about 60 mg of levorphanol or up to about 60 mg of a pharmaceutically acceptable salt thereof, such that a mean C_{\min} of levorphanol up to about 350 ng/mL after first administration or at steady state. In some embodiments, the mean C_{\min} of levorphanol is up to about 300 ng/mL, or about 250 ng/mL, or about 200 ng/mL, or about 150 ng/mL after first administration or at steady state.

[198] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations which provide a systemic exposure as assessed by the mean area under the plasma concentration time curve (AUC_{0-Tau} or AUC_{0-inf}) of about 5 ng.hr/mL to about 160 ng.hr/mL for each mg of levorphanol base administered orally as levorphanol base, the racemate of levorphanol (racemorphan) or a pharmaceutically acceptable salt of levorphanol or racemorphan; said AUC_{0-inf} after first administration and said AUC_{0-1} AUC_{0-Tau} at steady state. In other embodiments of the invention, said AUC_{0-Tau} or AUC_{0-inf} is from about 5 ng.hr/mL to about 150 ng.hr/mL, or from about 5 ng.hr/mL to about 120 ng.hr/mL, or from about 5 ng.hr/mL to about 110 ng.hr/mL, or from about 5 ng.hr/mL to about 100 ng.hr/mL, or from about 10 ng.hr/mL to about 100 ng.hr/mL, or from about 10 ng.hr/mL to about 160 ng.hr/mL.

[199] It is an object of certain embodiments of the invention to provide a method and formulations of extended release levorphanol formulations which provide pain control in substantially all patients by administering an oral solid extended release dosage formulation comprising up to about 60 mg of levorphanol or up to about 60 mg of a pharmaceutically acceptable salt thereof, such that a mean AUC_{0-Tau} or AUC_{0-inf} of levorphanol up to about 8000 ng.hr/mL after first administration or at steady state. In some embodiments, the mean AUC_{0-Tau} or AUC_{0-inf} of levorphanol is up to about 6000 ng.hr/mL, or about 4000 ng.hr/mL, or about 3000 ng.hr/mL, or about 2000 ng.hr/mL after first administration ($AUC_{0-\infty}$) or at steady state (AUC_{0-Tau}).

[200] In other preferred embodiments of the invention, there is provided an oral extended release dosage form of which maintains a plasma levorphanol or L3G concentration within 30%, or 40% , or 50% , 60%, or 80% of C_{\max} for about 6 to about 16 hours, or about 8 to about 18 hours, or about 10 to about 18 hours, or about 6 to about 14 hours, or about 8 to about 14 hours, or about 10 to about 14 hours, or about 5 to about 20 hours, or about 5 to about 18 hours, or about 5 to about 16

hours during a 24 hour dosing interval.

- [201] In some preferred embodiments of the invention, there is provided an extended release dosage form of levorphanol which provides a time to maximum plasma concentration (T_{max}) of levorphanol or L3G at about 2 to about 20 hours, or about 3 to about 16 hours, or about 4 to 14 hours, or about 6 to 14 hours after oral administration of the dosage form.
- [202] In other preferred embodiments of the invention, there is provided an extended release dosage form of levorphanol which provides a T_{max} of levorphanol or L3G at a time point 1 to 14 times later or 2 to 12 times later than the T_{max} provided by an equivalent dose of an immediate release levorphanol reference formulation.
- [203] In other preferred embodiments of the invention, there is provided an extended release dosage form of levorphanol which provides a mean in vivo extent of absorption of levorphanol or L3G from 0 to 4 hours which is at least 10%, or at least 15%, or at least 30%, or at least 40%, or at least 50% of the mean in vivo extent of absorption from 0 to 24 hours, wherein the mean in vivo extent of absorption is the area under the plasma or serum levorphanol concentration time curve from the time of drug administration to the specified time point.
- [204] In certain preferred embodiments the sustained release oral dosage form of the present invention provides levorphanol plasma levels which are effective for 24 hourly dosing, characterized by a W_{50} for levorphanol or L3G of between 4 and 22 hours. In certain embodiments, the W_{50} is at least 4 hours, preferably at least 12 hours, and more preferably at least 16 or 18 hours.
- [205] In certain preferred embodiments the sustained release oral dosage form of the present invention provides levorphanol plasma levels which are effective for 24 hourly dosing, characterized by a HVD for levorphanol or L3G of between 3 and 20 hours. In certain embodiments, the W_{50} is at least 5 hours, preferably at least 8 hours, and more preferably at least 14 or 16 hours.
- [206] In some embodiments, the oral extended release levorphanol dosage form of the invention is surprisingly best described by a pharmacokinetic model which has at least one less compartment than the commercially available immediate release levorphanol tablet dosage. For example, when the immediate release levorphanol dosage form is best described by a two compartment pharmacokinetic model, the extended release levorphanol dosage form of the invention is best described by a one compartment pharmacokinetic model. Similarly, when the immediate release levorphanol dosage form is best described by a three compartment pharmacokinetic model, the extended release levorphanol dosage form of the invention is best described by a one or two compartment pharmacokinetic model.
- [207] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; said dosage form providing a

mean C_{\max} of levorphanol from about 0.1 ng/mL to about 70 ng/mL. In other preferred embodiments, the dosage form provides a C_{\max} of levorphanol of about 0.2 ng/mL to about 70 ng/mL, or about 0.3 ng/mL to about 70 ng/mL, or about 0.4 ng/mL to about 70 ng/mL, or about 0.5 ng/mL to about 70 ng/mL, or about 0.6 ng/mL to about 70 ng/mL, or about 0.7 ng/mL to about 30 ng/mL, or about 0.8 ng/mL to about 70 ng/mL, or about 1 ng/mL to about 70 ng/mL, or about 1.2 ng/mL to about 70 ng/mL, or about 1.5 ng/mL to about 70 ng/mL, or about 1.75 ng/mL to about 70 ng/mL, or about 2 ng/mL to about 70 ng/mL, or about 2.25 ng/mL to about 70 ng/mL, or about 2.5 ng/mL to about 70 ng/mL, or about 0.2 ng/mL to about 60 ng/mL, or about 0.3 ng/mL to about 60 ng/mL, or about 0.4 ng/mL to about 60 ng/mL, or about 0.5 ng/mL to about 60 ng/mL, or about 0.6 ng/mL to about 60 ng/mL, or about 0.7 ng/mL to about 30 ng/mL, or about 0.8 ng/mL to about 60 ng/mL, or about 1 ng/mL to about 60 ng/mL, or about 1.2 ng/mL to about 60 ng/mL, or about 1.5 ng/mL to about 60 ng/mL, or about 1.75 ng/mL to about 60 ng/mL, or about 2 ng/mL to about 60 ng/mL, or about 2.25 ng/mL to about 60 ng/mL, or about 2.5 ng/mL to about 60 ng/mL, or about 0.2 ng/mL to about 50 ng/mL, or about 0.3 ng/mL to about 50 ng/mL, or about 0.4 ng/mL to about 50 ng/mL, or about 0.5 ng/mL to about 50 ng/mL, or about 0.6 ng/mL to about 50 ng/mL, or about 0.7 ng/mL to about 30 ng/mL, or about 0.8 ng/mL to about 50 ng/mL, or about 1 ng/mL to about 50 ng/mL, or about 1.2 ng/mL to about 50 ng/mL, or about 1.5 ng/mL to about 50 ng/mL, or about 1.75 ng/mL to about 50 ng/mL, or about 2 ng/mL to about 50 ng/mL, or about 2.25 ng/mL to about 50 ng/mL, or about 2.5 ng/mL to about 50 ng/mL, or about 0.2 ng/mL to about 35 ng/mL, or about 0.3 ng/mL to about 35 ng/mL, or about 0.4 ng/mL to about 35 ng/mL, or about 0.5 ng/mL to about 35 ng/mL, or about 0.6 ng/mL to about 35 ng/mL, or about 0.7 ng/mL to about 30 ng/mL, or about 0.8 ng/mL to about 35 ng/mL, or about 1 ng/mL to about 35 ng/mL, or about 1.2 ng/mL to about 35 ng/mL, or about 1.5 ng/mL to about 35 ng/mL, or about 1.75 ng/mL to about 35 ng/mL, or about 2 ng/mL to about 35 ng/mL, or about 2.25 ng/mL to about 35 ng/mL, or about 2.5 ng/mL to about 35 ng/mL, or about 0.2 ng/mL to about 25 ng/mL, or about 0.3 ng/mL to about 25 ng/mL, or about 0.4 ng/mL to about 25 ng/mL, or about 0.5 ng/mL to about 25 ng/mL, or about 0.6 ng/mL to about 25 ng/mL, or about 0.7 ng/mL to about 30 ng/mL, or about 0.8 ng/mL to about 25 ng/mL, or about 1 ng/mL to about 25 ng/mL, or about 1.2 ng/mL to about 25 ng/mL, or about 1.5 ng/mL to about 25 ng/mL, or about 1.75 ng/mL to about 25 ng/mL, or about 2 ng/mL to about 25 ng/mL, or about 2.25 ng/mL to about 25 ng/mL, or about 2.5 ng/mL to about 25 ng/mL, or about 0.2 ng/mL to about 20 ng/mL, or about 0.3 ng/mL to about 20 ng/mL, or about 0.4 ng/mL to about 20 ng/mL, or about 0.5 ng/mL to about 20 ng/mL, or about 0.6 ng/mL to about 20 ng/mL, or about 0.7 ng/mL to about 30 ng/mL, or about 0.8 ng/mL to about 20 ng/mL, or about 1 ng/mL to about 20 ng/mL, or about 1.2 ng/mL to about 20 ng/mL, or about 1.5 ng/mL to about 20 ng/mL, or about 1.75 ng/mL to about 20 ng/mL, or about 2 ng/mL to about 20 ng/mL, or about 2.25 ng/mL to about 20 ng/mL, or about 2.5 ng/mL to about 20 ng/mL. In more preferred embodiments, the dosage form provides a C_{\max} of

levorphanol of about 1 ng/mL to about 30 ng/mL, or about 1 ng/mL to about 25 ng/mL, or about 1 ng/mL to about 20 ng/mL, or about 0.5 ng/mL to about 25 ng/mL, or about 1.5 ng/mL to about 25 ng/mL, or about 2 ng/mL to about 30 ng/mL.

[208] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours, provides a C_{max} of levorphanol occurring from a mean of about 2 to about 38 hours. In other preferred embodiments, said C_{max} occurs from a mean of about 2.5 to about 30 hours, or about 3 to about 30 hours, or about 3 to about 26 hours, or about 3 to about 24 hours, or about 3 to about 20 hours, or about 3 to about 18 hours, or about 3 to about 15 hours, or about 5 to about 30 hours, or about 5 to about 25 hours, or about 5 to about 20 hours, or about 5 to about 18 hours, or about 5 to about 15 hours, or about 7 to about 30 hours, or about 7 to about 25 hours, or about 5 to about 20 hours, or about 7 to about 18 hours, or about 7 to about 15 hours, or about 9 to about 30 hours, or about 9 to about 25 hours, or about 9 to about 20 hours, or about 9 to about 18 hours, or about 9 to about 15 hours, or about 8 to about 18 hours, or about 8 to about 15 hours, or about 8 to about 14 hours, or about 8 to about 13 hours, or about 8 to about 12 hours.

[209] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours, provides a mean C_6 of levorphanol of about 0.2 ng/mL to about 70 ng/ml. In other preferred embodiments, said mean C_6 of levorphanol is of about 0.2 ng/mL to about 60 ng/ml, or of about 0.2 ng/mL to about 50 ng/ml, or of about 0.2 ng/mL to about 40 ng/ml, or of about 0.2 ng/mL to about 35 ng/ml, or of about 0.2 ng/mL to about 30 ng/ml, or of about 0.2 ng/mL to about 25 ng/ml, or of about 0.2 ng/mL to about 20 ng/ml, or of about 0.2 ng/mL to about 15 ng/ml, or of about 0.5 ng/mL to about 70 ng/ml, or of about 0.5 ng/mL to about 40 ng/ml, or of about 0.5 ng/mL to about 35 ng/ml, or of about 0.5 ng/mL to about 30 ng/ml, or of about 0.5 ng/mL to about 25 ng/ml, or of about 0.5 ng/mL to about 20 ng/ml, or of about 0.5 ng/mL to about 15 ng/ml, or of about 0.75 ng/mL to about 70 ng/ml, or of about 0.75 ng/mL to about 40 ng/ml, or of about 0.75 ng/mL to about 35 ng/ml, or of about 0.75 ng/mL to about 30 ng/ml, or of about 0.75 ng/mL to about 25 ng/ml, or of about 0.75 ng/mL to about 20 ng/ml, or of about 0.75 ng/mL to about 15 ng/ml.

[210] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours, provides a

mean C_8 of levorphanol of about 0.2 ng/mL to about 70 ng/ml. In other preferred embodiments, said mean C_8 of levorphanol is of about 0.2 ng/mL to about 60 ng/ml, or of about 0.2 ng/mL to about 50 ng/ml, or of about 0.2 ng/mL to about 40 ng/ml, or of about 0.2 ng/mL to about 35 ng/ml, or of about 0.2 ng/mL to about 30 ng/ml, or of about 0.2 ng/mL to about 25 ng/ml, or of about 0.2 ng/mL to about 20 ng/ml, or of about 0.2 ng/mL to about 15 ng/ml, or of about 0.5 ng/mL to about 70 ng/ml, or of about 0.5 ng/mL to about 40 ng/ml, or of about 0.5 ng/mL to about 35 ng/ml, or of about 0.5 ng/mL to about 30 ng/ml, or of about 0.5 ng/mL to about 25 ng/ml, or of about 0.5 ng/mL to about 20 ng/ml, or of about 0.5 ng/mL to about 15 ng/ml, or of about 0.75 ng/mL to about 70 ng/ml, or of about 0.75 ng/mL to about 40 ng/ml, or of about 0.75 ng/mL to about 35 ng/ml, or of about 0.75 ng/mL to about 30 ng/ml, or of about 0.75 ng/mL to about 25 ng/ml, or of about 0.75 ng/mL to about 20 ng/ml, or of about 0.75 ng/mL to about 15 ng/ml.

[211] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours, provides a mean C_{12} of levorphanol of about 0.2 ng/mL to about 70 ng/ml. In other preferred embodiments, said mean C_{12} of levorphanol is of about 0.2 ng/mL to about 60 ng/ml, or of about 0.2 ng/mL to about 50 ng/ml, or of about 0.2 ng/mL to about 40 ng/ml, or of about 0.2 ng/mL to about 35 ng/ml, or of about 0.2 ng/mL to about 30 ng/ml, or of about 0.2 ng/mL to about 25 ng/ml, or of about 0.2 ng/mL to about 20 ng/ml, or of about 0.2 ng/mL to about 15 ng/ml, or of about 0.5 ng/mL to about 70 ng/ml, or of about 0.5 ng/mL to about 40 ng/ml, or of about 0.5 ng/mL to about 35 ng/ml, or of about 0.5 ng/mL to about 30 ng/ml, or of about 0.5 ng/mL to about 25 ng/ml, or of about 0.5 ng/mL to about 20 ng/ml, or of about 0.5 ng/mL to about 15 ng/ml, or of about 0.75 ng/mL to about 70 ng/ml, or of about 0.75 ng/mL to about 40 ng/ml, or of about 0.75 ng/mL to about 35 ng/ml, or of about 0.75 ng/mL to about 30 ng/ml, or of about 0.75 ng/mL to about 25 ng/ml, or of about 0.75 ng/mL to about 20 ng/ml, or of about 0.75 ng/mL to about 15 ng/ml.

[212] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours, provides a mean C_{16} of levorphanol of about 0.1 ng/mL to about 50 ng/ml. In other preferred embodiments, said mean C_{16} of levorphanol is of about 0.1 ng/mL to about 40 ng/ml, or of about 0.1 ng/mL to about 35 ng/ml, or of about 0.1 ng/mL to about 30 ng/ml, or of about 0.1 ng/mL to about 25 ng/ml, or of about 0.1 ng/mL to about 20 ng/ml, or of about 0.1 ng/mL to about 15 ng/ml, or of about 0.25 ng/mL to about 50 ng/ml, or of about 0.25 ng/mL to about 40 ng/ml, or of about 0.25 ng/mL to about 35 ng/ml, or of about 0.25 ng/mL to about 30 ng/ml, or of about 0.25 ng/mL to about 25

ng/ml, or of about 0.25 ng/mL to about 20 ng/ml, or of about 0.25 ng/mL to about 15 ng/ml, or of about 0.5 ng/mL to about 50 ng/ml, or of about 0.5 ng/mL to about 40 ng/ml, or of about 0.5 ng/mL to about 35 ng/ml, or of about 0.5 ng/mL to about 30 ng/ml, or of about 0.5 ng/mL to about 25 ng/ml, or of about 0.5 ng/mL to about 20 ng/ml, or of about 0.5 ng/mL to about 15 ng/ml.

[213] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours, provides a mean C_{24} of levorphanol of about 0.1 ng/mL to about 40 ng/ml. In other preferred embodiments, said mean C_{24} of levorphanol is of about 0.1 ng/mL to about 35 ng/ml, or of about 0.1 ng/mL to about 30 ng/ml, or of about 0.1 ng/mL to about 25 ng/ml, or of about 0.1 ng/mL to about 20 ng/ml, or of about 0.1 ng/mL to about 15 ng/ml, or of about 0.2 ng/mL to about 50 ng/ml, or of about 0.2 ng/mL to about 40 ng/ml, or of about 0.2 ng/mL to about 35 ng/ml, or of about 0.2 ng/mL to about 30 ng/ml, or of about 0.2 ng/mL to about 25 ng/ml, or of about 0.2 ng/mL to about 20 ng/ml, or of about 0.2 ng/mL to about 15 ng/ml.

[214] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours, provides a mean C_{36} of levorphanol of about 0.05 ng/mL to about 30 ng/ml. In other preferred embodiments, said mean C_{36} of levorphanol is of about 0.05 ng/mL to about 28 ng/ml, or of about 0.05 ng/mL to about 25 ng/ml, or of about 0.05 ng/mL to about 20 ng/ml, or of about 0.05 ng/mL to about 15 ng/ml, or of about 0.05 ng/mL to about 12 ng/ml, or of about 0.05 ng/mL to about 10 ng/ml, or 0.1 ng/mL to about 28 ng/ml, or of about 0.1 ng/mL to about 25 ng/ml, or of about 0.1 ng/mL to about 20 ng/ml, or of about 0.1 ng/mL to about 15 ng/ml, or of about 0.1 ng/mL to about 12 ng/ml, or of about 0.1 ng/mL to about 10 ng/ml,

[215] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours, provides a mean C_{48} of levorphanol of about 0.01 ng/mL to about 20 ng/ml. In other preferred embodiments, said mean C_{48} of levorphanol is of about 0.01 ng/mL to about 15 ng/ml, or of about 0.01 ng/mL to about 10 ng/ml, or of about 0.01 ng/mL to about 8 ng/ml, or of about 0.01 ng/mL to about 7 ng/ml, or of about 0.01 ng/mL to about 6 ng/ml, or of about 0.01 ng/mL to about 5 ng/ml, or about 0.05 ng/mL to about 15 ng/ml, or of about 0.05 ng/mL to about 10 ng/ml, or of about 0.05 ng/mL to about 8 ng/ml, or of about 0.05 ng/mL to about 7 ng/ml, or of about 0.05 ng/mL to about 6 ng/ml,

or of about 0.05 ng/mL to about 5 ng/ml.

[216] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; said dosage suitable for dosing every 12 hours; said dosage from providing a C_{\min} of levorphanol of about 0.2 ng/mL to about 70 ng/ml. In other preferred embodiments, said mean C_{12} of levorphanol is of about 0.2 ng/mL to about 60 ng/ml, or of about 0.2 ng/mL to about 50 ng/ml, or of about 0.2 ng/mL to about 40 ng/ml, or of about 0.2 ng/mL to about 35 ng/ml, or of about 0.2 ng/mL to about 30 ng/ml, or of about 0.2 ng/mL to about 25 ng/ml, or of about 0.2 ng/mL to about 20 ng/ml, or of about 0.2 ng/mL to about 15 ng/ml, or of about 0.5 ng/mL to about 70 ng/ml, or of about 0.5 ng/mL to about 40 ng/ml, or of about 0.5 ng/mL to about 35 ng/ml, or of about 0.5 ng/mL to about 30 ng/ml, or of about 0.5 ng/mL to about 25 ng/ml, or of about 0.5 ng/mL to about 20 ng/ml, or of about 0.5 ng/mL to about 15 ng/ml, or of about 0.75 ng/mL to about 70 ng/ml, or of about 0.75 ng/mL to about 40 ng/ml, or of about 0.75 ng/mL to about 35 ng/ml, or of about 0.75 ng/mL to about 30 ng/ml, or of about 0.75 ng/mL to about 25 ng/ml, or of about 0.75 ng/mL to about 20 ng/ml, or of about 0.75 ng/mL to about 15 ng/ml; said C_{\min} measured from a mean of about 10 to about 14 hours after first administration or single dose administration.

[217] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; said dosage suitable for dosing every 24 hours; said dosage from providing a C_{\min} of levorphanol of about 0.1 ng/mL to about 40 ng/ml. In other preferred embodiments, said mean C_{24} of levorphanol is of about 0.1 ng/mL to about 30 ng/ml, or of about 0.1 ng/mL to about 25 ng/ml, or of about 0.1 ng/mL to about 20 ng/ml, or of about 0.1 ng/mL to about 15 ng/ml, or of about 0.2 ng/mL to about 50 ng/ml, or of about 0.2 ng/mL to about 40 ng/ml, or of about 0.2 ng/mL to about 35 ng/ml, or of about 0.2 ng/mL to about 30 ng/ml, or of about 0.2 ng/mL to about 25 ng/ml, or of about 0.2 ng/mL to about 20 ng/ml, or of about 0.2 ng/mL to about 15 ng/ml; said C_{\min} measured from a mean of about 20 to about 28 hours after first administration or single dose administration.

[218] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve to 48 hours post-dose (AUC_{0-48}) of about 4 ng.hr/mL to about 2480 ng.hr/mL. In other preferred embodiments, AUC_{0-48} is about 4 ng.hr/mL to about 2200 ng.hr/mL, or about 4 ng.hr/mL to about 2000 ng.hr/mL, or about 4 ng.hr/mL to about 1800 ng.hr/mL, or about 4 ng.hr/mL to about

1700 ng.hr/mL, or about 4 ng.hr/mL to about 1600 ng.hr/mL, or about 4 ng.hr/mL to about 1400 ng.hr/mL, or about 4 ng.hr/mL to about 1200 ng.hr/mL, or about 4 ng.hr/mL to about 1100 ng.hr/mL, or about 4 ng.hr/mL to about 1000 ng.hr/mL, or about 4 ng.hr/mL to about 900 ng.hr/mL, or about 4 ng.hr/mL to about 800 ng.hr/mL, or about 4 ng.hr/mL to about 700 ng.hr/mL, or about 4 ng.hr/mL to about 600 ng.hr/mL, or about 4 ng.hr/mL to about 550 ng.hr/mL, or about 4 ng.hr/mL to about 500 ng.hr/mL, or about 4 ng.hr/mL to about 475 ng.hr/mL, or about 4 ng.hr/mL to about 450 ng.hr/mL, or about 4 ng.hr/mL to about 425 ng.hr/mL, or about 4 ng.hr/mL to about 400 ng.hr/mL, or about 4 ng.hr/mL to about 375 ng.hr/mL, or about 4 ng.hr/mL to about 350 ng.hr/mL, or about 4 ng.hr/mL to about 325 ng.hr/mL, or about 4 ng.hr/mL to about 300 ng.hr/mL, or about 4 ng.hr/mL to about 275 ng.hr/mL, or about 4 ng.hr/mL to about 250 ng.hr/mL, or about 4 ng.hr/mL to about 225 ng.hr/mL, or about 4 ng.hr/mL to about 200 ng.hr/mL.

[219] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve to 48 hours post-dose (AUC_{0-48}) of about 10 ng.hr/mL to about 2480 ng.hr/mL. In other preferred embodiments, AUC_{0-48} is about 10 ng.hr/mL to about 2200 ng.hr/mL, or about 10 ng.hr/mL to about 2000 ng.hr/mL, or about 10 ng.hr/mL to about 1800 ng.hr/mL, or about 10 ng.hr/mL to about 1700 ng.hr/mL, or about 10 ng.hr/mL to about 1600 ng.hr/mL, or about 10 ng.hr/mL to about 1400 ng.hr/mL, or about 10 ng.hr/mL to about 1200 ng.hr/mL, or about 10 ng.hr/mL to about 1100 ng.hr/mL, or about 10 ng.hr/mL to about 1000 ng.hr/mL, or about 10 ng.hr/mL to about 900 ng.hr/mL, or about 10 ng.hr/mL to about 800 ng.hr/mL, or about 10 ng.hr/mL to about 700 ng.hr/mL, or about 10 ng.hr/mL to about 600 ng.hr/mL, or about 10 ng.hr/mL to about 550 ng.hr/mL, or about 10 ng.hr/mL to about 500 ng.hr/mL, or about 10 ng.hr/mL to about 475 ng.hr/mL, or about 10 ng.hr/mL to about 450 ng.hr/mL, or about 10 ng.hr/mL to about 425 ng.hr/mL, or about 10 ng.hr/mL to about 400 ng.hr/mL, or about 10 ng.hr/mL to about 375 ng.hr/mL, or about 10 ng.hr/mL to about 350 ng.hr/mL, or about 10 ng.hr/mL to about 325 ng.hr/mL, or about 10 ng.hr/mL to about 300 ng.hr/mL, or about 10 ng.hr/mL to about 275 ng.hr/mL, or about 10 ng.hr/mL to about 250 ng.hr/mL, or about 10 ng.hr/mL to about 225 ng.hr/mL, or about 10 ng.hr/mL to about 200 ng.hr/mL.

[220] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time

curve to 48 hours post-dose (AUC_{0-48}) of about 20 ng.hr/mL to about 2480 ng.hr/mL. In other preferred embodiments, AUC_{0-48} is about 20 ng.hr/mL to about 2200 ng.hr/mL, or about 20 ng.hr/mL to about 2000 ng.hr/mL, or about 20 ng.hr/mL to about 1800 ng.hr/mL, or about 20 ng.hr/mL to about 1700 ng.hr/mL, or about 20 ng.hr/mL to about 1600 ng.hr/mL, or about 20 ng.hr/mL to about 1400 ng.hr/mL, or about 20 ng.hr/mL to about 1200 ng.hr/mL, or about 20 ng.hr/mL to about 1100 ng.hr/mL, or about 20 ng.hr/mL to about 1000 ng.hr/mL, or about 20 ng.hr/mL to about 900 ng.hr/mL, or about 20 ng.hr/mL to about 800 ng.hr/mL, or about 20 ng.hr/mL to about 700 ng.hr/mL, or about 20 ng.hr/mL to about 600 ng.hr/mL, or about 20 ng.hr/mL to about 550 ng.hr/mL, or about 20 ng.hr/mL to about 500 ng.hr/mL, or about 20 ng.hr/mL to about 475 ng.hr/mL, or about 20 ng.hr/mL to about 450 ng.hr/mL, or about 20 ng.hr/mL to about 425 ng.hr/mL, or about 20 ng.hr/mL to about 400 ng.hr/mL, or about 20 ng.hr/mL to about 375 ng.hr/mL, or about 20 ng.hr/mL to about 350 ng.hr/mL, or about 20 ng.hr/mL to about 325 ng.hr/mL, or about 20 ng.hr/mL to about 300 ng.hr/mL, or about 20 ng.hr/mL to about 275 ng.hr/mL, or about 20 ng.hr/mL to about 250 ng.hr/mL, or about 20 ng.hr/mL to about 225 ng.hr/mL, or about 20 ng.hr/mL to about 200 ng.hr/mL.

[221] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve to 48 hours post-dose (AUC_{0-48}) of about 30 ng.hr/mL to about 2480 ng.hr/mL. In other preferred embodiments, AUC_{0-48} is about 30 ng.hr/mL to about 2200 ng.hr/mL, or about 30 ng.hr/mL to about 2000 ng.hr/mL, or about 30 ng.hr/mL to about 1800 ng.hr/mL, or about 30 ng.hr/mL to about 1700 ng.hr/mL, or about 30 ng.hr/mL to about 1600 ng.hr/mL, or about 30 ng.hr/mL to about 1400 ng.hr/mL, or about 30 ng.hr/mL to about 1200 ng.hr/mL, or about 30 ng.hr/mL to about 1100 ng.hr/mL, or about 30 ng.hr/mL to about 1000 ng.hr/mL, or about 30 ng.hr/mL to about 900 ng.hr/mL, or about 30 ng.hr/mL to about 800 ng.hr/mL, or about 30 ng.hr/mL to about 700 ng.hr/mL, or about 30 ng.hr/mL to about 600 ng.hr/mL, or about 30 ng.hr/mL to about 550 ng.hr/mL, or about 30 ng.hr/mL to about 500 ng.hr/mL, or about 30 ng.hr/mL to about 475 ng.hr/mL, or about 30 ng.hr/mL to about 450 ng.hr/mL, or about 30 ng.hr/mL to about 425 ng.hr/mL, or about 30 ng.hr/mL to about 400 ng.hr/mL, or about 30 ng.hr/mL to about 375 ng.hr/mL, or about 30 ng.hr/mL to about 350 ng.hr/mL, or about 30 ng.hr/mL to about 325 ng.hr/mL, or about 30 ng.hr/mL to about 300 ng.hr/mL, or about 30 ng.hr/mL to about 275 ng.hr/mL, or about 30 ng.hr/mL to about 250 ng.hr/mL, or about 30 ng.hr/mL to about 225 ng.hr/mL, or about 30 ng.hr/mL to about 200 ng.hr/mL.

[222] In some more preferred embodiments, the invention comprises an oral extended release

pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve to 48 hours post-dose (AUC_{0-48}) of about 10 ng.hr/mL to about 800 ng.hr/mL, or about 10 ng.hr/mL to about 600 ng.hr/mL, or about 15 ng.hr/mL to about 600 ng.hr/mL.

[223] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve to 48 hours post-dose (AUC_{0-48}) of not less than about 4 ng.hr/mL, or not less than about 6 ng.hr/mL, or not less than about 8 ng.hr/mL, or not less than about 10 ng.hr/mL, or not less than about 12 ng.hr/mL, or not less than about 15 ng.hr/mL, or not less than about 20 ng.hr/mL, or not less than about 30 ng.hr/mL.

[224] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 or 72 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to infinity (AUC_{0-inf}) of about 4 ng.hr/mL to about 2800 ng.hr/mL. In other preferred embodiments, AUC_{0-inf} is about 4 ng.hr/mL to about 2500 ng.hr/mL, or about 4 ng.hr/mL to about 2200 ng.hr/mL, or about 4 ng.hr/mL to about 1800 ng.hr/mL, or about 4 ng.hr/mL to about 1700 ng.hr/mL, or about 4 ng.hr/mL to about 1600 ng.hr/mL, or about 4 ng.hr/mL to about 1400 ng.hr/mL, or about 4 ng.hr/mL to about 1200 ng.hr/mL, or about 4 ng.hr/mL to about 1100 ng.hr/mL, or about 4 ng.hr/mL to about 1000 ng.hr/mL, or about 4 ng.hr/mL to about 900 ng.hr/mL, or about 4 ng.hr/mL to about 800 ng.hr/mL, or about 4 ng.hr/mL to about 700 ng.hr/mL, or about 4 ng.hr/mL to about 600 ng.hr/mL, or about 4 ng.hr/mL to about 550 ng.hr/mL, or about 4 ng.hr/mL to about 500 ng.hr/mL, or about 4 ng.hr/mL to about 475 ng.hr/mL, or about 4 ng.hr/mL to about 450 ng.hr/mL, or about 4 ng.hr/mL to about 425 ng.hr/mL, or about 4 ng.hr/mL to about 400 ng.hr/mL, or about 4 ng.hr/mL to about 375 ng.hr/mL, or about 4 ng.hr/mL to about 350 ng.hr/mL.

[225] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 or 72 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time

curve from 0 to infinity ($AUC_{0-\infty}$) of about 8 ng.hr/mL to about 2800 ng.hr/mL. In other preferred embodiments, $AUC_{0-\infty}$ is about 8 ng.hr/mL to about 2500 ng.hr/mL, or about 8 ng.hr/mL to about 2200 ng.hr/mL, or about 8 ng.hr/mL to about 1800 ng.hr/mL, or about 8 ng.hr/mL to about 1700 ng.hr/mL, or about 8 ng.hr/mL to about 1600 ng.hr/mL, or about 8 ng.hr/mL to about 1400 ng.hr/mL, or about 8 ng.hr/mL to about 1200 ng.hr/mL, or about 8 ng.hr/mL to about 1100 ng.hr/mL, or about 8 ng.hr/mL to about 1000 ng.hr/mL, or about 8 ng.hr/mL to about 900 ng.hr/mL, or about 8 ng.hr/mL to about 800 ng.hr/mL, or about 8 ng.hr/mL to about 700 ng.hr/mL, or about 8 ng.hr/mL to about 600 ng.hr/mL, or about 8 ng.hr/mL to about 550 ng.hr/mL, or about 8 ng.hr/mL to about 500 ng.hr/mL, or about 8 ng.hr/mL to about 475 ng.hr/mL, or about 8 ng.hr/mL to about 450 ng.hr/mL, or about 8 ng.hr/mL to about 425 ng.hr/mL, or about 8 ng.hr/mL to about 400 ng.hr/mL, or about 8 ng.hr/mL to about 375 ng.hr/mL, or about 8 ng.hr/mL to about 350 ng.hr/mL.

[226] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 or 72 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to infinity ($AUC_{0-\infty}$) of about 12 ng.hr/mL to about 2800 ng.hr/mL. In other preferred embodiments, $AUC_{0-\infty}$ is about 12 ng.hr/mL to about 2500 ng.hr/mL, or about 12 ng.hr/mL to about 2200 ng.hr/mL, or about 12 ng.hr/mL to about 1800 ng.hr/mL, or about 12 ng.hr/mL to about 1700 ng.hr/mL, or about 12 ng.hr/mL to about 1600 ng.hr/mL, or about 12 ng.hr/mL to about 1400 ng.hr/mL, or about 12 ng.hr/mL to about 1200 ng.hr/mL, or about 12 ng.hr/mL to about 1100 ng.hr/mL, or about 12 ng.hr/mL to about 1000 ng.hr/mL, or about 12 ng.hr/mL to about 900 ng.hr/mL, or about 12 ng.hr/mL to about 800 ng.hr/mL, or about 12 ng.hr/mL to about 700 ng.hr/mL, or about 12 ng.hr/mL to about 600 ng.hr/mL, or about 12 ng.hr/mL to about 550 ng.hr/mL, or about 12 ng.hr/mL to about 500 ng.hr/mL, or about 12 ng.hr/mL to about 475 ng.hr/mL, or about 12 ng.hr/mL to about 450 ng.hr/mL, or about 12 ng.hr/mL to about 425 ng.hr/mL, or about 12 ng.hr/mL to about 400 ng.hr/mL, or about 12 ng.hr/mL to about 375 ng.hr/mL, or about 12 ng.hr/mL to about 350 ng.hr/mL.

[227] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 or 72 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to infinity ($AUC_{0-\infty}$) of about 15 ng.hr/mL to about 2800 ng.hr/mL. In other preferred embodiments, $AUC_{0-\infty}$ is about 15 ng.hr/mL to about 2500 ng.hr/mL, or about 15 ng.hr/mL to about 2200 ng.hr/mL, or about 15 ng.hr/mL to about 1800 ng.hr/mL, or about 15 ng.hr/mL to about

1700 ng.hr/mL, or about 15 ng.hr/mL to about 1600 ng.hr/mL, or about 15 ng.hr/mL to about 1400 ng.hr/mL, or about 15 ng.hr/mL to about 1200 ng.hr/mL, or about 15 ng.hr/mL to about 1100 ng.hr/mL, or about 15 ng.hr/mL to about 1000 ng.hr/mL, or about 15 ng.hr/mL to about 900 ng.hr/mL, or about 15 ng.hr/mL to about 800 ng.hr/mL, or about 15 ng.hr/mL to about 700 ng.hr/mL, or about 15 ng.hr/mL to about 600 ng.hr/mL, or about 15 ng.hr/mL to about 550 ng.hr/mL, or about 15 ng.hr/mL to about 500 ng.hr/mL, or about 15 ng.hr/mL to about 475 ng.hr/mL, or about 15 ng.hr/mL to about 450 ng.hr/mL, or about 15 ng.hr/mL to about 425 ng.hr/mL, or about 15 ng.hr/mL to about 400 ng.hr/mL, or about 15 ng.hr/mL to about 375 ng.hr/mL, or about 15 ng.hr/mL to about 350 ng.hr/mL.

[228] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 or 72 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to infinity ($AUC_{0-\infty}$) of about 25 ng.hr/mL to about 2800 ng.hr/mL. In other preferred embodiments, $AUC_{0-\infty}$ is about 25 ng.hr/mL to about 2500 ng.hr/mL, or about 25 ng.hr/mL to about 2200 ng.hr/mL, or about 25 ng.hr/mL to about 1800 ng.hr/mL, or about 25 ng.hr/mL to about 1700 ng.hr/mL, or about 25 ng.hr/mL to about 1600 ng.hr/mL, or about 25 ng.hr/mL to about 1400 ng.hr/mL, or about 25 ng.hr/mL to about 1200 ng.hr/mL, or about 25 ng.hr/mL to about 1100 ng.hr/mL, or about 25 ng.hr/mL to about 1000 ng.hr/mL, or about 25 ng.hr/mL to about 900 ng.hr/mL, or about 25 ng.hr/mL to about 800 ng.hr/mL, or about 25 ng.hr/mL to about 700 ng.hr/mL, or about 25 ng.hr/mL to about 600 ng.hr/mL, or about 25 ng.hr/mL to about 550 ng.hr/mL, or about 25 ng.hr/mL to about 500 ng.hr/mL, or about 25 ng.hr/mL to about 475 ng.hr/mL, or about 25 ng.hr/mL to about 450 ng.hr/mL, or about 25 ng.hr/mL to about 425 ng.hr/mL, or about 25 ng.hr/mL to about 400 ng.hr/mL, or about 25 ng.hr/mL to about 375 ng.hr/mL, or about 25 ng.hr/mL to about 350 ng.hr/mL.

[229] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 or 72 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to infinity ($AUC_{0-\infty}$) of about 30 ng.hr/mL to about 2800 ng.hr/mL. In other preferred embodiments, $AUC_{0-\infty}$ is about 30 ng.hr/mL to about 2500 ng.hr/mL, or about 30 ng.hr/mL to about 2200 ng.hr/mL, or about 30 ng.hr/mL to about 1800 ng.hr/mL, or about 30 ng.hr/mL to about 1700 ng.hr/mL, or about 30 ng.hr/mL to about 1600 ng.hr/mL, or about 30 ng.hr/mL to about 1400 ng.hr/mL, or about 30 ng.hr/mL to about 1200 ng.hr/mL, or about 30 ng.hr/mL to about 1100

ng.hr/mL, or about 30 ng.hr/mL to about 1000 ng.hr/mL, or about 30 ng.hr/mL to about 900 ng.hr/mL, or about 30 ng.hr/mL to about 800 ng.hr/mL, or about 30 ng.hr/mL to about 700 ng.hr/mL, or about 30 ng.hr/mL to about 600 ng.hr/mL, or about 30 ng.hr/mL to about 550 ng.hr/mL, or about 30 ng.hr/mL to about 500 ng.hr/mL, or about 30 ng.hr/mL to about 475 ng.hr/mL, or about 30 ng.hr/mL to about 450 ng.hr/mL, or about 30 ng.hr/mL to about 425 ng.hr/mL, or about 30 ng.hr/mL to about 400 ng.hr/mL, or about 30 ng.hr/mL to about 375 ng.hr/mL, or about 30 ng.hr/mL to about 350 ng.hr/mL.

[230] In some more preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 or 72 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to infinity ($AUC_{0-\infty}$) of about 15 ng.hr/mL to about 1000 ng.hr/mL, or about 20 ng.hr/mL to about 700 ng.hr/mL, or about 20 ng.hr/mL to about 600 ng.hr/mL.

[231] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration and sequential venous sampling to 48 or 72 hours provides a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to infinity ($AUC_{0-\infty}$) of not less than about 4 ng.hr/mL, or not less than about 6 ng.hr/mL, or not less than about 8 ng.hr/mL, or not less than about 10 ng.hr/mL, or not less than about 12 ng.hr/mL, or not less than about 15 ng.hr/mL, or not less than about 20 ng.hr/mL, or not less than about 30 ng.hr/mL.

[232] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after administration to steady state provides a mean plasma concentration (C_{mean}) of levorphanol over the dosing interval of about 0.2 ng/mL to about 105 ng/mL, or about 0.2 ng/mL to about 90 ng/mL, or about 0.2 ng/mL to about 70 ng/mL, or about 0.2 ng/mL to about 60 ng/mL, or about 0.2 ng/mL to about 50 ng/mL, or about 0.2 ng/mL to about 40 ng/mL, or about 0.2 ng/mL to about 35 ng/mL, or about 0.2 ng/mL to about 30 ng/mL, or about 0.2 ng/mL to about 27 ng/mL, or about 0.2 ng/mL to about 25 ng/mL, or about 0.2 ng/mL to about 22 ng/mL, or about 0.2 ng/mL to about 18 ng/mL, or about 0.2 ng/mL to about 16 ng/mL, or about 0.2 ng/mL to about 14 ng/mL.

[233] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first

administration or single administration provides a mean C_{12}/C_{\max} ratio of about 0.25 to about 1.0, or about 0.35 to about 1.0, or about 0.45 to about 1.0, or about 0.55 to about 1.0, or about 0.6 to about 1.0, or about 0.65 to about 1.0, or about 0.7 to about 1.0, or about 0.75 to about 1.0, or about 0.8 to about 1.0, or about 0.85 to about 1.0, or about 0.6 to about 0.95, or about 0.65 to about 0.95, or about 0.7 to about 0.95, or about 0.75 to about 0.95, or about 0.8 to about 0.95.

[234] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration provides a mean C_{24}/C_{\max} ratio of about 0.25 to about 1.0, or about 0.35 to about 1.0, or about 0.4 to about 1.0, or about 0.45 to about 1.0, or about 0.5 to about 1.0, or about 0.55 to about 1.0, or about 0.4 to about 0.8, or about 0.45 to about 0.8, or about 0.5 to about 0.8, or about 0.4 to about 0.75, or about 0.45 to about 0.75, or about 0.5 to about 0.75, or about 0.4 to about 0.7, or about 0.45 to about 0.7, or about 0.5 to about 0.7, or about 0.4 to about 0.65, or about 0.45 to about 0.65, or about 0.5 to about 0.65, or about 0.4 to about 0.6, or about 0.45 to about 0.6, or about 0.5 to about 0.6.

[235] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration provides a mean C_{\min}/C_{\max} ratio of about 0.25 to about 1.0, or about 0.35 to about 1.0, or about 0.4 to about 1.0, or about 0.45 to about 1.0, or about 0.5 to about 1.0, or about 0.55 to about 1.0, or about 0.4 to about 0.8, or about 0.45 to about 0.8, or about 0.5 to about 0.8, or about 0.4 to about 0.75, or about 0.45 to about 0.75, or about 0.5 to about 0.75, or about 0.4 to about 0.7, or about 0.45 to about 0.7, or about 0.5 to about 0.7, or about 0.4 to about 0.65, or about 0.45 to about 0.65, or about 0.5 to about 0.65, or about 0.4 to about 0.6, or about 0.45 to about 0.6, or about 0.5 to about 0.6.

[236] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition suitable for every 12 hours or twice-a-day administration comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration provides a mean W_{50} of about 3 to about 12 hours, or about 4 to about 12 hours, or about 5 to about 12 hours, or about 6 to about 12 hours, or about 3 to about 11 hours, or about 3 to about 10 hours, or about 3 to about 9 hours, or about 3 to about 8 hours, or about 4 to about 10 hours, or about 4 to about 9 hours, or about 4 to about 11 hours, or about 5 to about 10.5 hours, or about 6 to about 11 hours, or about 6 to about 10.5 hours, or about 6 to about 10 hours, or about 7 to about 11 hours, or about 7 to about 10 hours, or about 7 to about 9.5 hours, or about 7 to about 9 hours, or about 7.5 to about 11 hours, or about 7.5 to about 10 hours, or about 7.5 to about 9.5 hours, or about 7.5

to about 9 hours, or about 8 to about 9.5 hours, or about 8 to about 9 hours.

[237] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition suitable for every 24 hours or once-a-day administration comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration provides a mean W_{50} of about 5 to about 24 hours, or about 5 to about 23 hours, or about 5 to about 22 hours, or about 5 to about 21 hours, or about 7 to about 24 hours, or about 7 to about 23 hours, or about 7 to about 22 hours, or about 7 to about 21 hours, or about 9 to about 24 hours, or about 9 to about 23 hours, or about 9 to about 22 hours, or about 9 to about 21 hours, or about 10 to about 24 hours, or about 10 to about 23 hours, or about 10 to about 22 hours, or about 10 to about 21 hours, or about 12 to about 24 hours, or about 12 to about 23 hours, or about 12 to about 22 hours, or about 12 to about 21 hours, or about 14 to about 24 hours, or about 14 to about 23 hours, or about 14 to about 22 hours, or about 14 to about 21 hours, or about 14 to about 20 hours, or about 14 to about 19 hours, or about 14 to about 18 hours, or about 14 to about 17.5 hours, or about 15 to about 24 hours, or about 15 to about 23 hours, or about 15 to about 22 hours, or about 15 to about 21 hours, or about 15 to about 20 hours, or about 15 to about 19 hours, or about 15 to about 18 hours, or about 15 to about 17.5 hours.

[238] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration provides a mean absorption rate constant of about 0.1 to 0.75 hr^{-1} . In other preferred embodiments, the mean absorption rate constant is from about 0.125 to about 0.75 hr^{-1} , or from about 0.125 to about 0.75 hr^{-1} , or from about 0.15 to about 0.75 hr^{-1} , or from about 0.175 to about 0.75 hr^{-1} , or from about 0.2 to about 0.75 hr^{-1} , or from about 0.21 to about 0.75 hr^{-1} , or from about 0.22 to about 0.75 hr^{-1} , or from about 0.23 to 0.75 hr^{-1} , or from about 0.24 to 0.75 hr^{-1} , or from about 0.25 to 0.75 hr^{-1} , or from about 0.26 to about 0.75 hr^{-1} , or from about 0.28 to about 0.75 hr^{-1} , or from about 0.30 to about 0.75 hr^{-1} , or from about 0.33 to about 0.75 hr^{-1} , or from about 0.36 to about 0.75 hr^{-1} , or from about 0.4 to 0.75 hr^{-1} , or from about 0.42 to 0.75 hr^{-1} , or from about 0.44 to 0.75 hr^{-1} , or from about 0.46 to about 0.75 hr^{-1} , or from about 0.48 to about 0.75 hr^{-1} , or from about 0.5 to about 0.75 hr^{-1} , or from about 0.52 to about 0.75 hr^{-1} , or from about 0.125 to about 0.65 hr^{-1} , or from about 0.125 to about 0.65 hr^{-1} , or from about 0.15 to about 0.65 hr^{-1} , or from about 0.175 to about 0.65 hr^{-1} , or from about 0.2 to about 0.65 hr^{-1} , or from about 0.21 to about 0.65 hr^{-1} , or from about 0.22 to about 0.65 hr^{-1} , or from about 0.23 to 0.65 hr^{-1} , or from about 0.24 to 0.65 hr^{-1} , or from about 0.25 to 0.65 hr^{-1} , or from about 0.26 to about 0.65 hr^{-1} , or from about 0.28 to about 0.65 hr^{-1} , or from about 0.30 to about 0.65 hr^{-1} , or from about 0.33 to about 0.65 hr^{-1} , or from about 0.36 to about 0.65 hr^{-1} , or from about 0.4 to 0.65 hr^{-1} , or from about

0.42 to 0.65 hr⁻¹, or from about 0.44 to 0.65 hr⁻¹, or from about 0.46 to about 0.65 hr⁻¹, or from about 0.48 to about 0.65 hr⁻¹, or from about 0.5 to about 0.65 hr⁻¹, or from about 0.52 to about 0.65 hr⁻¹, or from about 0.125 to about 0.6 hr⁻¹, or from about 0.125 to about 0.6 hr⁻¹, or from about 0.15 to about 0.6 hr⁻¹, or from about 0.175 to about 0.6 hr⁻¹, or from about 0.2 to about 0.6 hr⁻¹, or from about 0.21 to about 0.6 hr⁻¹, or from about 0.22 to about 0.6 hr⁻¹, or from about 0.23 to about 0.6 hr⁻¹, or from about 0.24 to about 0.6 hr⁻¹, or from about 0.25 to about 0.6 hr⁻¹, or from about 0.26 to about 0.6 hr⁻¹, or from about 0.28 to about 0.6 hr⁻¹, or from about 0.30 to about 0.6 hr⁻¹, or from about 0.33 to about 0.6 hr⁻¹, or from about 0.36 to about 0.6 hr⁻¹, or from about 0.4 to 0.6 hr⁻¹, or from about 0.42 to 0.6 hr⁻¹, or from about 0.44 to 0.6 hr⁻¹, or from about 0.46 to about 0.6 hr⁻¹, or from about 0.48 to about 0.6 hr⁻¹, or from about 0.5 to about 0.6 hr⁻¹, or from about 0.125 to about 0.5 hr⁻¹, or from about 0.125 to about 0.5 hr⁻¹, or from about 0.15 to about 0.5 hr⁻¹, or from about 0.175 to about 0.5 hr⁻¹, or from about 0.2 to about 0.5 hr⁻¹, or from about 0.21 to about 0.5 hr⁻¹, or from about 0.22 to about 0.5 hr⁻¹, or from about 0.23 to about 0.5 hr⁻¹, or from about 0.24 to about 0.5 hr⁻¹, or from about 0.25 to about 0.5 hr⁻¹, or from about 0.26 to about 0.5 hr⁻¹, or from about 0.28 to about 0.5 hr⁻¹, or from about 0.30 to about 0.5 hr⁻¹, or from about 0.33 to about 0.5 hr⁻¹, or from about 0.36 to about 0.5 hr⁻¹, or from about 0.4 to 0.5 hr⁻¹, or from about 0.42 to 0.5 hr⁻¹, or from about 0.125 to about 0.4 hr⁻¹, or from about 0.125 to about 0.4 hr⁻¹, or from about 0.15 to about 0.4 hr⁻¹, or from about 0.175 to about 0.4 hr⁻¹, or from about 0.2 to about 0.4 hr⁻¹, or from about 0.21 to about 0.4 hr⁻¹, or from about 0.22 to about 0.4 hr⁻¹, or from about 0.23 to about 0.4 hr⁻¹, or from about 0.24 to about 0.4 hr⁻¹, or from about 0.25 to about 0.4 hr⁻¹, or from about 0.26 to about 0.4 hr⁻¹, or from about 0.28 to about 0.4 hr⁻¹, or from about 0.30 to about 0.4 hr⁻¹, or from about 0.125 to about 0.35 hr⁻¹, or from about 0.125 to about 0.35 hr⁻¹, or from about 0.15 to about 0.35 hr⁻¹, or from about 0.175 to about 0.35 hr⁻¹, or from about 0.2 to about 0.35 hr⁻¹, or from about 0.21 to about 0.35 hr⁻¹, or from about 0.22 to about 0.35 hr⁻¹, or from about 0.125 to about 0.3 hr⁻¹, or from about 0.125 to about 0.3 hr⁻¹, or from about 0.15 to about 0.3 hr⁻¹, or from about 0.175 to about 0.3 hr⁻¹, or from about 0.2 to about 0.3 hr⁻¹, or from about 0.21 to about 0.3 hr⁻¹, or from about 0.22 to about 0.3 hr⁻¹. In some more preferred embodiments, the mean absorption rate constant is from about 0.1 to about 0.4 hr⁻¹, or from about 0.15 to about 0.4 hr⁻¹, or from about 0.15 to about 0.35 hr⁻¹, or from about 0.2 to about 0.4 hr⁻¹, or from about 0.2 to about 0.35 hr⁻¹, or from about 0.25 to about 0.65 hr⁻¹, or from about 0.25 to about 0.6 hr⁻¹, or from about 0.3 to 0.6 hr⁻¹, or from about 0.35 to about 0.65 hr⁻¹, or from about 0.35 to 0.6 hr⁻¹, or from about 0.4 to about 0.6 hr⁻¹.

[239] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which when compared with oral immediate release levorphanol provides an immediate release to extended release mean absorption rate constant mean ratio of about 14:1 to about 1.25:1, or about 12:1 to about 1.25:1, or

about 10:1 to about 1.25:1, or about 9:1 to about 1.25:1, or about 8:1 to about 1.25:1, or about 7.5:1 to about 1.25:1, or about 7:1 to about 1.25:1, or about 6:1 to about 1.25:1, or about 5:1 to about 1.25:1, or about 4:1 to about 1.25:1, or about 14:1 to about 1.75:1, or about 12:1 to about 1.75:1, or about 10:1 to about 1.75:1, or about 9:1 to about 1.75:1, or about 8:1 to about 1.75:1, or about 7.5:1 to about 1.75:1, or about 7:1 to about 1.75:1, or about 6:1 to about 1.75:1, or about 5:1 to about 1.75:1, or about 4:1 to about 1.75:1, or about 14:1 to about 2:1, or about 12:1 to about 2:1, or about 10:1 to about 2:1, or about 9:1 to about 2:1, or about 8:1 to about 2:1, or about 7.5:1 to about 2:1, or about 7:1 to about 2:1, or about 6:1 to about 2:1, or about 5:1 to about 2:1, or about 4:1 to about 2:1, or about 14:1 to about 3:1, or about 12:1 to about 3:1, or about 10:1 to about 3:1, or about 9:1 to about 3:1, or about 8:1 to about 3:1, or about 7.5:1 to about 3:1, or about 7:1 to about 3:1, or about 6:1 to about 3:1, or about 5:1 to about 3:1, or about 4:1 to about 3:1, or about 14:1 to about 4:1, or about 12:1 to about 4:1, or about 10:1 to about 4:1, or about 9:1 to about 4:1, or about 8:1 to about 4:1, or about 7.5:1 to about 4:1, or about 7:1 to about 4:1, or about 6:1 to about 4:1, or about 5:1 to about 4:1, or about 4:1 to about 4:1.

[240] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration provides a lag time (T_{lag}) from about 0.1 hr to about 6 hours, or from about 0.25 hr to about 3 hours, or from about 0.25 hr to about 2.75 hours, or from about 0.25 hr to about 2.5 hours, or from about 0.25 hr to about 2.25 hours, or from about 0.25 hr to about 2.1 hours, or from about 0.25 hr to about 2 hours, or from about 0.25 hr to about 1.9 hours, or from about 0.25 hr to about 1.8 hours, or from about 0.25 hr to about 1.7 hours, or from about 0.5 hr to about 3 hours, or from about 0.5 hr to about 2.75 hours, or from about 0.5 hr to about 2.5 hours, or from about 0.5 hr to about 2.25 hours, or from about 0.5 hr to about 2.1 hours, or from about 0.5 hr to about 2 hours, or from about 0.5 hr to about 1.9 hours, or from about 0.5 hr to about 1.8 hours, or from about 0.5 hr to about 1.7 hours, or from about 0.75 hr to about 3 hours, or from about 0.75 hr to about 2.75 hours, or from about 0.75 hr to about 2.5 hours, or from about 0.75 hr to about 2.25 hours, or from about 0.75 hr to about 2.1 hours, or from about 0.75 hr to about 2 hours, or from about 0.75 hr to about 1.9 hours, or from about 0.75 hr to about 1.8 hours, or from about 0.75 hr to about 1.7 hours, or from about 0.25 hr to about 3 hours, or from about 0.25 hr to about 2.75 hours, or from about 0.25 hr to about 2.5 hours, or from about 0.25 hr to about 2.23 hours, or from about 0.25 hr to about 2.1 hours, or from about 0.25 hr to about 2 hours, or from about 0.25 hr to about 1.9 hours, or from about 0.25 hr to about 1.8 hours, or from about 0.25 hr to about 1.7 hours.

[241] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which when compared with

oral immediate release levorphanol provides an extended release to immediate release mean lag time (T_{lag}) ratio of about 10:1 to about 1:1, or about 8:1 to about 1:1, or about 7:1 to about 1:1, or about 6:1 to about 1:1, or about 5:1 to about 1:1, or about 4:1 to about 1:1, or about 3.5:1 to about 1:1, or about 3:1 to about 1:1, or about 2.5:1 to about 1:1, or about 2:1 to about 1:1, or about 10:1 to about 1.5:1, or about 8:1 to about 1.5:1, or about 7:1 to about 1.5:1, or about 6:1 to about 1.5:1, or about 5:1 to about 1.5:1, or about 4:1 to about 1.5:1, or about 3.5:1 to about 1.5:1, or about 3:1 to about 1.5:1, or about 2.5:1 to about 1.5:1, or about 2:1 to about 1.5:1, or about 10:1 to about 2:1, or about 8:1 to about 2:1, or about 7:1 to about 2:1, or about 6:1 to about 2:1, or about 5:1 to about 2:1, or about 4:1 to about 2:1, or about 3.5:1 to about 2:1, or about 3:1 to about 2:1, or about 2.5:1 to about 2:1.

[242] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single administration provides a mean absorption time (MAT) from about 1.5 hours to about 18 hours, or about 2 hours to about 14 hours, or about 2 hours to about 12 hours, or about 2 hours to about 10 hours, or about 2 hours to about 9 hours, or about 2 hours to about 8 hours, or about 2 hours to about 7.5 hours, or about 2 hours to about 7 hours, or about 2 hours to about 6.5 hours, or about 2 hours to about 6 hours, or about 2 hours to about 5.5 hours, or about 2 hours to about 5 hours, or about 2.5 hours to about 16 hours, or about 2 hours to about 14 hours, or about 2.5 hours to about 12 hours, or about 2 hours to about 10 hours, or about 2.5 hours to about 9 hours, or about 2 hours to about 8 hours, or about 2.5 hours to about 7.5 hours, or about 2 hours to about 7 hours, or about 2.5 hours to about 6.5 hours, or about 2 hours to about 6 hours, or about 2.5 hours to about 5.5 hours, or about 2 hours to about 5 hours, or about 3 hours to about 16 hours, or about 2 hours to about 14 hours, or about 3 hours to about 12 hours, or about 2 hours to about 10 hours, or about 3 hours to about 9 hours, or about 2 hours to about 8 hours, or about 3 hours to about 7.5 hours, or about 2 hours to about 7 hours, or about 3 hours to about 6.5 hours, or about 2 hours to about 6 hours, or about 3 hours to about 5.5 hours, or about 2 hours to about 5 hours, or about 3.5 hours to about 16 hours, or about 2 hours to about 14 hours, or about 3.5 hours to about 12 hours, or about 2 hours to about 10 hours, or about 3.5 hours to about 9 hours, or about 2 hours to about 8 hours, or about 3.5 hours to about 7.5 hours, or about 2 hours to about 7 hours, or about 3.5 hours to about 6.5 hours, or about 2 hours to about 6 hours, or about 3.5 hours to about 5.5 hours, or about 2 hours to about 5 hours, or about 4 hours to about 16 hours, or about 2 hours to about 14 hours, or about 4 hours to about 12 hours, or about 2 hours to about 10 hours, or about 4 hours to about 9 hours, or about 2 hours to about 8 hours, or about 4 hours to about 7.5 hours, or about 2 hours to about 7 hours, or about 4 hours to about 6.5 hours, or about 2 hours to about 6 hours, or about 4 hours to about 5.5 hours, or about 2 hours to about 5 hours. In some more

preferred embodiments, said MAT is from about 1.5 hours to about 8 hours, or about 1.5 to about 5 hours, or about 2 hours to about 5 hours, or about 2 hours to about 4.5 hours, or about 2.5 hours to about 4 hours, or about 3.5 hours to about 6.5 hours, or about 3.5 hours to about 6 hours, or about 4 to about 6.25 hours, or about 4.5 hours to about 5.75.

[243] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which when compared with oral immediate release levorphanol provides an extended release to immediate release a mean absorption time (MAT) ratio of about 14:1 to about 1:1, or about 10:1 to about 1:1, or about 8:1 to about 1:1, or about 7:1 to about 1:1, or about 6:1 to about 1:1, or about 5:1 to about 1:1, or about 4:1 to about 1:1, or about 3:1 to about 1:1, or about 6:1 to about 1.5:1, or about 6:1 to about 1.75:1, or about 6:1 to about 2:1, or about 5.5:1 to about 1.5:1, or about 5.5:1 to about 1.75:1, or about 5.5:1 to about 2:1, or about 5:1 to about 1.5:1, or about 5:1 to about 1.75:1, or about 5:1 to about 2:1, or about 4.5:1 to about 1.5:1, or about 4.5:1 to about 1.75:1, or about 4.5:1 to about 2:1.

[244] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single dose administration and sequential venous sampling to 48 hours provides a mean unextrapolated mean residence time (MRT_{last}) from about 8 hours to about 30 hours. In other preferred embodiments, the MRT_{last} is about 10 hours to about 30 hours, or about 11 hours to about 30 hours, or about 14 hours to about 30 hours, or about 14.5 hours to about 30 hours, or about 15 hours to about 30 hours, or about 15.5 hours to about 30 hours, or about 16 hours to about 30 hours, or about 16.5 hours to about 30 hours, or about 17 hours to about 30 hours, or about 17.5 hours to about 30 hours, or about 18 hours to about 30 hours, or about 18.5 hours to about 30 hours, or about 19 hours to about 30 hours, or about 20 hours to about 30 hours, or 10 hours to about 28 hours, or about 11 hours to about 12 hours, or about 13 hours to about 14 hours, or about 14.5 hours to about 28 hours, or about 15 hours to about 28 hours, or about 15.5 hours to about 28 hours, or about 16 hours to about 28 hours, or about 16.5 hours to about 28 hours, or about 17 hours to about 28 hours, or about 17.5 hours to about 28 hours, or about 18 hours to about 28 hours, or about 18.5 hours to about 28 hours, or about 19 hours to about 28 hours, or about 20 hours to about 28 hours, or 10 hours to about 28 hours, or about 11 hours to about 28 hours, or about 14 hours to about 28 hours, or about 14.5 hours to about 28 hours, or about 15 hours to about 28 hours, or about 15.5 hours to about 28 hours, or about 16 hours to about 28 hours, or about 16.5 hours to about 28 hours, or about 17 hours to about 28 hours, or about 17.5 hours to about 28 hours, or about 18 hours to about 28 hours, or about 18.5 hours to about 28 hours, or about 19 hours to about 28 hours, or about 20 hours to about 28 hours, or 10 hours to about 26 hours, or about 11 hours to about 26 hours, or about 14

hours to about 26 hours, or about 14.5 hours to about 26 hours, or about 15 hours to about 26 hours, or about 15.5 hours to about 26 hours, or about 16 hours to about 26 hours, or about 16.5 hours to about 26 hours, or about 17 hours to about 26 hours, or about 17.5 hours to about 26 hours, or about 18 hours to about 26 hours, or about 18.5 hours to about 26 hours, or about 19 hours to about 26 hours, or about 20 hours to about 26 hours, or 10 hours to about 24 hours, or about 11 hours to about 24 hours, or about 14 hours to about 24 hours, or about 14.5 hours to about 24 hours, or about 15 hours to about 24 hours, or about 15.5 hours to about 24 hours, or about 16 hours to about 24 hours, or about 16.5 hours to about 24 hours, or about 17 hours to about 24 hours, or about 17.5 hours to about 24 hours, or about 18 hours to about 24 hours, or about 18.5 hours to about 24 hours, or about 19 hours to about 24 hours, or about 20 hours to about 24 hours, or 10 hours to about 22 hours, or about 11 hours to about 22 hours, or about 14 hours to about 22 hours, or about 14.5 hours to about 22 hours, or about 15 hours to about 22 hours, or about 15.5 hours to about 22 hours, or about 16 hours to about 22 hours, or about 16.5 hours to about 22 hours, or about 17 hours to about 22 hours, or about 17.5 hours to about 22 hours, or about 18 hours to about 22 hours, or about 18.5 hours to about 22 hours, or about 19 hours to about 22 hours, or about 20 hours to about 22 hours. In other more preferred embodiments, the MRT_{last} is about 15 hours to about 25 hours, or about 16 to 24 hours, or about 16 hours to about 22 hours, or about 17 hours to about 22 hours, or about 18 hours to about 25 hours, or about 20 hours to about 24 hours, or about 17 hours to about 21 hours.

[245] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof, which after first administration or single dose administration and sequential venous sampling to 48 hours provides a mean observed mean residence time extrapolated to infinity ($MRT_{Infinity}$ Observed MRT_{INF_obs}) from about 12 hours to about 30 hours. In other preferred embodiments, the MRT_{INF_obs} is about 10 hours to about 30 hours, or about 11 hours to about 30 hours, or about 14 hours to about 30 hours, or about 14.5 hours to about 30 hours, or about 15 hours to about 30 hours, or about 15.5 hours to about 30 hours, or about 16 hours to about 30 hours, or about 16.5 hours to about 30 hours, or about 17 hours to about 30 hours, or about 17.5 hours to about 30 hours, or about 18 hours to about 30 hours, or about 18.5 hours to about 30 hours, or about 19 hours to about 30 hours, or about 20 hours to about 30 hours, or 10 hours to about 28 hours, or about 11 hours to about 12 hours, or about 13 hours to about 14 hours, or about 14.5 hours to about 28 hours, or about 15 hours to about 28 hours, or about 15.5 hours to about 28 hours, or about 16 hours to about 28 hours, or about 16.5 hours to about 28 hours, or about 17 hours to about 28 hours, or about 17.5 hours to about 28 hours, or about 18 hours to about 28 hours, or about 18.5 hours to about 28 hours, or about 19 hours to about 28 hours, or about 20 hours to about 28 hours, or 10 hours to about 28 hours, or about 11 hours to about 28 hours, or about 14 hours to about 28 hours, or about 14.5 hours to about 28 hours,

or about 15 hours to about 28 hours, or about 15.5 hours to about 28 hours, or about 16 hours to about 28 hours, or about 16.5 hours to about 28 hours, or about 17 hours to about 28 hours, or about 17.5 hours to about 28 hours, or about 18 hours to about 28 hours, or about 18.5 hours to about 28 hours, or about 19 hours to about 28 hours, or about 20 hours to about 28 hours, or 10 hours to about 26 hours, or about 11 hours to about 26 hours, or about 14 hours to about 26 hours, or about 14.5 hours to about 26 hours, or about 15 hours to about 26 hours, or about 15.5 hours to about 26 hours, or about 16 hours to about 26 hours, or about 16.5 hours to about 26 hours, or about 17 hours to about 26 hours, or about 17.5 hours to about 26 hours, or about 18 hours to about 26 hours, or about 18.5 hours to about 26 hours, or about 19 hours to about 26 hours, or about 20 hours to about 26 hours, or 10 hours to about 24 hours, or about 11 hours to about 24 hours, or about 14 hours to about 24 hours, or about 14.5 hours to about 24 hours, or about 15 hours to about 24 hours, or about 15.5 hours to about 24 hours, or about 16 hours to about 24 hours, or about 16.5 hours to about 24 hours, or about 17 hours to about 24 hours, or about 17.5 hours to about 24 hours, or about 18 hours to about 24 hours, or about 18.5 hours to about 24 hours, or about 19 hours to about 24 hours, or about 20 hours to about 24 hours, or 10 hours to about 22 hours, or about 11 hours to about 22 hours, or about 14 hours to about 22 hours, or about 14.5 hours to about 22 hours, or about 15 hours to about 22 hours, or about 15.5 hours to about 22 hours, or about 16 hours to about 22 hours, or about 16.5 hours to about 22 hours, or about 17 hours to about 22 hours, or about 17.5 hours to about 22 hours, or about 18 hours to about 22 hours, or about 18.5 hours to about 22 hours, or about 19 hours to about 22 hours, or about 20 hours to about 22 hours. In other more preferred embodiments, the MRTINF_obs is about 15 hours to about 25 hours, or about 16 to 24 hours, or about 16 hours to about 22 hours, or about 17 hours to about 22 hours, or about 18 hours to about 25 hours, or about 20 hours to about 24 hours, or about 17 hours to about 21 hours.

[246] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof which after first administration or single dose administration provides a mean minimum levorphanol plasma concentration (C_{min}) of about 0.01 ng/mL to about 120 ng/mL, or about 0.01 ng/mL to about 100 ng/mL, or about 0.01 ng/mL to about 90 ng/mL, or about 0.01 ng/mL to about 80 ng/mL, or about 0.01 ng/mL to about 75 ng/mL, or about 0.01 ng/mL to about 70 ng/mL, or about 0.01 ng/mL to about 65 ng/mL, or about 0.01 ng/mL to about 60 ng/mL, or about 0.01 ng/mL to about 55 ng/mL, or about 0.01 ng/mL to about 50 ng/mL, or about 0.01 ng/mL to about 45 ng/mL, or about 0.01 ng/mL to about 42 ng/mL, or about 0.01 ng/mL to about 40 ng/mL, or about 0.01 ng/mL to about 38 ng/mL, or about 0.01 ng/mL to about 35 ng/mL, or about 0.01 ng/mL to about 32 ng/mL, or about 0.01 ng/mL to about 30 ng/mL, or about 0.01 ng/mL to about 28 ng/mL, or about 0.01 ng/mL to about 25 ng/mL, or about 0.01 ng/mL to about 22 ng/mL, or about 0.01 ng/mL to about 20

0.7 ng/mL to about 65 ng/mL, or about 0.7 ng/mL to about 60 ng/mL, or about 0.7 ng/mL to about 55 ng/mL, or about 0.7 ng/mL to about 50 ng/mL, or about 0.7 ng/mL to about 45 ng/mL, or about 0.7 ng/mL to about 42 ng/mL, or about 0.7 ng/mL to about 40 ng/mL, or about 0.7 ng/mL to about 38 ng/mL, or about 0.7 ng/mL to about 35 ng/mL, or about 0.7 ng/mL to about 32 ng/mL, or about 0.7 ng/mL to about 30 ng/mL, or about 0.7 ng/mL to about 28 ng/mL, or about 0.7 ng/mL to about 25 ng/mL, or about 0.7 ng/mL to about 22 ng/mL, or about 0.7 ng/mL to about 20 ng/mL, or about 0.7 ng/mL to about 18 ng/mL, or about 0.7 ng/mL to about 16 ng/mL, or about 0.7 ng/mL to about 12 ng/mL, or about 0.7 ng/mL to about 11 ng/mL, or about 0.7 ng/mL to about 10 ng/mL. In some preferred embodiments, the foregoing composition is suitable for every 12 hour or twice-a-day administration, or intended for every 12 hour or twice-a-day administration and said C_{\min} is determined from about 10 hours to about 14 hours after administration of said composition. In other preferred embodiments, the foregoing composition is suitable for every 24 hour or once-a-day administration, or intended for every 24 hour or once-a-day administration and said C_{\min} is determined from about 22 hours to about 26 hours after administration of said composition.

[247] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition suitable for every 12 hour or twice-a-day administration, or intended for every 12 hour or twice-a-day administration comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof which after first administration or single dose administration provides a percent fluctuation of about 2% to about 300%, or about 2% to about 250%, or about 5% to about 220%, or about 2% to about 200%, or about 2% to about 180%, or about 2% to about 150%, or about 2% to about 120%, or about 2% to about 100%, or about 2% to about 80%, or about 2% to about 70%, or about 2% to about 60%, or about 2% to about 50%, or about 2% to about 40%, or about 2% to about 35%, or about 2% to about 30%, or about 2% to about 25%, or about 2% to about 20%, or about 5% to about 300%, or about 5% to about 250%, or about 5% to about 220%, or about 5% to about 200%, or about 5% to about 180%, or about 5% to about 150%, or about 5% to about 120%, or about 5% to about 100%, or about 5% to about 80%, or about 5% to about 70%, or about 5% to about 60%, or about 5% to about 50%, or about 5% to about 40%, or about 5% to about 35%, or about 5% to about 30%, or about 5% to about 25%, or about 5% to about 20%, or about 10% to about 300%, or about 10% to about 250%, or about 10% to about 220%, or about 10% to about 200%, or about 10% to about 180%, or about 10% to about 150%, or about 10% to about 120%, or about 10% to about 100%, or about 10% to about 80%, or about 10% to about 70%, or about 10% to about 60%, or about 10% to about 50%, or about 10% to about 40%, or about 10% to about 35%, or about 10% to about 30%, or about 10% to about 25%, or about 10% to about 20%, or about 12% to about 300%, or about 12% to about 250%, or about 12% to about 220%, or about 12% to about 200%, or about 12% to about 180%, or about 12% to about 150%, or about 12% to about 120%, or about 12% to about 100%, or

about 12% to about 80%, or about 12% to about 70%, or about 12% to about 60%, or about 12% to about 50%, or about 12% to about 40%, or about 12% to about 35%, or about 12% to about 30%, or about 12% to about 25%, or about 12% to about 20%. In some more preferred embodiments of the foregoing, said percent fluctuation is about 6% to about 24%, or about 7% to about 22%, or about 9% to about 20%, or about 11% to about 20%, or about 14% to about 19%, or about 14% to about 18%, or about 10% to about 16%, or about 15% to about 22%.

[248] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition suitable for every 24 hour or once-a-day administration, or intended for every 24 hour or once-a-day administration comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof which after first administration or single dose administration provides a percent fluctuation of about 2% to about 300%, or about 2% to about 250%, or about 5% to about 220%, or about 2% to about 200%, or about 2% to about 180%, or about 2% to about 150%, or about 2% to about 120%, or about 2% to about 100%, or about 2% to about 80%, or about 2% to about 70%, or about 2% to about 60%, or about 2% to about 50%, or about 2% to about 40%, or about 2% to about 35%, or about 2% to about 30%, or about 2% to about 25%, or about 2% to about 20%, or about 5% to about 300%, or about 15% to about 300%, or about 15% to about 250%, or about 15% to about 220%, or about 15% to about 200%, or about 15% to about 180%, or about 15% to about 150%, or about 15% to about 120%, or about 15% to about 100%, or about 15% to about 80%, or about 15% to about 70%, or about 15% to about 60%, or about 15% to about 50%, or about 15% to about 40%, or about 15% to about 35%, or about 15% to about 30%, or about 15% to about 25%, or about 30% to about 300%, or about 30% to about 250%, or about 30% to about 220%, or about 30% to about 200%, or about 30% to about 180%, or about 30% to about 150%, or about 30% to about 120%, or about 30% to about 100%, or about 30% to about 80%, or about 30% to about 70%, or about 30% to about 60%, or about 30% to about 50%. In some more preferred embodiments of the foregoing, said percent fluctuation is about 20% to about 120%, or about 20% to about 100%, or about 30% to about 120%, or about 30% to about 110%, or about 30% to about 90%, or about 40% to about 120%, or about 40% to about 100%, or about 50% to about 120%, or about 50% to about 110%, or about 50% to about 100%, or about 60% to about 120%, or about 60% to about 110%, or about 65% to about 100%, or about 65% to about 110%, or about 65% to about 100%, or about 70% to about 110%, or about 70% to about 100%, or about 70% to about 90%, or about 75% to about 100%, or about 75% to about 95%, or about 30% to about 60%, or about 40% to about 80%, or about 20% to about 60%.

[249] **Pharmacokinetics of Levorphanol-3-Glucuronide**

[250] Levorphanol-3-glucuronide ("L3G") is a major metabolite of levorphanol.

[251] It is an object of certain embodiments of the present invention to provide oral controlled

release levorphanol which provide a systemic exposure as assessed by the mean L3G area under the plasma concentration time curve (AUC_{0-inf}) of about 30 ng.hr/mL to about 4000 ng.hr/mL for every 1 mg of levorphanol base administered orally as the base, pharmaceutically acceptable salts thereof or mixtures thereof. In other embodiments of the invention, said AUC_{0-inf} is from about 30 ng.hr/mL to about 6000 ng.hr/mL, or about 30 ng.hr/mL to about 5500 ng.hr/mL, or about 30 ng.hr/mL to about 5000 ng.hr/mL, or about 30 ng.hr/mL to about 4500 ng.hr/mL, or about 30 ng.hr/mL to about 4000 ng.hr/mL, or about 30 ng.hr/mL to about 3500 ng.hr/mL, or about 30 ng.hr/mL to about 3000 ng.hr/mL, or about 30 ng.hr/mL to about 2500 ng.hr/mL, or about 30 ng.hr/mL to about 2000 ng.hr/mL, or about 30 ng.hr/mL to about 1500 ng.hr/mL, or about 30 ng.hr/mL to about 1250 ng.hr/mL, or about 30 ng.hr/mL to about 1000 ng.hr/mL, or about 30 ng.hr/mL to about 800 ng.hr/mL, or about 30 ng.hr/mL to about 600 ng.hr/mL, or about 30 ng.hr/mL to about 400 ng.hr/mL, or about 30 ng.hr/mL to about 200 ng.hr/mL, or about 60 ng.hr/mL to about 4000 ng.hr/mL, or about 60 ng.hr/mL to about 2000 ng.hr/mL, or about 60 ng.hr/mL to about 1000 ng.hr/mL, or about 100 ng.hr/mL to about 4000 ng.hr/mL, or about 100 ng.hr/mL to about 3000 ng.hr/mL, or about 100 ng.hr/mL to about 2000 ng.hr/mL, or about 100 ng.hr/mL to about 1000 ng.hr/mL, or about 100 ng.hr/mL to about 800 ng.hr/mL, or about 100 ng.hr/mL to about 600 ng.hr/mL, or about 100 ng.hr/mL to about 500 ng.hr/mL, or about 100 ng.hr/mL to about 350 ng.hr/mL, or about 200 ng.hr/mL to about 6000 ng.hr/mL, or about 200 ng.hr/mL to about 4000 ng.hr/mL, or about 200 ng.hr/mL to about 3000 ng.hr/mL, or about 200 ng.hr/mL to about 2000 ng.hr/mL, or about 200 ng.hr/mL to about 1000 ng.hr/mL, or about 200 ng.hr/mL to about 600 ng.hr/mL, or about 300 ng.hr/mL to about 6000 ng.hr/mL, or about 300 ng.hr/mL to about 4000 ng.hr/mL, or about 300 ng.hr/mL to about 2000 ng.hr/mL, or about 300 ng.hr/mL to about 1000 ng.hr/mL, or about 500 ng.hr/mL to about 6000 ng.hr/mL, or about 500 ng.hr/mL to about 4000 ng.hr/mL, or about 500 ng.hr/mL to about 2000 ng.hr/mL, or about 500 ng.hr/mL to about 1000 ng.hr/mL for every 1 mg of levorphanol base as a controlled release dosage form of the invention.

[252] It is an object of certain embodiments of the present invention to provide oral controlled release levorphanol which provide a systemic exposure as assessed by the mean L3G area under the plasma concentration time curve (AUC_{0-inf}) of up to about 4000 ng.hr/mL for every 1 mg of levorphanol base administered orally as the base, pharmaceutically acceptable salts thereof or mixtures thereof. In other embodiments of the invention, said AUC_{0-inf} is of up to about 6000 ng.hr/mL, or of up to about 5000 ng.hr/mL, or of up to about 3000 ng.hr/mL, or of up to about 2000 ng.hr/mL, or of up to about 1500 ng.hr/mL, or of up to about 1000 ng.hr/mL, or of up to about 800 ng.hr/mL, or of up to about 600 ng.hr/mL, or of up to about 400 ng.hr/mL, or of up to about 300 ng.hr/mL, or of up to about 200 ng.hr/mL, or of up to about 150 ng.hr/mL, or of up to about 100 ng.hr/mL, or of up to about 80 ng.hr/mL, or of up to about 60 ng.hr/mL for every 1 mg of levorphanol base as a controlled release dosage form of the invention.

[253] It is an object of certain embodiments of the present invention to provide a mean L3G to levorphanol AUC_{0-inf} ratio of about 1.5 to about 30 after administration of an oral controlled release dosage form of levorphanol as the base, pharmaceutically acceptable salts thereof or mixtures. In other embodiments of the invention, said AUC_{0-12} , AUC_{0-24} , or AUC_{0-inf} ratio is greater than about 3, or greater than about 4, or greater than about 5, or greater than about 6, or greater than about 8, or greater than about 10, or greater than about 11, or greater than about 12, or greater than about 14, or greater than about 15, or about 1.5 to about 25, or about 1.5 to about 22, or about 1.5 to about 20, or about 1.5 to about 18, or about 1.5 to about 16, or about 1.5 to about 15, or about 1.5 to about 14, or about 1.5 to about 12, or about 1.5 to about 11, or about 1.5 to about 10, or about 1.5 to about 8, or about 1.5 to about 7, or about 1.5 to about 6.5, or about 1.5 to about 5, or about 1.5 to about 4, or about 1.5 to about 3, or about 1.5 to about 2.5, or about 1.5 to about 2, or about 2.5 to about 30, or about 2.5 to about 25, or about 2.5 to about 20, or about 2.5 to about 15, or about 2.5 to about 12, or about 2.5 to about 11, or about 2.5 to about 10, or about 2.5 to about 8, or about 2.5 to about 7, or about 2.5 to about 6, or about 2.5 to about 5, or about 2.5 to about 4, or about 4 to about 30, or about 4 to about 25, or about 4 to about 20, or about 4 to about 15, or about 4 to about 12, or about 4 to about 11, or about 4 to about 10, or about 4 to about 8, or about 4 to about 7, or about 4 to about 6, or about 6 to about 30, or about 6 to about 25, or about 6 to about 20, or about 6 to about 15, or about 6 to about 12, or about 6 to about 11, or about 6 to about 10, or about 6 to about 8, or about 8 to about 30, or about 8 to about 25, or about 8 to about 20, or about 8 to about 15, or about 8 to about 14, or about 8 to about 12, or about 8 to about 11, or about 8 to about 10, or about 10 to about 30, or about 10 to about 25, or about 10 to about 20, or about 10 to about 18, or about 10 to about 15, or about 10 to about 14, or about 10 to about 12, or about 11 to about 30, or about 11 to about 25, or about 11 to 11, or about 11 to about 20, or about 11 to about 18, or about 11 to about 15, or about 11 to about 14, or about 12 to about 30, or about 12 to about 25, or about 12 to 12, or about 12 to about 20, or about 12 to about 18, or about 12 to about 15, or about 12 to about 14, or about 14 to about 30, or about 14 to about 25, or about 14 to 14, or about 14 to about 20, or about 14 to about 18, or about 3.5 to about 25, or about 3.5 to about 20, or about 4 to 20, or about 4 to about 15, or about 4 to about 8, or about 5 to about 20, or about 5 to about 18, or about 5 to about 15, or about 5 to 12, or about 5 to about 9, or about 6 to about 26, or about 6 to about 23, or about 6 to about 18, or about 6 to about 14, or about 6 to 12, or about 6 to about 10, or about 8 to about 30, or about 8 to about 24, or about 10 to about 30, or about 10 to about 25, or about 10 to about 20, or about 10 to about 15, or about 10 to about 14, or about 11 to about 30, or about 11 to about 25, or about 11 to about 20, or about 11 to about 18, or about 12 to about 30, or about 12 to about 25, or about 12 to about 21, or about 12 to about 18, or about 14 to about 30, or about 14 to about 25, or about 14 to about 21, or about 14 to about 19, or less than about 25, or less than about 20, or less than about 18, or less than about 15, or less than about 12, or less than about 11, or less than about

10, or less than about 9, or less than about 7, or less than about 6, or less than about 5, or less than about 4.5, or less than about 4, or less than about 3, or less than about 2.

[254] It is an object of certain embodiments of the present invention to provide a mean L3G to levorphanol C_{max} ratio of about 1.5 to about 30 after administration of an oral controlled release dosage form of levorphanol as the base, pharmaceutically acceptable salts thereof or mixtures. In other embodiments of the invention, said C_{max} ratio is greater than about 3, or greater than about 4, or greater than about 5, or greater than about 6, or greater than about 8, or greater than about 10, or greater than about 11, or greater than about 12, or greater than about 14, or greater than about 15, or about 1.5 to about 25, or about 1.5 to about 22, or about 1.5 to about 20, or about 1.5 to about 18, or about 1.5 to about 16, or about 1.5 to about 15, or about 1.5 to about 14, or about 1.5 to about 12, or about 1.5 to about 11, or about 1.5 to about 10, or about 1.5 to about 8, or about 1.5 to about 7, or about 1.5 to about 6.5, or about 1.5 to about 5, or about 1.5 to about 4, or about 1.5 to about 3, or about 1.5 to about 2.5, or about 1.5 to about 2, or about 2.5 to about 30, or about 2.5 to about 25, or about 2.5 to about 20, or about 2.5 to about 15, or about 2.5 to about 12, or about 2.5 to about 11, or about 2.5 to about 10, or about 2.5 to about 8, or about 2.5 to about 7, or about 2.5 to about 6, or about 2.5 to about 5, or about 2.5 to about 4, or about 4 to about 30, or about 4 to about 25, or about 4 to about 20, or about 4 to about 15, or about 4 to about 12, or about 4 to about 11, or about 4 to about 10, or about 4 to about 8, or about 4 to about 7, or about 4 to about 6, or about 6 to about 30, or about 6 to about 25, or about 6 to about 20, or about 6 to about 15, or about 6 to about 12, or about 6 to about 11, or about 6 to about 10, or about 6 to about 8, or about 8 to about 30, or about 8 to about 25, or about 8 to about 20, or about 8 to about 15, or about 8 to about 14, or about 8 to about 12, or about 8 to about 11, or about 8 to about 10, or about 10 to about 30, or about 10 to about 25, or about 10 to about 20, or about 10 to about 18, or about 10 to about 15, or about 10 to about 14, or about 10 to about 12, or about 11 to about 30, or about 11 to about 25, or about 11 to about 11, or about 11 to about 20, or about 11 to about 18, or about 11 to about 15, or about 11 to about 14, or about 12 to about 30, or about 12 to about 25, or about 12 to about 12, or about 12 to about 20, or about 12 to about 18, or about 12 to about 15, or about 12 to about 14, or about 14 to about 30, or about 14 to about 25, or about 14 to about 14, or about 14 to about 20, or about 14 to about 18, or about 3.5 to about 25, or about 3.5 to about 20, or about 4 to about 20, or about 4 to about 15, or about 4 to about 8, or about 5 to about 20, or about 5 to about 18, or about 5 to about 15, or about 5 to about 12, or about 5 to about 9, or about 6 to about 26, or about 6 to about 23, or about 6 to about 18, or about 6 to about 14, or about 6 to about 12, or about 6 to about 10, or about 8 to about 30, or about 8 to about 24, or about 10 to about 30, or about 10 to about 25, or about 10 to about 20, or about 10 to about 15, or about 10 to about 14, or about 11 to about 30, or about 11 to about 25, or about 11 to about 20, or about 11 to about 18, or about 12 to about 30, or about 12 to about 25, or about 12 to about 21, or about 12 to about 18, or about 14 to about 30, or about 14 to about 25, or about 14 to about 21, or

about 14 to about 19, or less than about 25, or less than about 20, or less than about 18, or less than about 15, or less than about 12, or less than about 11, or less than about 10, or less than about 9, or less than about 7, or less than about 6, or less than about 5, or less than about 4.5, or less than about 4, or less than about 3, or less than about 2.

[255] It is an object of certain embodiments of the present invention to provide a mean L3G to levorphanol C_{12} ratio of about 1.5 to about 30 after administration of an oral controlled release dosage form of levorphanol as the base, pharmaceutically acceptable salts thereof or mixtures. In other embodiments of the invention, said C_{12} ratio is greater than about 3, or greater than about 4, or greater than about 5, or greater than about 6, or greater than about 8, or greater than about 10, or greater than about 11, or greater than about 12, or greater than about 14, or greater than about 15, or about 1.5 to about 25, or about 1.5 to about 22, or about 1.5 to about 20, or about 1.5 to about 18, or about 1.5 to about 16, or about 1.5 to about 15, or about 1.5 to about 14, or about 1.5 to about 12, or about 1.5 to about 11, or about 1.5 to about 10, or about 1.5 to about 8, or about 1.5 to about 7, or about 1.5 to about 6.5, or about 1.5 to about 5, or about 1.5 to about 4, or about 1.5 to about 3, or about 1.5 to about 2.5, or about 1.5 to about 2, or about 2.5 to about 30, or about 2.5 to about 25, or about 2.5 to about 20, or about 2.5 to about 15, or about 2.5 to about 12, or about 2.5 to about 11, or about 2.5 to about 10, or about 2.5 to about 8, or about 2.5 to about 7, or about 2.5 to about 6, or about 2.5 to about 5, or about 2.5 to about 4, or about 4 to about 30, or about 4 to about 25, or about 4 to about 20, or about 4 to about 15, or about 4 to about 12, or about 4 to about 11, or about 4 to about 10, or about 4 to about 8, or about 4 to about 7, or about 4 to about 6, or about 6 to about 30, or about 6 to about 25, or about 6 to about 20, or about 6 to about 15, or about 6 to about 12, or about 6 to about 11, or about 6 to about 10, or about 6 to about 8, or about 8 to about 30, or about 8 to about 25, or about 8 to about 20, or about 8 to about 15, or about 8 to about 14, or about 8 to about 12, or about 8 to about 11, or about 8 to about 10, or about 10 to about 30, or about 10 to about 25, or about 10 to about 20, or about 10 to about 18, or about 10 to about 15, or about 10 to about 14, or about 10 to about 12, or about 11 to about 30, or about 11 to about 25, or about 11 to about 11, or about 11 to about 20, or about 11 to about 18, or about 11 to about 15, or about 11 to about 14, or about 12 to about 30, or about 12 to about 25, or about 12 to about 12, or about 12 to about 20, or about 12 to about 18, or about 12 to about 15, or about 12 to about 14, or about 14 to about 30, or about 14 to about 25, or about 14 to about 14, or about 14 to about 20, or about 14 to about 18, or about 3.5 to about 25, or about 3.5 to about 20, or about 4 to about 20, or about 4 to about 15, or about 4 to about 8, or about 5 to about 20, or about 5 to about 18, or about 5 to about 15, or about 5 to about 12, or about 5 to about 9, or about 6 to about 26, or about 6 to about 23, or about 6 to about 18, or about 6 to about 14, or about 6 to about 12, or about 6 to about 10, or about 8 to about 30, or about 8 to about 24, or about 10 to about 30, or about 10 to about 25, or about 10 to about 20, or about 10 to about 15, or about 10 to about 14, or about 11 to about 30, or about 11 to about 25, or about 11 to about 20, or

about 11 to about 18, or about 12 to about 30, or about 12 to about 25, or about 12 to about 21, or about 12 to about 18, or about 14 to about 30, or about 14 to about 25, or about 14 to about 21, or about 14 to about 19, or less than about 25, or less than about 20, or less than about 18, or less than about 15, or less than about 12, or less than about 11, or less than about 10, or less than about 9, or less than about 7, or less than about 6, or less than about 5, or less than about 4.5, or less than about 4, or less than about 3, or less than about 2.

[256] It is an object of certain embodiments of the present invention to provide a mean L3G to levorphanol C_{24} ratio of about 1.5 to about 30 after administration of an oral controlled release dosage form of levorphanol as the base, pharmaceutically acceptable salts thereof or mixtures. In other embodiments of the invention, said C_{24} ratio is greater than about 3, or greater than about 4, or greater than about 5, or greater than about 6, or greater than about 8, or greater than about 10, or greater than about 11, or greater than about 12, or greater than about 14, or greater than about 15, or about 1.5 to about 25, or about 1.5 to about 22, or about 1.5 to about 20, or about 1.5 to about 18, or about 1.5 to about 16, or about 1.5 to about 15, or about 1.5 to about 14, or about 1.5 to about 12, or about 1.5 to about 11, or about 1.5 to about 10, or about 1.5 to about 8, or about 1.5 to about 7, or about 1.5 to about 6.5, or about 1.5 to about 5, or about 1.5 to about 4, or about 1.5 to about 3, or about 1.5 to about 2.5, or about 1.5 to about 2, or about 2.5 to about 30, or about 2.5 to about 25, or about 2.5 to about 20, or about 2.5 to about 15, or about 2.5 to about 12, or about 2.5 to about 11, or about 2.5 to about 10, or about 2.5 to about 8, or about 2.5 to about 7, or about 2.5 to about 6, or about 2.5 to about 5, or about 2.5 to about 4, or about 4 to about 30, or about 4 to about 25, or about 4 to about 20, or about 4 to about 15, or about 4 to about 12, or about 4 to about 11, or about 4 to about 10, or about 4 to about 8, or about 4 to about 7, or about 4 to about 6, or about 6 to about 30, or about 6 to about 25, or about 6 to about 20, or about 6 to about 15, or about 6 to about 12, or about 6 to about 11, or about 6 to about 10, or about 6 to about 8, or about 8 to about 30, or about 8 to about 25, or about 8 to about 20, or about 8 to about 15, or about 8 to about 14, or about 8 to about 12, or about 8 to about 11, or about 8 to about 10, or about 10 to about 30, or about 10 to about 25, or about 10 to about 20, or about 10 to about 18, or about 10 to about 15, or about 10 to about 14, or about 10 to about 12, or about 11 to about 30, or about 11 to about 25, or about 11 to about 11, or about 11 to about 20, or about 11 to about 18, or about 11 to about 15, or about 11 to about 14, or about 12 to about 30, or about 12 to about 25, or about 12 to about 12, or about 12 to about 20, or about 12 to about 18, or about 12 to about 15, or about 12 to about 14, or about 14 to about 30, or about 14 to about 25, or about 14 to about 14, or about 14 to about 20, or about 14 to about 18, or about 3.5 to about 25, or about 3.5 to about 20, or about 4 to about 20, or about 4 to about 15, or about 4 to about 8, or about 5 to about 20, or about 5 to about 18, or about 5 to about 15, or about 5 to about 12, or about 5 to about 9, or about 6 to about 26, or about 6 to about 23, or about 6 to about 18, or about 6 to about 14, or about 6 to about 12, or about 6 to about 10, or about 8 to about 30, or about 8 to about 24,

or about 10 to about 30, or about 10 to about 25, or about 10 to about 20, or about 10 to about 15, or about 10 to about 14, or about 11 to about 30, or about 11 to about 25, or about 11 to about 20, or about 11 to about 18, or about 12 to about 30, or about 12 to about 25, or about 12 to about 21, or about 12 to about 18, or about 14 to about 30, or about 14 to about 25, or about 14 to about 21, or about 14 to about 19, or less than about 25, or less than about 20, or less than about 18, or less than about 15, or less than about 12, or less than about 11, or less than about 10, or less than about 9, or less than about 7, or less than about 6, or less than about 5, or less than about 4.5, or less than about 4, or less than about 3, or less than about 2.

[257] It is an object of certain embodiments of the present invention to provide oral controlled release levorphanol formulations which provide a mean maximum plasma concentration (C_{\max}) of L3G from about 4.5 ng/mL to about 440 ng/mL for every 1 mg of levorphanol base administered orally as the base, pharmaceutically acceptable salts thereof or mixtures thereof. In other embodiments of the invention, said C_{\max} is from about 4.5 ng/mL to about 420 ng/mL, or from about 4.5 ng/mL to about 400 ng/mL, or from about 4.5 ng/mL to about 380 ng/mL, or from about 4.5 ng/mL to about 330 ng/mL, or from about 4.5 ng/mL to about 300 ng/mL, or from about 4.5 ng/mL to about 250 ng/mL, or from about 4.5 ng/mL to about 220 ng/mL, or from about 4.5 ng/mL to about 180 ng/mL, or from about 4.5 ng/mL to about 150 ng/mL, or from about 4.5 ng/mL to about 120 ng/mL, or from about 4.5 ng/mL to about 100 ng/mL, or from about 4.5 ng/mL to about 80 ng/mL, or from about 4.5 ng/mL to about 60 ng/mL, or from about 4.5 ng/mL to about 50 ng/mL, or from about 4.5 ng/mL to about 40 ng/mL, or from about 4.5 ng/mL to about 30 ng/mL, or from about 4.5 ng/mL to about 20 ng/mL, or from about 4.5 ng/mL to about 10 ng/mL, or from about 6 ng/mL to about 440 ng/mL, or from about 10 ng/mL to about 440 ng/mL, or from about 20 ng/mL to about 440 ng/mL, or from about 40 ng/mL to about 440 ng/mL, or from about 60 ng/mL to about 440 ng/mL, or from about 80 ng/mL to about 440 ng/mL, or from about 100 ng/mL to about 440 ng/mL, or from about 120 ng/mL to about 440 ng/mL, or from about 150 ng/mL to about 440 ng/mL, or from about 180 ng/mL to about 440 ng/mL, or from about 220 ng/mL to about 440 ng/mL, or from about 280 ng/mL to about 440 ng/mL, or from about 15 ng/mL to about 400 ng/mL, or from about 15 ng/mL to about 300 ng/mL, or from about 15 ng/mL to about 200 ng/mL, or from about 15 ng/mL to about 150 ng/mL, or from about 15 ng/mL to about 100 ng/mL, or from about 15 ng/mL to about 80 ng/mL, or from about 15 ng/mL to about 60 ng/mL, or from about 20 ng/mL to about 440 ng/mL, or from about 20 ng/mL to about 350 ng/mL, or from about 20 ng/mL to about 300 ng/mL, or from about 20 ng/mL to about 250 ng/mL, or from about 20 ng/mL to about 200 ng/mL, or from about 20 ng/mL to about 150 ng/mL, or from about 20 ng/mL to about 100 ng/mL, or from about 30 ng/mL to about 440 ng/mL, or from about 30 ng/mL to about 300 ng/mL, or from about 30 ng/mL to about 200 ng/mL, or from about 30 ng/mL to about 100 ng/mL, or from about 40 ng/mL to about 440 ng/mL, or from about 40 ng/mL to about 300 ng/mL, or from about 40 ng/mL

to about 200 ng/mL, or from about 40 ng/mL to about 150 ng/mL, or from about 60 ng/mL to about 440 ng/mL, or from about 60 ng/mL to about 400 ng/mL, or from about 60 ng/mL to about 300 ng/mL, or from about 60 ng/mL to about 200 ng/mL, or from about 80 ng/mL to about 400 ng/mL, or from about 80 ng/mL to about 300 ng/mL, or from about 80 ng/mL to about 200 ng/mL, or from about 100 ng/mL to about 440 ng/mL, or from about 100 ng/mL to about 400 ng/mL, or from about 100 ng/mL to about 300 ng/mL, or from about 100 ng/mL to about 200 ng/mL, or from about 25 ng/mL to about 250 ng/mL, or from about 50 ng/mL to about 350 ng/mL, or from about 75 ng/mL to about 375 ng/mL, or from about 3 ng/mL to about 600 ng/mL.

[258] It is an object of certain embodiments of the present invention to provide oral controlled release levorphanol formulations which provide a mean maximum plasma concentration (C_{max}) of L3G of up to about 440 ng/mL for every 1 mg of levorphanol base administered orally as the base, pharmaceutically acceptable salts thereof or mixtures thereof. In other embodiments of the invention, said C_{max} up to about 400 ng/mL, or up to about 350 ng/mL, or up to about 300 ng/mL, or up to about 250 ng/mL, or up to about 200 ng/mL, or up to about 150 ng/mL, or up to about 120 ng/mL, or up to about 100 ng/mL, or up to about 80 ng/mL, or up to about 50 ng/mL, or up to about 500 ng/mL, or up to about 600 ng/mL, or up to about 700 ng/mL.

[259] In some preferred embodiments, the oral levorphanol dosage form has a levorphanol T_{max} that exceeds its dosing frequency.

[260] **Comparison of Extended Release and Immediate Release Levorphanol**

[261] Commercially available levorphanol tartrate tablets must be stored between 20 °C to 25 °C. In some embodiments, the extended release dosage form of the invention may be stored from about 5 °C to about 40 °C, or from about 5 °C to 35 °C, or from about 5 °C to about 30 °C, or from about 5 °C to 25 °C, or stored from about 5 °C to about 20 °C, or from about 10 °C to 45 °C, or from about 10 °C to about 35 °C, or from about 10 °C to 30 °C, or from about 10 °C to about 25 °C, or from about 15 °C to 40 °C, or stored from about 15 °C to about 35 °C, or from about 15 °C to 30 °C, or from about 15 °C to about 25 °C.

[262] In some preferred embodiments, the levorphanol T_{max} ratio of the oral levorphanol dosage form of the invention to oral immediate release levorphanol is ≥ 1.25 , or ≥ 1.5 , or ≥ 1.75 , or ≥ 2 , or ≥ 2.5 , or ≥ 3 , or ≥ 3.5 , or ≥ 4 , or ≥ 4.5 , or ≥ 5 , or ≥ 5.5 , or ≥ 6 , or ≥ 6.5 , or ≥ 7 , or ≥ 7.5 , or ≥ 8 , or ≥ 8.5 , or ≥ 9 , or ≥ 9.5 , or ≥ 10 , or ≥ 10.5 , or ≥ 12 , or ≥ 14 , or ≥ 16 , or ≥ 18 , or ≥ 20 .

[263] In some preferred embodiments, the levorphanol C_{max} ratio after oral immediate release levorphanol, to the oral levorphanol dosage form of the invention given orally is ≥ 1.1 , or ≥ 1.2 , or ≥ 1.3 , or ≥ 1.5 , or ≥ 1.5 , or ≥ 1.6 , or ≥ 1.7 , or ≥ 1.8 , or ≥ 1.9 , or ≥ 2 , or ≥ 2.2 , or ≥ 2.5 , or ≥ 3 , or ≥ 3.5 , or ≥ 4 , or ≥ 4.5 , or ≥ 5 , or ≥ 5.5 , or ≥ 6 , or ≥ 6.5 , or ≥ 7 , or ≥ 7.5 , or ≥ 8 , or ≥ 8.5 , or ≥ 9 , or ≥ 9.5 , or ≥ 10 , or ≥ 10.5 , or ≥ 12 , or ≥ 14 , or ≥ 16 , or ≥ 18 , or ≥ 20 .

[264] In some preferred embodiments, the extended release dosage form of the invention provides

oral bioavailability which is substantially similar to oral immediate-release levorphanol.

- [265] In some preferred embodiments, the extended release dosage form of the invention is bioequivalent with respect to extent of absorption, when compared with to oral immediate-release levorphanol (i.e., the 90% confidence interval of AUC_{0-Tau} at steady state or the AUC_{0-inf} after first administration are within the 80.00 to 125.00%).
- [266] In some preferred embodiments, the extended release dosage form of the invention provides a mean extent of absorption which is not less than the mean extent of absorption after oral immediate-release levorphanol, when measured using AUC_{0-Tau} at steady state or the AUC_{0-inf} after first administration.
- [267] In some preferred embodiments, the extended release dosage form of the invention provides a mean extent of absorption which is within 3%, 5%, 7%, 10%, 12%, 15%, 18% or 21% of the mean extent of absorption after oral immediate-release levorphanol, when measured using AUC_{0-Tau} at steady state or the AUC_{0-inf} after first administration.
- [268] Unless specifically modified (e.g., “bioequivalent with respect to extent of absorption”), as used herein, “bioequivalent” and “bioequivalence” means that the 90% Confidence Interval (CI) of the relative mean C_{max} , $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of the drug under test and reference conditions (e.g., generic vs. brand name, or fed versus fasted, or with and without concurrent alcohol) is within 80% to 125%, when tested in accordance with U.S. FDA guidelines (see “Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations”, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, July 2002 and “Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis and Labeling”, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, October, 2001, which are hereby incorporated by reference).
- [269] In some preferred embodiments, the extended release dosage form of the invention provides a mean accumulation index which is within 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40% or 50% of the mean accumulation index after oral immediate-release levorphanol, when measured using AUC_{0-Tau} at steady state or the AUC_{0-inf} after first administration.
- [270] In some preferred embodiments, the extended release dosage form of the invention suitable for up to once-a-day provides about the same or lower accumulation index as oral immediate-release levorphanol.
- [271] In some preferred embodiments, the extended release dosage form of the invention provides a mean accumulation index which is within 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40% or 50% of the mean accumulation index after oral immediate-release levorphanol, given every 4, 6 or 8 hours.
- [272] In some preferred embodiments, the extended release dosage form of the invention provides a mean accumulation index which is at least 20%, 30%, 40%, 50% or 60% less than the mean

accumulation index after oral immediate-release levorphanol, given every 4, 6 or 8 hours.

- [273] When the commercially available oral immediate release are 2 mg tablets are subjected dissolution, the in-vitro release rate by weight of levorphanol by the USP Paddle Method at 50 rpm is more than 85% at about 10 minutes and more than 95% at about 20 minutes. Despite the rapid release of substantially all or all of the levorphanol from commercially available immediate-release tablet dosage form when tested in vitro using accepted dissolution methods, levorphanol provides a suboptimal biological (or in vivo) response by the oral route.
- [274] Without being bound by theory, the applicant asserts that the particle size of the levorphanol API in the only commercially available immediate release oral levorphanol tablets may adversely impact the in vivo efficiency and efficacy of the dosage form, which despite a rapid in vitro dissolution rate is responsible for one or more of the following: (i) lack of commercial success despite an attractive pharmacologic profile is due to in part to its failure of commercially available levorphanol tartrate tablets to provide an optimal or robust therapeutic effect; (ii) slow onset of pain relief; (iii) suboptimal maximal relief from pain; (iv) suboptimal total relief from pain; (v) early and greater need for supplemental (or rescue) analgesic when testing analgesic efficacy (e.g., after third molar extraction or after bunionectomy surgery); (vi) one or more excipients in the presently available dosage form, chosen from the group comprising lactose, corn starch, stearic acid, magnesium stearate and talc, adversely impact the in vivo efficiency and efficacy of the dosage form; and (vii) a very high variability in the absorption rate constant.
- [275] In addition, it has now been surprisingly discovered that the commercially available oral immediate-release levorphanol tartrate tablet (i) has a very small gastrointestinal absorption rate constant when evaluated using a two compartment pharmacokinetic model; (ii) the mean absorption time (MAT) is incompatible with robust analgesic efficacy at recommended doses; and (iii) fraction of dose absorbed immediately after administration (e.g. 0.5, 0.75, 1, 1.25 and 1.5 hours) is substantially less than for commercially available oral immediate-release morphine, commercially available oral immediate-release hydromorphone, commercially available oral immediate-release oxymorphone and commercially available oral immediate-release oxycodone. Without being bound by theory, the applicant asserts that the foregoing is due at least in part to the particle size of the levorphanol API in the only commercially available immediate release oral levorphanol tablets.
- [276] In some preferred embodiments, the pharmaceutical composition of the invention comprises levorphanol with particles smaller than 50,000 nm, or 45,000 nm, or 42, 000 nm, or 40,000 nm, or 38,000 nm, or 35, 000 nm, or 32,000 nm, or 30,000 nm, or 28,000 nm.
- [277] In some preferred embodiments, the pharmaceutical composition of the invention comprises levorphanol with particles smaller than 26,000 nm, or 24, 000 nm, or 20,000 nm, or 18,000 nm, or 16, 000 nm, or 14,000 nm, or 12,000 nm, or 10,000 nm.

- [278] In some preferred embodiments, the pharmaceutical composition of the invention comprises levorphanol with particles smaller than 9,000 nm, or 8,000 nm, or 7,000 nm, or 6,000 nm, or 5,000 nm, or 4,000 nm, or 3,000 nm.
- [279] In some preferred embodiments, the pharmaceutical composition of the invention comprises levorphanol with particles smaller than 2,000 nm, or 1,800 nm, or 1,600 nm, or 1,200 nm, or 1,000 nm, or 800 nm, or 600 nm, or 500 nm.
- [280] In some preferred embodiments, the pharmaceutical composition of the invention comprises levorphanol with a substantial percentage of particles smaller than 35,000 nm, or 32,000 nm, or 30,000 nm, or 28,000 nm.
- [281] In some preferred embodiments, the pharmaceutical composition of the invention comprises levorphanol with a substantial percentage of particles smaller than 26,000 nm, or 24,000 nm, or 20,000 nm, or 18,000 nm, or 16,000 nm, or 14,000 nm, or 12,000 nm, or 10,000 nm.
- [282] In some preferred embodiments, the pharmaceutical composition of the invention comprises levorphanol with a substantial percentage of particles smaller than 9,000 nm, or 8,000 nm, or 7,000 nm, or 6,000 nm, or 5,000 nm, or 4,000 nm, or 3,000 nm.
- [283] In some preferred embodiments, the pharmaceutical composition of the invention comprises levorphanol with a substantial percentage of particles smaller than 2,000 nm, or 1,800 nm, or 1,600 nm, or 1,200 nm, or 1,000 nm, or 800 nm, or 600 nm, or 500 nm.
- [284] In some preferred embodiments, the pharmaceutical composition of the invention comprises levorphanol with a significant percentage of particles smaller than 32,000 nm, or 30,000 nm, or 28,000 nm, or 26,000 nm, or 24,000 nm, or 20,000 nm, or 18,000 nm, or 16,000 nm, or 14,000 nm, or 12,000 nm, or 10,000 nm.
- [285] In some preferred embodiments, the pharmaceutical composition of the invention comprises levorphanol with a significant percentage of particles smaller than 9,000 nm, or 8,000 nm, or 7,000 nm, or 6,000 nm, or 5,000 nm, or 4,000 nm, or 3,000 nm.
- [286] In some preferred embodiments, the pharmaceutical composition of the invention comprises levorphanol with a significant percentage of particles smaller than 2,000 nm, or 1,800 nm, or 1,600 nm, or 1,200 nm, or 1,000 nm, or 800 nm, or 600 nm, or 500 nm.
- [287] As used herein, the term "particles smaller than" when used in reference to the size of levorphanol particles means that at least 90% of the levorphanol particles are less than the specified size (d_{90}). For example, "particles smaller than 26,000 nm" means that at least 90% of the levorphanol particles have a particle size of less than 26,000 nm.
- [288] As used herein, the term "substantial percentage of particles smaller than" when used in reference to the size of levorphanol particles means that at least 70% of the levorphanol particles are less than the specified size (d_{70}). For example, "substantial percentage of particles smaller than 26,000 nm" means that at least 70% of the levorphanol particles have a particle size of less than

26,000 nm.

- [289] As used herein, the term "significant percentage of particles smaller than" when used in reference to the size of levorphanol particles means that at least 60% of the levorphanol particles are less than the specified size (d_{60}). For example, "significant percentage of particles smaller than 26,000 nm" means that at least 60% of the levorphanol particles have a particle size of less than 26,000 nm.
- [290] A wide variety of methods are known in the art to measure particle size, including the sieving method (aided by air-jet or sonic sifting) and the use of laser diffraction (e.g., the Malvern Mastersizer 2000 particle size analyzer).
- [291] In addition, most matrix formulations usually contained a multitude of pharmaceutical excipients. Although use of such excipients is widespread in oral pharmaceutical dosage forms and such excipients are generally regarded as safe, the use of excipients can have a number of disadvantages, including, without limitation, (i) increased costs associated with sourcing, excipient facility inspection, acquisition, quality control and release; (ii) increased costs and complexity of manufacture; (iii) increased risk drug excipient and excipient-excipient interaction; (iv) increased technical challenges and costs in making dose proportional modifications to the dosage form when dictated by therapeutic or commercial needs (e.g., doubling the excipients when doubling the dose to obtain the same or very similar release profile); (v) increased validation costs when changing suppliers; (vi) increased need for work place safety controls when handling the excipients; and (vii) known or idiosyncratic adverse reactions in medical users of the dosage form.
- [292] Furthermore, in the case of levorphanol, which is an abusable opioid analgesic subject to intravenous and inhalational abuse, some of the excipients can produce serious cardiac and pulmonary complications upon tampering and intravenous on inhalation use.
- [293] In some preferred embodiments, the composition is a liquid filled thermosoftening extended release dispersion systems which provides an alternative dosage form and method and process of manufacture of extended release levorphanol. This dosage form is advantageously utilized to prepare a robust, cost effective formulation of the invention which (i) avoids one or more or all of the excipients in commercially available oral immediate-release levorphanol tartrate tablets and their associated adverse impact on the in vivo performance of the levorphanol as discussed herein; (ii) substantially reduces or eliminates the need for pharmaceutical excipients generally recommended or considered necessary in a solid the dosage form (e.g. glidants, lubricants, diluents, fillers, binders, disintegrants and antioxidants), with associated cost, workplace safety and patient safety advantages discussed herein; (iii) is relatively easy to scale-up to manufacturing batch size; and (iv) requires a relatively simple manufacturing process, which may optionally be performed entirely in situ in a single heated mixing vessel prior to transfer to a filling machine for encapsulation. This method also overcomes many of the disadvantages of conventional extended

release dosage forms (for example, matrix formulations) referred to herein.

- [294] Commercially available immediate-release dosage forms of levorphanol contain levorphanol tartrate in combination with (i) lactose, corn starch, stearic acid, magnesium stearate and talc; or (ii) lactose, stearic acid and talc; or (iii) lactose, corn starch, stearic acid and talc. When the commercially available oral immediate release levorphanol 2 mg tablets are subjected dissolution, the in-vitro release rate by weight of levorphanol by the USP Paddle Method at 50 rpm is more than 85% at about 10 minutes and more than 95% at about 20 minutes. Despite the rapid release of substantially all or all of the levorphanol from commercially available immediate-release tablet dosage form when tested in vitro using accepted dissolution methods, levorphanol provides a suboptimal biological (or in vivo) response by the oral route.
- [295] Without being bound by theory, the applicant asserts one or more or all of the following to be true under certain conditions of use of commercially available levorphanol tartrate tablets: (i) lack of commercial success despite an attractive pharmacologic profile is due to in part to its failure of commercially available levorphanol tartrate tablets to provide an optimal or robust therapeutic effect; (ii) slow onset of pain relief; (iii) suboptimal maximal relief from pain; (iv) suboptimal total relief from pain; (v) early and greater need for supplemental (or rescue) analgesic when testing analgesic efficacy (e.g., after third molar extraction or after bunionectomy surgery); (vi) one or more excipients in the presently available dosage form, chosen from the group comprising lactose, corn starch, stearic acid, magnesium stearate and talc, adversely impact the in vivo efficiency and efficacy of the dosage form; and (vii) a very high variability in the absorption rate constant.
- [296] In addition, it has now been surprisingly discovered that the commercially available oral immediate-release levorphanol tartrate tablet (i) has a very small gastrointestinal absorption rate constant when evaluated using a two compartment pharmacokinetic model; (ii) the mean absorption time (MAT) is incompatible with robust analgesic efficacy at recommended doses; and (iii) fraction of dose absorbed immediately after administration (e.g. 0.5, 0.75, 1, 1.25 and 1.5 hours) is substantially less than for commercially available oral immediate-release morphine, commercially available oral immediate-release hydromorphone, commercially available oral immediate-release oxymorphone and commercially available oral immediate-release oxycodone. Without being bound by theory, the applicant asserts that the foregoing is due at least in part to the excipients in the only commercially available immediate release oral levorphanol tablets.
- [297] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention contains at least about 5%, or 10%, or 15%, or 20 %, or 25%, or 30%, or 40%, or 50%, or 60%, or 60%, or 80%, or 90% (expressed as weight %) less excipient than commercially available oral immediate-release levorphanol tartrate tablets.
- [298] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention contains at least about 5%, or 10%, or 15%, or 20 %, or 25%, or 30%, or 40%, or 50%, or

60%, or 70%, 80%, or 90% (expressed as weight %) less excipient per mg of levorphanol in the dosage form, when compared with commercially available oral immediate-release levorphanol tartrate tablets.

[299] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention weighs 5%, or 10%, or 15%, or 20 %, or 25%, or 30%, or 40%, or 50%, or 60%, or 70%, or 80%, or 90% less per mg of levorphanol in the dosage form, when compared with commercially available oral immediate-release levorphanol tartrate tablets.

[300] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention contains at least about 5%, or 10%, or 15%, or 20 %, or 25%, or 30%, or 40%, or 50%, or 60%, or 60%, or 80%, or 90% (expressed as weight %) less excipient chosen from the group comprising anhydrous lactose, corn starch, magnesium stearate, stearic acid and talc.

[301] In some preferred embodiments, the extended release levorphanol dosage form of the invention is devoid or one or more or all of the excipient chosen from the group comprising anhydrous lactose, corn starch, magnesium stearate, stearic acid and talc.

[302] Talc is used as a lubricant and diluent in oral dosage forms. It is a naturally occurring hydropolysilicate mineral found in many parts of the world. It is a purified, hydrated, magnesium silicate. It may contain small, variable amounts of aluminum silicate and iron. It is an accepted for use as a food additive in Europe and it is included in the FDA Inactive Ingredients Guide in oral dosage forms. Talc is regarded as an essentially a nontoxic material. However, inhalation of talc dust causes respiratory irritation. Prolonged exposure to talc dust may cause pneumoconiosis.

[303] Magnesium stearate is very fine, light white, precipitated or milled, powder of low bulk density. It is a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. It is also widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. The physical properties of magnesium stearate can vary among batches from different manufacturers and from batch to batch because the solid-state characteristics of the powder are influenced by manufacturing variables.

[304] Anhydrous lactose is O- β -D-galactopyranosyl-(1 \rightarrow 4)- β -D-glucopyranose; or a mixture of O- β -D-galactopyranosyl-(1 \rightarrow 4)- α -D-glucopyranose and O- β -D-galactopyranosyl-(1 \rightarrow 4)- β -D-glucopyranose. Anhydrous lactose is used primarily as a binding agent, directly compressible tableting excipient, and tablet and capsule filler. Mold growth may occur when lactose is stored under conditions of high humidity. In addition, lactose may develop a brown coloration on storage, particularly in warm, damp conditions.

[305] Corn starch (maize starch, *Zea mays*) consists of amylose and amylopectin, two polysaccharides based on α -glucose. It is an odorless fine, white-colored powder. Corn starch is used as a binder, diluent, and disintegrant in oral dosage forms. As a diluent, corn starch is used for

the preparation of triturates of potent drugs or dyes to facilitate subsequent blending or mixing. Corn starch is also used in uncompressed capsule formulations for volume adjustment. Corn starch is also used as a binder in tablet formulations at a concentration of 5–25% w/w. Corn starch is also used as a tablet disintegrants at concentrations of 3–15% w/w.

[306] Stearic acid as a mixture of stearic acid and palmitic acid, typically with a stearic acid content of not less than 40.0% and a combined stearic acid and palmitic acid content of not less than 90.0%. It is widely used in oral dosage forms, mainly as a tablet and capsule lubricant. It has also been used as a binder and for tablet coating.

[307] In some preferred embodiments, when the stearic acid in the dosage form functions as a lubricant, it is replaced by another lubricant. Non-limiting alternatives to stearic acid as a lubricant include polyethylene glycol (PEG), , magnesium stearate, calcium hydroxide, talc, colloidal silicon dioxide, sodium stearyl fumarate, hydrogenated vegetable oil, glyceryl behenate, magnesium, calcium and sodium stearates, talc, waxes, boric acid, sodium benzoate, sodium acetate, sodium chloride, DL-leucine, polyethylene glycols, sodium oleate, or sodium lauryl sulfate. In some embodiments, the dosage form excludes magnesium stearate and/or talc.

[308] In some preferred embodiments, when the stearic acid in the dosage form functions as a binder, it is replaced by another binder. Non-limiting alternatives to stearic acid as a binder include acacia, alginic acid and salts thereof, cellulose derivatives, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, magnesium aluminum silicate, polyethylene glycol, various gums, polyvinylpyrrolidone, polysaccharide acids, bentonites, hydroxypropyl methylcellulose, gelatin, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, crospovidone, povidone, polymethacrylates, hydroxypropylmethylcellulose, hydroxypropylcellulose, starch, pregelatinized starch, ethylcellulose, tragacanth, dextrin, microcrystalline cellulose, sucrose, sodium alginate, or glucose. In some embodiments, the dosage form excludes starch and/or pregelatinized starch. In some embodiments, a preferred binder is selected from the group comprising polyvinylpyrrolidone, microcrystalline cellulose, and/or microcrystalline dextrose.

[309] In some preferred embodiments, when the lactose in the dosage form functions as a binder, it is replaced by another binder. Non-limiting alternatives to lactose as a binder include acacia, alginic acid and salts thereof, cellulose derivatives, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, magnesium aluminum silicate, polyethylene glycol, various gums, polyvinylpyrrolidone, polysaccharide acids, bentonites, hydroxypropyl methylcellulose, gelatin, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, crospovidone, povidone, polymethacrylates, hydroxypropylmethylcellulose, hydroxypropylcellulose, starch, pregelatinized starch, ethylcellulose, tragacanth, dextrin, microcrystalline cellulose, sucrose, sodium alginate, or glucose. In some embodiments, the dosage form excludes stearic acid, starch and/or pregelatinized starch. In some embodiments, a preferred binder is selected from the group comprising

polyvinylpyrrolidone, microcrystalline cellulose, and/or microcrystalline dextrose.

- [310] In some preferred embodiments, when the magnesium stearate in the dosage form in the dosage form functions as a lubricant, it is replaced by another lubricant. Non-limiting alternatives to magnesium stearate as a lubricant include talc, polyethylene glycol (PEG), magnesium stearate, calcium hydroxide, colloidal silicon dioxide, sodium stearyl fumarate, hydrogenated vegetable oil, stearic acid, glyceryl behenate, magnesium, calcium and sodium stearates, stearic acid, talc, waxes, boric acid, sodium benzoate, sodium acetate, sodium chloride, DL-leucine, polyethylene glycols, sodium oleate, or sodium lauryl sulfate. In some embodiments, the dosage form excludes talc and/or stearic acid and/or calcium and sodium stearates.
- [311] In some preferred embodiments, when the talc in the dosage form in the dosage form functions as a lubricant, it is replaced by another lubricant. Non-limiting alternatives to talc as a lubricant include polyethylene glycol (PEG) magnesium stearate, calcium hydroxide, colloidal silicon dioxide, sodium stearyl fumarate, hydrogenated vegetable oil, stearic acid, glyceryl behenate, magnesium, calcium and sodium stearates, stearic acid, waxes, boric acid, sodium benzoate, sodium acetate, sodium chloride, DL-leucine, polyethylene glycols, sodium oleate, or sodium lauryl sulfate. In some embodiments, the dosage form excludes magnesium stearate and/or stearic acid and/or calcium and sodium stearates.
- [312] In some preferred embodiments, when the talc in the dosage form in the dosage form functions as a diluent, it is replaced by another diluent. Non-limiting alternatives to talc as a diluent include lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, dibasic calcium phosphate, sorbitol, inositol kaolin, sucrose-based diluents, confectioner's sugar, monobasic calcium sulfate monohydrate, calcium sulfate dihydrate, calcium lactate trihydrate, dextrates, inositol, hydrolyzed cereal solids, amylose, powdered cellulose, calcium carbonate, glycine, or bentonite. In some embodiments, the dosage form excludes lactose and/or starch. In some embodiments, the dosage form excludes lactose, and/or amylose and/or starch.
- [313] In some preferred embodiments, when the starch in the dosage form in the dosage form functions as a diluent, it is replaced by another diluent. Non-limiting alternatives to starch and corn starch as a diluent include lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, dibasic calcium phosphate, sorbitol, inositol kaolin, sucrose-based diluents, confectioner's sugar, monobasic calcium sulfate monohydrate, calcium sulfate dihydrate, calcium lactate trihydrate, dextrates, inositol, hydrolyzed cereal solids, amylose, powdered cellulose, calcium carbonate, glycine, or bentonite. In some embodiments, the dosage form excludes lactose and/or talc. In some embodiments, the dosage form excludes lactose, and/or amylose and/or starch.
- [314] In some preferred embodiments, when the starch in the dosage form functions as a disintegrant, it is replaced by another disintegrant. Non-limiting alternatives to starch as a disintegrant include celluloses, cross-linked carboxymethylcellulose, crospovidone, cross-linked

polyvinylpyrrolidone, a calcium sodium alginate complex or a sodium alginate complex, clays, alginates, gums, or sodium starch glycolate.

[315] In some preferred embodiments, when the talc in the dosage form in the dosage form functions as a glidant, it is replaced by another glidant. Non-limiting alternatives to talc as a glidant include corn starch, DL-leucine, sodium lauryl sulfate, and magnesium, calcium, or sodium stearates, and colloidal silicon dioxide. In some embodiments, the dosage form excludes starch and/or magnesium stearates, and/or calcium or sodium stearates. In some embodiments, a preferred glidant is colloidal silicon dioxide.

[316] In some embodiments, an excipient in the dosage form may serve several different purposes. In some embodiments, the colloidal silicon dioxide serves both as a lubricant and as a glidant.

[317] **Controlled Release Rate of Extended Release Levorphanol**

[318] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol and controlled release material to render said dosage form suitable for extended release, said dosage form releasing or delivering unsalified levorphanol (levorphanol base) at a controlled rate of release of about 0.05 mg/hr, or 0.1 mg/hr, or 0.15 mg/hr, or 0.2 mg/hr, or 0.25 mg/hr, or 0.3 mg/hr, or 0.35 mg/hr, or 0.4 mg/hr, or 0.45 mg/hr, or 0.5 mg/hr, or 0.6 mg/hr, or 0.7 mg/hr, or 0.8 mg/hr, or 0.9 mg/hr, or 1 mg/hr, or 1.1 mg/hr, or 1.2 mg/hr, or 1.3 mg/hr, or 1.4 mg/hr, or 1.5 mg/hr, or 1.6 mg/hr, or 1.7 mg/hr, or 1.8 mg/hr, or 1.9 mg/hr, or 2 mg/hr, or 2.1 mg/hr, or 2.2 mg/hr, or 2.3 mg/hr, or 2.4 mg/hr, or 2.5 mg/hr, or 2.7 mg/hr, or 3 mg/hr, or 3.2 mg/hr, or 3.5 mg/hr, or 3.8 mg/hr, or 3.9 mg/hr, or 4 mg/hr.

[319] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol and controlled release material to render said dosage form suitable for extended release, said dosage form releasing or delivering unsalified levorphanol (levorphanol base) at a controlled rate of release of not less than about 0.05 mg/hr, or 0.1 mg/hr, or 0.15 mg/hr, or 0.2 mg/hr, or 0.25 mg/hr, or 0.3 mg/hr, or 0.35 mg/hr, or 0.4 mg/hr, or 0.45 mg/hr, or 0.5 mg/hr, or 0.6 mg/hr, or 0.7 mg/hr, or 0.8 mg/hr, or 0.9 mg/hr, or 1 mg/hr, or 1.1 mg/hr, or 1.2 mg/hr, or 1.3 mg/hr, or 1.4 mg/hr, or 1.5 mg/hr, or 1.6 mg/hr, or 1.7 mg/hr, or 1.8 mg/hr, or 1.9 mg/hr, or 2 mg/hr, or 2.1 mg/hr, or 2.2 mg/hr, or 2.3 mg/hr, or 2.4 mg/hr, or 2.5 mg/hr, or 2.7 mg/hr, or 3 mg/hr, or 3.2 mg/hr, or 3.5 mg/hr, or 3.8 mg/hr, or 3.9 mg/hr, or 4 mg/hr.

[320] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol and controlled release material to render said dosage form suitable for extended release, said dosage form releasing or delivering unsalified levorphanol (levorphanol base) at a controlled rate of release of about 0.05 mg/hr to about 8 mg/hr, or about 0.05 mg/hr to about 7 mg/hr, or about 0.05 mg/hr to

about 6 mg/hr, or about 0.05 mg/hr to about 5 mg/hr, or 0.5 mg/hr to about 4.5 mg/hr, or about 0.05 mg/hr to about 4 mg/hr, or about 0.05 mg/hr to about 3.5 mg/hr, or about 0.05 mg/hr to about 3.2 mg/hr, or about 0.05 mg/hr to about 3 mg/hr, or about 0.05 mg/hr to about 2.8 mg/hr, or about 0.05 mg/hr to about 2.5 mg/hr, or about 0.05 mg/hr to about 2.2 mg/hr, or 0.5 mg/hr to about 2 mg/hr, or about 0.05 mg/hr to about 1.8 mg/hr, or about 0.05 mg/hr to about 1.5 mg/hr, or about 0.05 mg/hr to about 1.2 mg/hr, or about 0.05 mg/hr to about 1.1 mg/hr, or about 0.05 mg/hr to about 1 mg/hr, or about 0.05 mg/hr to about 0.8 mg/hr, or about 0.05 mg/hr to about 0.7 mg/hr, or about 0.05 mg/hr to about 0.6 mg/hr, or about 0.05 mg/hr to about 0.5 mg/hr, or about 0.05 mg/hr to about 0.4 mg/hr, or about 0.05 mg/hr to about 0.35 mg/hr, or about 0.05 mg/hr to about 0.3 mg/hr, or about 0.05 mg/hr to about 0.25 mg/hr, or about 0.05 mg/hr to about 0.2 mg/hr.

[321] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol and controlled release material to render said dosage form suitable for extended release, said dosage form releasing or delivering unsalified levorphanol (levorphanol base) at a controlled rate of release of about 0.1 mg/hr to about 8 mg/hr, or about 0.1 mg/hr to about 7 mg/hr, or about 0.1 mg/hr to about 6 mg/hr, or about 0.1 mg/hr to about 5 mg/hr, or 0.5 mg/hr to about 4.5 mg/hr, or 0.1 mg/hr to about 4 mg/hr, or about 0.1 mg/hr to about 3.5 mg/hr, or about 0.1 mg/hr to about 3.2 mg/hr, or about 0.1 mg/hr to about 3 mg/hr, or about 0.1 mg/hr to about 2.8 mg/hr, or about 0.1 mg/hr to about 2.5 mg/hr, or about 0.1 mg/hr to about 2.2 mg/hr, or 0.5 mg/hr to about 2 mg/hr, or 0.1 mg/hr to about 1.8 mg/hr, or about 0.1 mg/hr to about 1.5 mg/hr, or about 0.1 mg/hr to about 1.2 mg/hr, or about 0.1 mg/hr to about 1.1 mg/hr, or about 0.1 mg/hr to about 1 mg/hr, or about 0.1 mg/hr to about 0.8 mg/hr, or about 0.1 mg/hr to about 0.7 mg/hr, or 0.1 mg/hr to about 0.6 mg/hr, or 0.1 mg/hr to about 0.5 mg/hr, or about 0.1 mg/hr to about 0.4 mg/hr, or about 0.1 mg/hr to about 0.35 mg/hr, or about 0.1 mg/hr to about 0.3 mg/hr, or about 0.1 mg/hr to about 0.25 mg/hr, or about 0.1 mg/hr to about 0.2 mg/hr.

[322] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol and controlled release material to render said dosage form suitable for extended release, said dosage form releasing or delivering unsalified levorphanol (levorphanol base) at a controlled rate of release of about 0.15 mg/hr to about 8 mg/hr, or about 0.15 mg/hr to about 7 mg/hr, or about 0.15 mg/hr to about 6 mg/hr, or about 0.15 mg/hr to about 5 mg/hr, or 0.5 mg/hr to about 4.5 mg/hr, or 0.15 mg/hr to about 4 mg/hr, or about 0.15 mg/hr to about 3.5 mg/hr, or about 0.15 mg/hr to about 3.2 mg/hr, or about 0.15 mg/hr to about 3 mg/hr, or about 0.15 mg/hr to about 2.8 mg/hr, or about 0.15 mg/hr to about 2.5 mg/hr, or about 0.15 mg/hr to about 2.2 mg/hr, or 0.5 mg/hr to about 2 mg/hr, or 0.15 mg/hr to about 1.8 mg/hr, or about 0.15 mg/hr to about 1.5 mg/hr, or about 0.15 mg/hr to about 1.2 mg/hr, or about 0.15 mg/hr to about 1.1 mg/hr, or about 0.15 mg/hr to about 1 mg/hr, or about 0.15

mg/hr to about 0.8 mg/hr, or about 0.15 mg/hr to about 0.7 mg/hr, or 0.15 mg/hr to about 0.6 mg/hr, or 0.15 mg/hr to about 0.5 mg/hr, or about 0.15 mg/hr to about 0.4 mg/hr, or about 0.15 mg/hr to about 0.35 mg/hr, or about 0.15 mg/hr to about 0.3 mg/hr, or about 0.15 mg/hr to about 0.25 mg/hr, or about 0.15 mg/hr to about 0.2 mg/hr.

[323] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol and controlled release material to render said dosage form suitable for extended release, said dosage form releasing or delivering unsalified levorphanol (levorphanol base) at a controlled rate of release of about 0.2 mg/hr to about 8 mg/hr, or about 0.2 mg/hr to about 7 mg/hr, or about 0.2 mg/hr to about 6 mg/hr, or about 0.2 mg/hr to about 5 mg/hr, or 0.5 mg/hr to about 4.5 mg/hr, or 0.2 mg/hr to about 4 mg/hr, or about 0.2 mg/hr to about 3.5 mg/hr, or about 0.2 mg/hr to about 3.2 mg/hr, or about 0.2 mg/hr to about 3 mg/hr, or about 0.2 mg/hr to about 2.8 mg/hr, or about 0.2 mg/hr to about 2.5 mg/hr, or about 0.2 mg/hr to about 2.2 mg/hr, or 0.5 mg/hr to about 2 mg/hr, or 0.2 mg/hr to about 1.8 mg/hr, or about 0.2 mg/hr to about 1.5 mg/hr, or about 0.2 mg/hr to about 1.2 mg/hr, or about 0.2 mg/hr to about 1.1 mg/hr, or about 0.2 mg/hr to about 1 mg/hr, or about 0.2 mg/hr to about 0.8 mg/hr, or about 0.2 mg/hr to about 0.7 mg/hr, or 0.2 mg/hr to about 0.6 mg/hr, or 0.2 mg/hr to about 0.5 mg/hr, or about 0.2 mg/hr to about 0.4 mg/hr, or about 0.2 mg/hr to about 0.35 mg/hr, or about 0.2 mg/hr to about 0.3 mg/hr, or about 0.2 mg/hr to about 0.25 mg/hr, or about 0.2 mg/hr to about 0.2 mg/hr.

[324] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol and controlled release material to render said dosage form suitable for controlled release or delayed onset, extended release in a human patient, said dosage form releasing or delivering levorphanol at a controlled rate of release of about 0.1 mg/hr to about 4 mg/hr, or about 0.2 mg/hr to about 4 mg/hr, or about 0.3 mg/hr to about 4 mg/hr, or about 0.4 mg/hr to about 4 mg/hr, or 0.5 mg/hr to about 4 mg/hr, or 0.6 mg/hr to about 4 mg/hr, or about 0.7 mg/hr to about 4 mg/hr, or about 0.8 mg/hr to about 4 mg/hr, or about 0.9 mg/hr to about 4 mg/hr, or about 1 mg/hr to about 4 mg/hr, or about 1.2 mg/hr to about 4 mg/hr, or about 1.4 mg/hr to about 4 mg/hr, or 1.5 mg/hr to about 4 mg/hr, or 1.6 mg/hr to about 4 mg/hr, or about 1.8 mg/hr to about 4 mg/hr, or about 2 mg/hr to about 4 mg/hr.

[325] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol and controlled release material to render said dosage form suitable for controlled release or delayed onset, extended release in a human patient, said dosage form releasing or delivering levorphanol at a controlled rate of release of about 0.1 mg/hr to about 3 mg/hr, or about 0.2 mg/hr to about 3 mg/hr, or about 0.3 mg/hr to about 3 mg/hr, or about 0.4 mg/hr to about 3 mg/hr, or 0.5 mg/hr to

about 3 mg/hr, or 0.6 mg/hr to about 3 mg/hr, or about 0.7 mg/hr to about 3 mg/hr, or about 0.8 mg/hr to about 3 mg/hr, or about 0.9 mg/hr to about 3 mg/hr, or about 1 mg/hr to about 3 mg/hr, or about 1.2 mg/hr to about 3 mg/hr, or about 1.4 mg/hr to about 3 mg/hr, or 1.5 mg/hr to about 3 mg/hr, or 1.6 mg/hr to about 3 mg/hr, or about 1.8 mg/hr to about 3 mg/hr, or about 2 mg/hr to about 3 mg/hr.

[326] In some preferred embodiments, the extended release dosage form releases or delivers levorphanol at a controlled rate of release for a period of about not less than about 6, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22 or 24 hours.

[327] As used herein, "controlled rate of release" refers to the release or delivery of the active drug from the oral dosage form of the invention at rate per unit time over an extended period of time (e.g., over 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28 or 32 hours), or any time period over 1.5 to 40 hours.

[328] In some preferred embodiments, the oral extended release levorphanol pharmaceutical composition comprises a therapeutically effective amount of levorphanol, said dosage form providing a mean in vitro controlled release rate of levorphanol of about 0.02 mg per hour to 4 mg per hour for at least about 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30, 36 or 40 hours, said dosage form suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours) . In some preferred embodiments, the foregoing mean release rate is about 0.05 mg per hour to about 4 mg per hour, or about 0.1 mg per hour to about 4 mg per hour, or about 0.2 mg per hour to about 4 mg per hour, or about 0.3 mg per hour to about 4 mg per hour, or about 0.4 mg per hour to about 4 mg per hour, or about 0.5 mg per hour to about 4 mg per hour, or about 0.6 mg per hour to about 4 mg per hour, or about 0.7 mg per hour to about 4 mg per hour, or about 0.8 mg per hour to about 4 mg per hour, or about 0.9 mg per hour to about 4 mg per hour, or about 1 mg per hour to about 4 mg per hour, or about 1.2 mg per hour to about 4 mg per hour, or about 1.4 mg per hour to about 4 mg per hour, or about 1.6 mg per hour to about 4 mg per hour, or about 1.8 mg per hour to about 4 mg per hour, or about 2 mg per hour to about 4 mg per hour, or about 0.02 mg per hour to 3 mg per hour, or about 0.05 mg per hour to about 3 mg per hour, or about 0.1 mg per hour to about 3 mg per hour, or about 0.2 mg per hour to about 3 mg per hour, or about 0.3 mg per hour to about 3 mg per hour, or about 0.3 mg per hour to about 3 mg per hour, or about 0.5 mg per hour to about 3 mg per hour, or about 0.6 mg per hour to about 3 mg per hour, or about 0.7 mg per hour to about 3 mg per hour, or about 0.8 mg per hour to about 3 mg per hour, or about 0.9 mg per hour to about 3 mg per hour, or about 1 mg per hour to about 3 mg per hour, or about 1.2 mg per hour to about 3 mg per hour, or about 1.3 mg per hour to about 3 mg per hour, or about 1.6 mg per hour to about 3 mg per hour, or about 1.8 mg per hour to about 3 mg per hour, or about 2 mg per hour to about 3 mg per hour, or about 0.025 mg per hour to 2.5 mg per hour, or about 0.05 mg per hour to about 2.5 mg per hour, or about 0.1 mg per hour to about 2.5 mg per hour, or about 0.25

0.1 mg per hour to about 0.8 mg per hour, or about 0.1 mg per hour to about 0.7 mg per hour.

[329] Systemic Exposure After Extended Release Levorphanol

[330] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 100 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 200 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 300 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 400 ng.hr/mL at 4 hours, from about 0 ng.hr/mL to about 500 ng.hr/mL at 5 hours, from about 0 ng.hr/mL to about 600 ng.hr/mL at 6 hours, from about 1ng.hr/mL to about 700 ng.hr/mL at 7 hours, from about 2 ng.hr/mL to about 800 ng.hr/mL at 8 hours, from about 4 ng.hr/mL to about 1000 ng.hr/mL at 10 hours, from about 4 ng.hr/mL to about 1200 ng.hr/mL at 12 hours, from about 6 ng.hr/mL to about 1400 ng.hr/mL at 14 hours, from about 6 ng.hr/mL to about 1600 ng.hr/mL at 16 hours, from about 8 ng.hr/mL to about 2000 ng.hr/mL at 20 hours, from about 10 ng.hr/mL to about 2400 ng.hr/mL at 24 hours, from about 12 ng.hr/mL to about 2800 ng.hr/mL at 28 hours, from about 16 ng.hr/mL to about 3600 ng.hr/mL at 36 hours, and from about 20 ng.hr/mL to about 4800 ng.hr/mL at 48 hours.

[331] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 50 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 100 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 150 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 200 ng.hr/mL at 4 hours, from about 0 ng.hr/mL to about 250 ng.hr/mL at 5 hours, from about 0 ng.hr/mL to about 300 ng.hr/mL at 6 hours, from about 1ng.hr/mL to about 350 ng.hr/mL at 7 hours, from about 2 ng.hr/mL to about 400 ng.hr/mL at 8 hours, from about 4 ng.hr/mL to about 500 ng.hr/mL at 10 hours, from about 4 ng.hr/mL to about 600 ng.hr/mL at 12 hours, from about 6 ng.hr/mL to about 700 ng.hr/mL at 14 hours, from about 6 ng.hr/mL to about 800 ng.hr/mL at 16 hours, from about 8 ng.hr/mL to about 1000 ng.hr/mL at 20 hours, from about 10 ng.hr/mL to about 1200 ng.hr/mL at 24 hours, from about 12 ng.hr/mL to about 1400 ng.hr/mL at 28 hours, from about 16 ng.hr/mL to about 1800 ng.hr/mL at 36 hours, and from about 20 ng.hr/mL to about 2400 ng.hr/mL at 48 hours.

[332] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 25 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 50 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 75 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 100 ng.hr/mL at 4 hours, from about 0 ng.hr/mL to about 125 ng.hr/mL at 5 hours, from about 0 ng.hr/mL to about 150 ng.hr/mL at 6 hours, from about 1ng.hr/mL to about 175 ng.hr/mL at 7 hours, from about 2 ng.hr/mL to about 200 ng.hr/mL at 8 hours, from about 4 ng.hr/mL to about 250 ng.hr/mL at 10 hours, from about 4 ng.hr/mL to about 300 ng.hr/mL at 12 hours, from about 6 ng.hr/mL to about 350 ng.hr/mL at 14 hours, from about 6 ng.hr/mL to about 400 ng.hr/mL at 16 hours, from about 8 ng.hr/mL to about 500 ng.hr/mL at 20 hours, from about 10 ng.hr/mL to about 600 ng.hr/mL at 24 hours, from about 12 ng.hr/mL to about 700 ng.hr/mL at 28 hours, from about 16 ng.hr/mL to about 900 ng.hr/mL at 36 hours, and from about 20 ng.hr/mL to about 1200 ng.hr/mL at 48 hours.

[333] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 15 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 25 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 30 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 50 ng.hr/mL at 4 hours, from about 0 ng.hr/mL to about 60 ng.hr/mL at 5 hours, from about 0 ng.hr/mL to about 75 ng.hr/mL at 6 hours, from about 1ng.hr/mL to about 80 ng.hr/mL at 7 hours, from about 2 ng.hr/mL to about 100 ng.hr/mL at 8 hours, from about 4 ng.hr/mL to about 125 ng.hr/mL at 10 hours, from about 4 ng.hr/mL to about 150 ng.hr/mL at 12 hours, from about 6 ng.hr/mL to about 175 ng.hr/mL at 14 hours, from about 6 ng.hr/mL to about 200 ng.hr/mL at 16 hours, from about 8 ng.hr/mL to about 250 ng.hr/mL at 20 hours, from about 10 ng.hr/mL to about 300 ng.hr/mL at 24 hours, from about 12 ng.hr/mL to about 350 ng.hr/mL at 28 hours, from about 16 ng.hr/mL to about 450 ng.hr/mL at 36 hours, and from about 20 ng.hr/mL to about 600 ng.hr/mL at 48 hours.

[334] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a

controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 25 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 50 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 75 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 100 ng.hr/mL at 4 hours, from about 1 ng.hr/mL to about 150 ng.hr/mL at 5 hours, from about 1 ng.hr/mL to about 225 ng.hr/mL at 6 hours, from about 4 ng.hr/mL to about 275 ng.hr/mL at 7 hours, from about 6 ng.hr/mL to about 320 ng.hr/mL at 8 hours, from about 8 ng.hr/mL to about 450 ng.hr/mL at 10 hours, from about 12 ng.hr/mL to about 620 ng.hr/mL at 12 hours, from about 12 ng.hr/mL to about 700 ng.hr/mL at 14 hours, from about 16 ng.hr/mL to about 1000 ng.hr/mL at 16 hours, from about 18 ng.hr/mL to about 1200 ng.hr/mL at 20 hours, from about 22 ng.hr/mL to about 1400 ng.hr/mL at 24 hours, from about 24 ng.hr/mL to about 1600 ng.hr/mL at 28 hours, from about 28 ng.hr/mL to about 1800 ng.hr/mL at 36 hours, and from about 36 ng.hr/mL to about 2200 ng.hr/mL at 48 hours.

[335] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 12 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 25 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 40 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 50 ng.hr/mL at 4 hours, from about 1 ng.hr/mL to about 75 ng.hr/mL at 5 hours, from about 1 ng.hr/mL to about 110 ng.hr/mL at 6 hours, from about 3 ng.hr/mL to about 130 ng.hr/mL at 7 hours, from about 3 ng.hr/mL to about 160 ng.hr/mL at 8 hours, from about 6 ng.hr/mL to about 225 ng.hr/mL at 10 hours, from about 12 ng.hr/mL to about 310 ng.hr/mL at 12 hours, from about 10 ng.hr/mL to about 350 ng.hr/mL at 14 hours, from about 12 ng.hr/mL to about 500 ng.hr/mL at 16 hours, from about 14 ng.hr/mL to about 600 ng.hr/mL at 20 hours, from about 18 ng.hr/mL to about 700 ng.hr/mL at 24 hours, from about 24 ng.hr/mL to about 800 ng.hr/mL at 28 hours, from about 24 ng.hr/mL to about 900 ng.hr/mL at 36 hours, and from about 32 ng.hr/mL to about 1200 ng.hr/mL at 48 hours.

[336] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage

form after first administration or single dose administration provides systemic exposure of levorphanol as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 16 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 36 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 48 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 96 ng.hr/mL at 4 hours, from about 1 ng.hr/mL to about 144 ng.hr/mL at 5 hours, from about 3 ng.hr/mL to about 225 ng.hr/mL at 6 hours, from about 5 ng.hr/mL to about 270 ng.hr/mL at 7 hours, from about 6 ng.hr/mL to about 320 ng.hr/mL at 8 hours, from about 8 ng.hr/mL to about 450 ng.hr/mL at 10 hours, from about 12 ng.hr/mL to about 620 ng.hr/mL at 12 hours, from about 12 ng.hr/mL to about 700 ng.hr/mL at 14 hours, from about 16 ng.hr/mL to about 1000 ng.hr/mL at 16 hours, from about 18 ng.hr/mL to about 1200 ng.hr/mL at 20 hours, from about 22 ng.hr/mL to about 1400 ng.hr/mL at 24 hours, from about 24 ng.hr/mL to about 1600 ng.hr/mL at 28 hours, from about 28 ng.hr/mL to about 1800 ng.hr/mL at 36 hours, and from about 36 ng.hr/mL to about 2200 ng.hr/mL at 48 hours.

[337] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 8 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 16 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 24 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 48 ng.hr/mL at 4 hours, from about 1 ng.hr/mL to about 72 ng.hr/mL at 5 hours, from about 3 ng.hr/mL to about 115 ng.hr/mL at 6 hours, from about 5 ng.hr/mL to about 140 ng.hr/mL at 7 hours, from about 6 ng.hr/mL to about 160 ng.hr/mL at 8 hours, from about 6 ng.hr/mL to about 225 ng.hr/mL at 10 hours, from about 12 ng.hr/mL to about 310 ng.hr/mL at 12 hours, from about 10 ng.hr/mL to about 350 ng.hr/mL at 14 hours, from about 12 ng.hr/mL to about 500 ng.hr/mL at 16 hours, from about 14 ng.hr/mL to about 600 ng.hr/mL at 20 hours, from about 18 ng.hr/mL to about 700 ng.hr/mL at 24 hours, from about 24 ng.hr/mL to about 800 ng.hr/mL at 28 hours, from about 24 ng.hr/mL to about 900 ng.hr/mL at 36 hours, and from about 32 ng.hr/mL to about 1200 ng.hr/mL at 48 hours.

[338] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol

area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 0.02 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 0.15 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 0.4 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 0.8 ng.hr/mL at 4 hours, from about 0.1 ng.hr/mL to about 1.2 ng.hr/mL at 5 hours, from about 0.3 ng.hr/mL to about 1.8 ng.hr/mL at 6 hours, from about 0.4 ng.hr/mL to about 2.6 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 3.2 ng.hr/mL at 8 hours, from about 0.7 ng.hr/mL to about 4.6 ng.hr/mL at 10 hours, from about 0.9 ng.hr/mL to about 5.8 ng.hr/mL at 12 hours, from about 1.1 ng.hr/mL to about 7.0 ng.hr/mL at 14 hours, from about 1.3 ng.hr/mL to about 8.2 ng.hr/mL at 16 hours, from about 1.7 ng.hr/mL to about 11 ng.hr/mL at 20 hours, from about 2 ng.hr/mL to about 13 ng.hr/mL at 24 hours, from about 2.4 ng.hr/mL to about 14 ng.hr/mL at 28 hours, from about 3 ng.hr/mL to about 16 ng.hr/mL at 36 hours, and from about 3.7 ng.hr/mL to about 18 ng.hr/mL at 48 hours.

[339] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 0.015 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 0.1 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 0.3 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 0.6 ng.hr/mL at 4 hours, from about 0.1 ng.hr/mL to about 1 ng.hr/mL at 5 hours, from about 0.3 ng.hr/mL to about 1.1 ng.hr/mL at 6 hours, from about 0.4 ng.hr/mL to about 1.8 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 2.5 ng.hr/mL at 8 hours, from about 0.7 ng.hr/mL to about 3.2 ng.hr/mL at 10 hours, from about 0.9 ng.hr/mL to about 4 ng.hr/mL at 12 hours, from about 1.1 ng.hr/mL to about 5 ng.hr/mL at 14 hours, from about 1.3 ng.hr/mL to about 6 ng.hr/mL at 16 hours, from about 1.7 ng.hr/mL to about 8 ng.hr/mL at 20 hours, from about 2 ng.hr/mL to about 10 ng.hr/mL at 24 hours, from about 2.4 ng.hr/mL to about 14 ng.hr/mL at 28 hours, from about 3 ng.hr/mL to about 12 ng.hr/mL at 36 hours, and from about 3.7 ng.hr/mL to about 14 ng.hr/mL at 48 hours.

[340] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 0.01 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 0.2 ng.hr/mL at 2 hours, from about 0 ng.hr/mL

to about 0.9 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 1.8 ng.hr/mL at 4 hours, from about 0.005 ng.hr/mL to about 3.1 ng.hr/mL at 5 hours, from about 0.1 ng.hr/mL to about 4.6 ng.hr/mL at 6 hours, from about 0.3 ng.hr/mL to about 7 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 8 ng.hr/mL at 8 hours, from about 0.75 ng.hr/mL to about 11 ng.hr/mL at 10 hours, from about 1 ng.hr/mL to about 15 ng.hr/mL at 12 hours, from about 1.2 ng.hr/mL to about 18 ng.hr/mL at 14 hours, from about 1.5 ng.hr/mL to about 21 ng.hr/mL at 16 hours, from about 2 ng.hr/mL to about 26 ng.hr/mL at 20 hours, from about 2.5 ng.hr/mL to about 30 ng.hr/mL at 24 hours, from about 3 ng.hr/mL to about 35 ng.hr/mL at 28 hours, from about 4 ng.hr/mL to about 40 ng.hr/mL at 36 hours, and from about 5 ng.hr/mL to about 95 ng.hr/mL at 48 hours.

[341] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 0.01 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 0.12 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 0.32 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 0.7 ng.hr/mL at 4 hours, from about 0.005 ng.hr/mL to about 1.3 ng.hr/mL at 5 hours, from about 0.1 ng.hr/mL to about 1.9 ng.hr/mL at 6 hours, from about 0.3 ng.hr/mL to about 2.5 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 3.2 ng.hr/mL at 8 hours, from about 0.75 ng.hr/mL to about 4.5 ng.hr/mL at 10 hours, from about 1 ng.hr/mL to about 5.7 ng.hr/mL at 12 hours, from about 1.2 ng.hr/mL to about 7 ng.hr/mL at 14 hours, from about 1.5 ng.hr/mL to about 8.2 ng.hr/mL at 16 hours, from about 2 ng.hr/mL to about 10.3 ng.hr/mL at 20 hours, from about 2.5 ng.hr/mL to about 12 ng.hr/mL at 24 hours, from about 3 ng.hr/mL to about 13.6 ng.hr/mL at 28 hours, from about 4 ng.hr/mL to about 16 ng.hr/mL at 36 hours, and from about 5 ng.hr/mL to about 17 ng.hr/mL at 48 hours.

[342] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 0.1 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 0.2 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 0.5 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 1 ng.hr/mL at 4 hours, from about

0.005 ng.hr/mL to about 2 ng.hr/mL at 5 hours, from about 0.1 ng.hr/mL to about 3 ng.hr/mL at 6 hours, from about 0.3 ng.hr/mL to about 4 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 5 ng.hr/mL at 8 hours, from about 0.75 ng.hr/mL to about 6 ng.hr/mL at 10 hours, from about 1 ng.hr/mL to about 8 ng.hr/mL at 12 hours, from about 1.2 ng.hr/mL to about 10 ng.hr/mL at 14 hours, from about 1.5 ng.hr/mL to about 12 ng.hr/mL at 16 hours, from about 2 ng.hr/mL to about 14 ng.hr/mL at 20 hours, from about 2.5 ng.hr/mL to about 15 ng.hr/mL at 24 hours, from about 3 ng.hr/mL to about 15.5 ng.hr/mL at 28 hours, from about 4 ng.hr/mL to about 16 ng.hr/mL at 36 hours, and from about 5 ng.hr/mL to about 17 ng.hr/mL at 48 hours.

[343] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 1 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 1.2 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 1.5 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 2 ng.hr/mL at 4 hours, from about 0.005 ng.hr/mL to about 3 ng.hr/mL at 5 hours, from about 0.1 ng.hr/mL to about 4 ng.hr/mL at 6 hours, from about 0.3 ng.hr/mL to about 6 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 8 ng.hr/mL at 8 hours, from about 0.75 ng.hr/mL to about 10 ng.hr/mL at 10 hours, from about 1 ng.hr/mL to about 12 ng.hr/mL at 12 hours, from about 1.2 ng.hr/mL to about 14 ng.hr/mL at 14 hours, from about 1.5 ng.hr/mL to about 16 ng.hr/mL at 16 hours, from about 2 ng.hr/mL to about 16.5 ng.hr/mL at 20 hours, from about 2.5 ng.hr/mL to about 16.5 ng.hr/mL at 24 hours, from about 3 ng.hr/mL to about 16.5 ng.hr/mL at 28 hours, from about 4 ng.hr/mL to about 16.5 ng.hr/mL at 36 hours, and from about 5 ng.hr/mL to about 17 ng.hr/mL at 48 hours.

[344] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 2 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 3 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 4 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 6 ng.hr/mL at 4 hours, from about 0.005 ng.hr/mL to about 8 ng.hr/mL at 5 hours, from about 0.1 ng.hr/mL to about 9 ng.hr/mL at 6 hours, from about 0.3 ng.hr/mL to about 10 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 12

ng.hr/mL at 8 hours, from about 1 ng.hr/mL to about 10 ng.hr/mL at 14 hours, from about 4 ng.hr/mL to about 16 ng.hr/mL at 12 hours, from about 5 ng.hr/mL to about 16 ng.hr/mL at 14 hours, from about 5.5 ng.hr/mL to about 16 ng.hr/mL at 16 hours, from about 6 ng.hr/mL to about 16.5 ng.hr/mL at 20 hours, from about 6.5 ng.hr/mL to about 16.5 ng.hr/mL at 24 hours, from about 7 ng.hr/mL to about 16.5 ng.hr/mL at 28 hours, from about 4 ng.hr/mL to about 16.5 ng.hr/mL at 36 hours, and from about 8 ng.hr/mL to about 17 ng.hr/mL at 48 hours.

[345] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 4 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 7 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 8 ng.hr/mL at 3 hours, from about 0.05 ng.hr/mL to about 10 ng.hr/mL at 4 hours, from about 0.1 ng.hr/mL to about 10 ng.hr/mL at 5 hours, from about 0.2 ng.hr/mL to about 12 ng.hr/mL at 6 hours, from about 2.5 ng.hr/mL to about 12 ng.hr/mL at 7 hours, from about 2.75 ng.hr/mL to about 12 ng.hr/mL at 8 hours, from about 3 ng.hr/mL to about 12 ng.hr/mL at 14 hours, from about 3 ng.hr/mL to about 13 ng.hr/mL at 12 hours, from about 3.5 ng.hr/mL to about 13 ng.hr/mL at 14 hours, from about 3.5 ng.hr/mL to about 14 ng.hr/mL at 16 hours, from about 4 ng.hr/mL to about 14 ng.hr/mL at 20 hours, from about 4.5 ng.hr/mL to about 14 ng.hr/mL at 24 hours, from about 5 ng.hr/mL to about 14 ng.hr/mL at 28 hours, from about 5.5 ng.hr/mL to about 14 ng.hr/mL at 36 hours, and from about 6 ng.hr/mL to about 14 ng.hr/mL at 48 hours.

[346] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 1.5 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 2 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 2.5 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 3 ng.hr/mL at 4 hours, from about 0.005 ng.hr/mL to about 4 ng.hr/mL at 5 hours, from about 0.1 ng.hr/mL to about 5 ng.hr/mL at 6 hours, from about 0.3 ng.hr/mL to about 8 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 10 ng.hr/mL at 8 hours, from about 0.75 ng.hr/mL to about 12 ng.hr/mL at 10 hours, from about 1 ng.hr/mL to about 14 ng.hr/mL at 12 hours, from about 1.2 ng.hr/mL to about 16 ng.hr/mL at 14

hours, from about 1.5 ng.hr/mL to about 17 ng.hr/mL at 16 hours, from about 2 ng.hr/mL to about 17 ng.hr/mL at 20 hours, from about 2.5 ng.hr/mL to about 17 ng.hr/mL at 24 hours, from about 3 ng.hr/mL to about 17 ng.hr/mL at 28 hours, from about 4 ng.hr/mL to about 17 ng.hr/mL at 36 hours, and from about 5 ng.hr/mL to about 17 ng.hr/mL at 48 hours.

[347] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 1.5 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 2.5 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 4 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 5 ng.hr/mL at 4 hours, from about 0.005 ng.hr/mL to about 7 ng.hr/mL at 5 hours, from about 0.1 ng.hr/mL to about 9 ng.hr/mL at 6 hours, from about 0.3 ng.hr/mL to about 10 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 12 ng.hr/mL at 8 hours, from about 0.75 ng.hr/mL to about 14 ng.hr/mL at 10 hours, from about 1 ng.hr/mL to about 16 ng.hr/mL at 12 hours, from about 1.2 ng.hr/mL to about 16 ng.hr/mL at 14 hours, from about 1.5 ng.hr/mL to about 17 ng.hr/mL at 16 hours, from about 2 ng.hr/mL to about 17 ng.hr/mL at 20 hours, from about 2.5 ng.hr/mL to about 17 ng.hr/mL at 24 hours, from about 3 ng.hr/mL to about 17 ng.hr/mL at 28 hours, from about 4 ng.hr/mL to about 17 ng.hr/mL at 36 hours, and from about 5 ng.hr/mL to about 17 ng.hr/mL at 48 hours.

[348] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 2 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 4 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 6 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 8 ng.hr/mL at 4 hours, from about 0.005 ng.hr/mL to about 10 ng.hr/mL at 5 hours, from about 0.1 ng.hr/mL to about 12 ng.hr/mL at 6 hours, from about 0.3 ng.hr/mL to about 14 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 16 ng.hr/mL at 8 hours, from about 0.75 ng.hr/mL to about 16 ng.hr/mL at 10 hours, from about 1 ng.hr/mL to about 16 ng.hr/mL at 12 hours, from about 1.2 ng.hr/mL to about 16 ng.hr/mL at 14 hours, from about 1.5 ng.hr/mL to about 17 ng.hr/mL at 16 hours, from about 2 ng.hr/mL to about 17 ng.hr/mL at 20 hours, from about 2.5 ng.hr/mL to about 17 ng.hr/mL at 24 hours, from about 3

ng.hr/mL to about 17 ng.hr/mL at 28 hours, from about 4 ng.hr/mL to about 17 ng.hr/mL at 36 hours, and from about 5 ng.hr/mL to about 17 ng.hr/mL at 48 hours.

[349] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 0.01 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 0.2 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 0.9 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 1 ng.hr/mL at 4 hours, from about 0.005 ng.hr/mL to about 2 ng.hr/mL at 5 hours, from about 0.1 ng.hr/mL to about 3 ng.hr/mL at 6 hours, from about 0.3 ng.hr/mL to about 4 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 5 ng.hr/mL at 8 hours, from about 0.75 ng.hr/mL to about 7 ng.hr/mL at 10 hours, from about 1 ng.hr/mL to about 10 ng.hr/mL at 12 hours, from about 1.2 ng.hr/mL to about 12 ng.hr/mL at 14 hours, from about 1.5 ng.hr/mL to about 15 ng.hr/mL at 16 hours, from about 2 ng.hr/mL to about 16 ng.hr/mL at 20 hours, from about 2.5 ng.hr/mL to about 20 ng.hr/mL at 24 hours, from about 3 ng.hr/mL to about 26 ng.hr/mL at 28 hours, from about 4 ng.hr/mL to about 30 ng.hr/mL at 36 hours, and from about 5 ng.hr/mL to about 60 ng.hr/mL at 48 hours.

[350] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 0.02 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 0.5 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 1.8 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 3.6 ng.hr/mL at 4 hours, from about 0.005 ng.hr/mL to about 6.2 ng.hr/mL at 5 hours, from about 0.1 ng.hr/mL to about 9.3 ng.hr/mL at 6 hours, from about 0.3 ng.hr/mL to about 14 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 16 ng.hr/mL at 8 hours, from about 0.75 ng.hr/mL to about 22 ng.hr/mL at 10 hours, from about 1 ng.hr/mL to about 30 ng.hr/mL at 12 hours, from about 1.2 ng.hr/mL to about 36 ng.hr/mL at 14 hours, from about 1.5 ng.hr/mL to about 42 ng.hr/mL at 16 hours, from about 2 ng.hr/mL to about 52 ng.hr/mL at 20 hours, from about 2.5 ng.hr/mL to about 60 ng.hr/mL at 24 hours, from about 3 ng.hr/mL to about 70 ng.hr/mL at 28 hours, from about 4 ng.hr/mL to about 80 ng.hr/mL at 36 hours, and from about 5 ng.hr/mL to about 190 ng.hr/mL at 48 hours.

[351] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 0.5 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 1 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 1.5 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 5 ng.hr/mL at 4 hours, from about 0.005 ng.hr/mL to about 7 ng.hr/mL at 5 hours, from about 0.1 ng.hr/mL to about 10 ng.hr/mL at 6 hours, from about 0.3 ng.hr/mL to about 16 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 18 ng.hr/mL at 8 hours, from about 0.75 ng.hr/mL to about 22 ng.hr/mL at 10 hours, from about 1 ng.hr/mL to about 30 ng.hr/mL at 12 hours, from about 1.2 ng.hr/mL to about 36 ng.hr/mL at 14 hours, from about 1.5 ng.hr/mL to about 42 ng.hr/mL at 16 hours, from about 2 ng.hr/mL to about 52 ng.hr/mL at 20 hours, from about 2.5 ng.hr/mL to about 60 ng.hr/mL at 24 hours, from about 3 ng.hr/mL to about 70 ng.hr/mL at 28 hours, from about 4 ng.hr/mL to about 80 ng.hr/mL at 36 hours, and from about 5 ng.hr/mL to about 190 ng.hr/mL at 48 hours.

[352] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 1 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 2 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 3 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 10 ng.hr/mL at 4 hours, from about 0.005 ng.hr/mL to about 15 ng.hr/mL at 5 hours, from about 0.1 ng.hr/mL to about 20 ng.hr/mL at 6 hours, from about 0.3 ng.hr/mL to about 26 ng.hr/mL at 7 hours, from about 0.5 ng.hr/mL to about 32 ng.hr/mL at 8 hours, from about 0.75 ng.hr/mL to about 36 ng.hr/mL at 10 hours, from about 1 ng.hr/mL to about 38 ng.hr/mL at 12 hours, from about 1.2 ng.hr/mL to about 44 ng.hr/mL at 14 hours, from about 1.5 ng.hr/mL to about 46 ng.hr/mL at 16 hours, from about 2 ng.hr/mL to about 52 ng.hr/mL at 20 hours, from about 2.5 ng.hr/mL to about 60 ng.hr/mL at 24 hours, from about 3 ng.hr/mL to about 64 ng.hr/mL at 28 hours, from about 4 ng.hr/mL to about 68 ng.hr/mL at 36 hours, and from about 5 ng.hr/mL to about 70 ng.hr/mL at 48 hours.

[353] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a

controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form after first administration or single dose administration provides systemic exposure of levorphanol, for each mg of levorphanol tartrate, as assessed by the mean cumulative levorphanol area under the plasma concentration time curve (AUC) from about 0 ng.hr/mL to about 2 ng.hr/mL at 1 hour, from about 0 ng.hr/mL to about 4 ng.hr/mL at 2 hours, from about 0 ng.hr/mL to about 8 ng.hr/mL at 3 hours, from about 0 ng.hr/mL to about 12 ng.hr/mL at 4 hours, from about 0.005 ng.hr/mL to about 14 ng.hr/mL at 5 hours, from about 0.5 ng.hr/mL to about 15 ng.hr/mL at 6 hours, from about 1 ng.hr/mL to about 15.5 ng.hr/mL at 7 hours, from about 1.5 ng.hr/mL to about 15.5 ng.hr/mL at 8 hours, from about 2 ng.hr/mL to about 15.5 ng.hr/mL at 16 hours, from about 2 ng.hr/mL to about 16 ng.hr/mL at 12 hours, from about 3 ng.hr/mL to about 16 ng.hr/mL at 14 hours, from about 3 ng.hr/mL to about 16 ng.hr/mL at 16 hours, from about 5 ng.hr/mL to about 16 ng.hr/mL at 20 hours, from about 6 ng.hr/mL to about 17 ng.hr/mL at 24 hours, from about 7 ng.hr/mL to about 17 ng.hr/mL at 28 hours, from about 7.5 ng.hr/mL to about 17 ng.hr/mL at 36 hours, and from about 8 ng.hr/mL to about 17 ng.hr/mL at 48 hours.

[354] In some preferred embodiments, the dosage form of the invention provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol to treat children. In such cases, the doses provided herein may be multiplied by the ratio obtained from the child's weight in kilograms divided by 70 kilograms.

[355] **Extended Release Levorphanol Dosing**

[356] In some embodiments, the present invention discloses that the dose range required to control pain with oral levorphanol dosage forms of the invention in about 90% of subjects is less than or substantially less than with other opioids, thereby providing several potential benefits, including more efficient titration process (adjusting the subject's dosage to provide acceptable pain relief without unacceptable side effects), more therapeutically and cost efficient control of symptoms, faster control of symptoms, reduced cost of goods, reduced need for dose titration, reduced need for additional visits to the clinician, reduced need for a wider range of dosage strengths and reduced pharmacy inventory.

[357] In some embodiments, the present invention discloses that the dose range required to control pain with oral levorphanol dosage forms of the invention in about 90% of subjects is less than or substantially less than the 8-fold dose range required with morphine. In some other embodiments, said dose range of extended release oral levorphanol dosage forms of the invention is at least about 5%, 7%, 10%, 12%, 15%, 17%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70% or 75% less than for oral morphine. In some embodiments, said morphine is oral immediate release morphine. In other embodiments, said morphine is oral extended release morphine. In yet other embodiments,

said morphine is oral extended release morphine for Q12H or Q24H administration.

[358] In some embodiments, the present invention discloses that the dose range required to control pain with oral levorphanol dosage forms of the invention in about 90% of subjects is less than or substantially less than the 4-fold dose range required for oxycodone. In some embodiments, said dose range of extended release oral levorphanol dosage forms of the invention is at least about 5%, 7%, 10%, 12%, 15%, 17%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% less than for oral oxycodone. In some embodiments, said oxycodone is oral immediate release oxycodone. In other embodiments, said oxycodone is oral extended release oxycodone. In yet other embodiments, said oxycodone is oral extended release oxycodone for Q12H or Q24H administration.

[359] In some embodiments, the present invention discloses that the dose range required to control pain with oral levorphanol dosage forms of the invention in about 90% of subjects is less than or substantially less than said dose range for hydromorphone. In some embodiments, said dose range of extended release oral levorphanol dosage forms of the invention is at least about 5%, 7%, 10%, 12%, 15%, 17%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% less than for oral hydromorphone. In some embodiments, said hydromorphone is oral immediate release hydromorphone. In other embodiments, said hydromorphone is oral extended release oxycodone. In yet other embodiments, said hydromorphone is oral extended release hydromorphone for Q12H or Q24H administration.

[360] In some preferred embodiments, the dose range of extended release oral levorphanol required to control pain in about 90% of subjects is less than about 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold or 4 fold, or not more than about 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 5.5 fold, 6 fold, 6.5 fold or 7 fold.

[361] In some preferred embodiments, the daily dose range of extended release oral levorphanol tartrate required to control pain in about 90% of subjects is 4 mg to 30 mg, or 4 mg to 28 mg, or 4 mg to 26 mg, or 4 mg to 25 mg, or 4 mg to 24 mg, or 4 mg to 23 mg, or 4 mg to 22 mg, or 4 mg to 21 mg, or 4 mg to 20 mg, or 4 mg to 19 mg, or 4 mg to 18 mg, or 4 mg to 17 mg, or 4 mg to 16 mg, or 4 mg to 15 mg.

[362] In some preferred embodiments, the daily dose range of extended release oral levorphanol tartrate required to control pain in about 90% of subjects is 5 mg to 35 mg, or 5 mg to 34 mg, or 5 mg to 32 mg, or 5 mg to 30 mg, or 5 mg to 28 mg, or 5 mg to 26 mg, or 5 mg to 25 mg, or 5 mg to 24 mg, or 5 mg to 23 mg, or 5 mg to 22 mg, or 5 mg to 21 mg, or 5 mg to 20 mg,

[363] In some preferred embodiments, the daily dose range of extended release oral levorphanol tartrate required to control pain in about 90% of subjects is 6 mg to 42 mg, or 6 mg to 40 mg, or 6 mg to 38 mg, or 6 mg to 36 mg, or 6 mg to 35 mg, or 6 mg to 34 mg, or 6 mg to 32 mg, or 6 mg to 30 mg, or 6 mg to 28 mg, or 6 mg to 26 mg, or 6 mg to 25 mg, or 6 mg to 24 mg, or 6 mg to 23 mg, or 6 mg to 22 mg, or 6 mg to 21 mg, or 6 mg to 20 mg, or 6 mg to 20 mg, or 6 mg to 18 mg, or 6 mg to 16 mg, or 6 mg to 15 mg, or 6 mg to 14 mg, or 6 mg to 12 mg.

- [364] In some preferred embodiments, the daily dose range of extended release oral levorphanol tartrate required to control pain in about 90% of subjects is 7.5 mg to 52 mg, or 7.5 mg to 50 mg, or 7.5 mg to 48 mg, or 7.5 mg to 46 mg, or 7.5 mg to 44 mg, or 7.5 mg to 42 mg, or 7.5 mg to 40 mg, or 7.5 mg to 38 mg, or 7.5 mg to 36 mg, or 7.5 mg to 35 mg, or 7.5 mg to 34 mg, or 7.5 mg to 32 mg, or 7.5 mg to 30 mg, or 7.5 mg to 28 mg, or 7.5 mg to 26 mg, or 7.5 mg to 25 mg, or 7.5 mg to 22 mg, or 7.5 mg to 20 mg, or 7.5 mg to 18 mg, or 7.5 mg to 15 mg.
- [365] In some preferred embodiments, the daily dose range of extended release oral levorphanol tartrate required to control pain in about 90% of subjects is 10 mg to 72 mg, or 10 mg to 70 mg, or 10 mg to 68 mg, or 10 mg to 64 mg, or 10 mg to 62 mg, or 10 mg to 60 mg, or 10 mg to 58 mg, or 10 mg to 56 mg, or 10 mg to 50 mg, or 10 mg to 48 mg, or 10 mg to 46 mg, or 10 mg to 44 mg, or 10 mg to 42 mg, or 10 mg to 40 mg, or 10 mg to 38 mg, or 10 mg to 36 mg, or 10 mg to 35 mg, or 10 mg to 34 mg, or 10 mg to 32 mg, or 10 mg to 30 mg, or 10 mg to 28 mg, or 10 mg to 26 mg, or 10 mg to 25 mg, or 10 mg to 24 mg, or 10 mg to 22 mg, or 10 mg to 20 mg .
- [366] In certain more preferred embodiments, the oral levorphanol tartrate daily dose range required to control pain in about 90% of subjects is 5 mg to 30 mg, or 5 mg to 25 mg, or 5 mg to 20 mg, or 5 mg to 15 mg, or 5 mg to 10 mg, or 10 mg to 60 mg or 10 mg to 50 mg, or 10 mg to 40 mg, or 10 mg to 30 mg, or 10 mg to 20 mg, or 15 mg to 90 mg, or 15 mg to 80 mg or 15 mg to 75 mg, or 15 mg to 60 mg, or 15 mg to 50 mg, or 15 mg to 40 mg, or 15 mg to 30 mg.
- [367] In some preferred embodiments, the dose range of extended release oral levorphanol tartrate required to control pain in about 90% of subjects is 2.5 mg to 17 mg, or 2.5 mg to 16 mg, or 2.5 mg to 15 mg, or 2.5 mg to 14 mg, or 2.5 mg to 12 mg, or 2.5 mg to 10 mg, or 2.5 mg to 17 mg, or 2.5 mg to 9 mg, or 2.5 mg to 8 mg, each dose given every 12 hours or 22.5 hours.
- [368] In some preferred embodiments, the dose range of extended release oral levorphanol tartrate required to control pain in about 90% of subjects is 4 mg to 30 mg, or 4 mg to 28 mg, or 4 mg to 26 mg, or 4 mg to 25 mg, or 4 mg to 24 mg, or 4 mg to 23 mg, or 4 mg to 22 mg, or 4 mg to 21 mg, or 4 mg to 20 mg, or 4 mg to 19 mg, or 4 mg to 18 mg, or 4 mg to 17 mg, or 4 mg to 16 mg, or 4 mg to 15 mg, each dose given every 12 hours or 24 hours.
- [369] In some preferred embodiments, the dose range of extended release oral levorphanol tartrate required to control pain in about 90% of subjects is 5 mg to 35 mg, or 5 mg to 34 mg, or 5 mg to 32 mg, or 5 mg to 30 mg, or 5 mg to 28 mg, or 5 mg to 26 mg, or 5 mg to 25 mg, or 5 mg to 24 mg, or 5 mg to 23 mg, or 5 mg to 22 mg, or 5 mg to 21 mg, or 5 mg to 20 mg, each dose given every 12 hours or 24 hours,
- [370] In some preferred embodiments, the dose range of extended release oral levorphanol tartrate required to control pain in about 90% of subjects is 6 mg to 42 mg, or 6 mg to 40 mg, or 6 mg to 38 mg, or 6 mg to 36 mg, or 6 mg to 35 mg, or 6 mg to 34 mg, or 6 mg to 32 mg, or 6 mg to 30 mg, or 6 mg to 28 mg, or 6 mg to 26 mg, or 6 mg to 25 mg, or 6 mg to 24 mg, or 6 mg to 23 mg, or 6 mg to

22 mg, or 6 mg to 21 mg, or 6 mg to 20 mg, or 6 mg to 20 mg, or 6 mg to 18 mg, or 6 mg to 16 mg, or 6 mg to 15 mg, or 6 mg to 14 mg, or 6 mg to 12 mg, each dose given every 12 hours or 24 hours.

[371] In some preferred embodiments, the dose range of extended release oral levorphanol tartrate required to control pain in about 90% of subjects is 7.5 mg to 52 mg, or 7.5 mg to 50 mg, or 7.5 mg to 48 mg, or 7.5 mg to 46 mg, or 7.5 mg to 44 mg, or 7.5 mg to 42 mg, or 7.5 mg to 40 mg, or 7.5 mg to 38 mg, or 7.5 mg to 36 mg, or 7.5 mg to 35 mg, or 7.5 mg to 34 mg, or 7.5 mg to 32 mg, or 7.5 mg to 30 mg, or 7.5 mg to 28 mg, or 7.5 mg to 26 mg, or 7.5 mg to 25 mg, or 7.5 mg to 22 mg, or 7.5 mg to 20 mg, or 7.5 mg to 18 mg, or 7.5 mg to 15 mg, each dose given every 12 hours or 24 hours.

[372] In some preferred embodiments, the daily dose range of extended release oral levorphanol tartrate required to control pain in about 90% of subjects is 10 mg to 72 mg, or 10 mg to 70 mg, or 10 mg to 68 mg, or 10 mg to 64 mg, or 10 mg to 62 mg, or 10 mg to 60 mg, or 10 mg to 58 mg, or 10 mg to 56 mg, or 10 mg to 50 mg, or 10 mg to 48 mg, or 10 mg to 46 mg, or 10 mg to 44 mg, or 10 mg to 42 mg, or 10 mg to 40 mg, or 10 mg to 38 mg, or 10 mg to 36 mg, or 10 mg to 35 mg, or 10 mg to 34 mg, or 10 mg to 32 mg, or 10 mg to 30 mg, or 10 mg to 28 mg, or 10 mg to 26 mg, or 10 mg to 25 mg, or 10 mg to 24 mg, or 10 mg to 22 mg, or 10 mg to 20 mg, each dose given every 12 hours or 24 hours.

[373] In certain more preferred embodiments, the oral levorphanol tartrate dose range required to control pain in about 90% of subjects is 2.5 mg to 15 mg, or 5 mg to 30 mg, or 5 mg to 25 mg, or 5 mg to 20 mg, or 5 mg to 15 mg, or 5 mg to 10 mg, or 10 mg to 60 mg or 10 mg to 50 mg, or 10 mg to 40 mg, or 10 mg to 30 mg, or 10 mg to 20 mg, or 15 mg to 90 mg, or 15 mg to 80 mg or 15 mg to 75 mg, or 15 mg to 60 mg, or 15 mg to 50 mg, or 15 mg to 40 mg, or 15 mg to 30 mg, each dose given every 12 hours or 24 hours.

[374] It should be noted that while the oral levorphanol tartrate dose range or daily dose range required to control pain in about 90% of subjects in some embodiments of the invention is less than or substantially less than the 8-fold dose range seen with morphine which is the prototype opioid agonist, some patients will require doses that exceed or far exceed the dose range required to control pain in a substantial majority of subjects (e.g., 5, 10, 15 or 20 fold higher than the dose range required to control pain in about 90% of subjects), due to a variety of pharmacokinetic and pharmacodynamic factors known in the art.

[375] In some preferred embodiments, the invention provides a method for reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 2 mg to about 40 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours provides a systemic exposure of levorphanol as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to 48 hours after first

administration or single dose administration (AUC_{0-48}) of about 7 ng.hr/mL to about 715 ng.hr/mL, and a mean maximum plasma concentration of levorphanol from about 0.1 ng/mL to about 70 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[376] In some preferred embodiments, the invention provides a method for reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 2 mg to about 40 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours provides a systemic exposure of levorphanol as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to 48 hours after first administration or single dose administration (AUC_{0-48}) of about 10 ng.hr/mL to about 600 ng.hr/mL, and a mean maximum plasma concentration of levorphanol from about 0.2 ng/mL to about 50 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[377] In some preferred embodiments, the invention provides a method for reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 2 mg to about 40 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours, provides a mean maximum plasma concentration of levorphanol of about 0.1 ng/mL to about 70 ng/mL from a mean of about 3 hours to about 24 hours, and C_{12} plasma concentration of levorphanol of about 0.05 ng/mL to about 60 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[378] In some preferred embodiments, the invention provides a method for reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 2 mg to about 40 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours, provides a mean maximum plasma concentration of levorphanol of about 0.2 ng/mL to about 50 ng/mL from a mean of about 3 hours to about 24 hours, and C_{12} plasma concentration of levorphanol of about 0.1 ng/mL to about 45 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[379] In some preferred embodiments, the invention provides a method for reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 4 mg to about 80 mg of levorphanol tartrate, which after first administration or single dose administration and sequential

venous sampling to 48 hours provides a systemic exposure of levorphanol as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to 48 hours after first administration or single dose administration (AUC_{0-48}) of about 14 ng.hr/mL to about 1430 ng.hr/mL, and a mean maximum plasma concentration of levorphanol from about 0.2 ng/mL to about 70 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[380] In some preferred embodiments, the invention provides a method for reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 4 mg to about 80 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours provides a systemic exposure of levorphanol as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to 48 hours after first administration or single dose administration (AUC_{0-48}) of about 20 ng.hr/mL to about 1200 ng.hr/mL, and a mean maximum plasma concentration of levorphanol from about 0.4 ng/mL to about 50 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[381] In some preferred embodiments, the invention provides a method for reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 4 mg to about 80 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours, provides a mean maximum plasma concentration of levorphanol of about 0.2 ng/mL to about 70 ng/mL from a mean of about 3 hours to about 24 hours, and C_{12} plasma concentration of levorphanol of about 0.1 ng/mL to about 60 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[382] In some preferred embodiments, the invention provides a method for reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 4 mg to about 80 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours, provides a mean maximum plasma concentration of levorphanol of about 0.4 ng/mL to about 50 ng/mL from a mean of about 3 hours to about 24 hours, and C_{12} plasma concentration of levorphanol of about 0.2 ng/mL to about 45 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[383] In some preferred embodiments, the invention provides a method for reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an

extended release oral levorphanol dosage form comprising from about 10 mg to about 60 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours provides a systemic exposure of levorphanol as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to 48 hours after first administration or single dose administration (AUC_{0-48}) of about 20 ng.hr/mL to about 1100 ng.hr/mL, and a mean maximum plasma concentration of levorphanol from about 0.5 ng/mL to about 80 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[384] In some preferred embodiments, the invention provides a method for reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 10 mg to about 60 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours provides a systemic exposure of levorphanol as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to 48 hours after first administration or single dose administration (AUC_{0-48}) of about 30 ng.hr/mL to about 1000 ng.hr/mL, and a mean maximum plasma concentration of levorphanol from about 0.75 ng/mL to about 60 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[385] In some preferred embodiments, the invention provides a method for reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 10 mg to about 60 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours, provides a mean maximum plasma concentration of levorphanol of about 0.5 ng/mL to about 80 ng/mL from a mean of about 3 hours to about 24 hours, and C_{12} plasma concentration of levorphanol of about 0.25 ng/mL to about 75 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[386] In some preferred embodiments, the invention provides a method for reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 2 mg to about 40 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours, provides a mean maximum plasma concentration of levorphanol of about 0.75 ng/mL to about 60 ng/mL from a mean of about 3 hours to about 24 hours, and C_{12} plasma concentration of levorphanol of about 0.5 ng/mL to about 55 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

- [387] In some preferred embodiments, the invention provides a method for reducing the number of dose adjustments or dose titrations required to control pain over the first month of treatment in substantially all patients, comprising administering an extended release oral levorphanol comprising
- [388] In some preferred embodiments, the invention provides a method for reducing the number of dose adjustments or dose titrations required to control pain over the first month of treatment in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 2 mg to about 40 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours provides a systemic exposure of levorphanol as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to 48 hours after first administration or single dose administration (AUC_{0-48}) of about 7 ng.hr/mL to about 715 ng.hr/mL, and a mean maximum plasma concentration of levorphanol from about 0.1 ng/mL to about 80 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.
- [389] In some preferred embodiments, the invention provides a method for reducing the number of dose adjustments or dose titrations required to control pain over the first month of treatment in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 2 mg to about 40 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours provides a systemic exposure of levorphanol as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to 48 hours after first administration or single dose administration (AUC_{0-48}) of about 10 ng.hr/mL to about 600 ng.hr/mL, and a mean maximum plasma concentration of levorphanol from about 0.2 ng/mL to about 40 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.
- [390] In some preferred embodiments, the invention provides a method for reducing the number of dose adjustments or dose titrations required to control pain over the first month of treatment in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 2 mg to about 40 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours, provides a mean maximum plasma concentration of levorphanol of about 0.1 ng/mL to about 70 ng/mL from a mean of about 3 hours to about 24 hours, and C_{12} plasma concentration of levorphanol of about 0.05 ng/mL to about 65 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.
- [391] In some preferred embodiments, the invention provides a method for reducing the number of dose adjustments or dose titrations required to control pain over the first month of treatment in

substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 2 mg to about 40 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours, provides a mean maximum plasma concentration of levorphanol of about 0.2 ng/mL to about 50 ng/mL from a mean of about 3 hours to about 24 hours, and C_{12} plasma concentration of levorphanol of about 0.1 ng/mL to about 45 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[392] In some preferred embodiments, the invention provides a method for reducing the number of dose adjustments or dose titrations required to control pain over the first month of treatment in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 4 mg to about 80 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours provides a systemic exposure of levorphanol as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to 48 hours after first administration or single dose administration (AUC_{0-48}) of about 14 ng.hr/mL to about 1430 ng.hr/mL, and a mean maximum plasma concentration of levorphanol from about 0.2 ng/mL to about 80 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[393] In some preferred embodiments, the invention provides a method for reducing the number of dose adjustments or dose titrations required to control pain over the first month of treatment in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 4 mg to about 80 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours provides a systemic exposure of levorphanol as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to 48 hours after first administration or single dose administration (AUC_{0-48}) of about 20 ng.hr/mL to about 1200 ng.hr/mL, and a mean maximum plasma concentration of levorphanol from about 0.4 ng/mL to about 60 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[394] In some preferred embodiments, the invention provides a method for reducing the number of dose adjustments or dose titrations required to control pain over the first month of treatment in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 4 mg to about 80 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours, provides a mean maximum plasma concentration of levorphanol of about 0.2 ng/mL to about 70 ng/mL from a mean of about 3 hours to about 24 hours, and C_{12} plasma concentration of levorphanol of about 0.1

ng/mL to about 65 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[395] In some preferred embodiments, the invention provides a method for reducing the number of dose adjustments or dose titrations required to control pain over the first month of treatment in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 4 mg to about 80 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours, provides a mean maximum plasma concentration of levorphanol of about 0.4 ng/mL to about 50 ng/mL from a mean of about 3 hours to about 24 hours, and C_{12} plasma concentration of levorphanol of about 0.2 ng/mL to about 50 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[396] In some preferred embodiments, the invention provides a method for reducing the number of dose adjustments or dose titrations required to control pain over the first month of treatment in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 10 mg to about 60 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours provides a systemic exposure of levorphanol as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to 48 hours after first administration or single dose administration (AUC_{0-48}) of about 20 ng.hr/mL to about 1100 ng.hr/mL, and a mean maximum plasma concentration of levorphanol from about 0.5 ng/mL to about 45 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[397] In some preferred embodiments, the invention provides a method for reducing the number of dose adjustments or dose titrations required to control pain over the first month of treatment in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 10 mg to about 60 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours provides a systemic exposure of levorphanol as assessed by the mean levorphanol area under the plasma concentration time curve from 0 to 48 hours after first administration or single dose administration (AUC_{0-48}) of about 30 ng.hr/mL to about 1000 ng.hr/mL, and a mean maximum plasma concentration of levorphanol from about 0.75 ng/mL to about 35 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[398] In some preferred embodiments, the invention provides a method for reducing the number of dose adjustments or dose titrations required to control pain over the first month of treatment in substantially all patients, comprising administering an extended release oral levorphanol dosage

form comprising from about 10 mg to about 60 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours, provides a mean maximum plasma concentration of levorphanol of about 0.5 ng/mL to about 45 ng/mL from a mean of about 3 hours to about 24 hours, and C₁₂ plasma concentration of levorphanol of about 0.25 ng/mL to about 40 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[399] In some preferred embodiments, the invention provides a method for reducing the number of dose adjustments or dose titrations required to control pain over the first month of treatment in substantially all patients, comprising administering an extended release oral levorphanol dosage form comprising from about 2 mg to about 40 mg of levorphanol tartrate, which after first administration or single dose administration and sequential venous sampling to 48 hours, provides a mean maximum plasma concentration of levorphanol of about 0.75 ng/mL to about 25 ng/mL from a mean of about 3 hours to about 24 hours, and C₁₂ plasma concentration of levorphanol of about 0.5 ng/mL to about 23 ng/mL, said dosage form suitable for administration about every 12 hours or about every 24 hours to subjects in need of extended release oral levorphanol.

[400] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; an oral controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said dosing regimen associated with reduced side effects, improved tolerability, improved efficiency of therapeutic response, reduced breakthrough symptoms (e.g., breakthrough pain) and reduced treatment discontinuation due to side effects.

[401] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; an oral controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a levorphanol dose (expressed in mg of levorphanol tartrate) of about 2 mg to about 10 mg for about 3 to about 10 days, then about 2 mg to about 20 mg for about 3 to about 10 days, and then about 10 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 10 mg for about 4 to about 7 days, then about 10 mg to about 80 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 20 mg for about 1 to about 7 days, then about 10 mg to about 40 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 20 mg for about 4 to about 7 days, then about 10 mg to about 80 mg for about 4 to about 7 days, and then about 20 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 15 mg for about 3 to about 10 days, then about 2 mg to about 40 mg for about 3 to about 10 days, and then about 10 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about

10 mg to about 15 mg for about 4 to about 7 days, then about 20 mg to about 60 mg for about 4 to about 7 days, and then about 30 mg to 600 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 10 mg for about 3 to about 10 days, then about 10 mg to about 20 mg for about 3 to about 10 days, and then about 25 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 30 mg for about 4 to about 7 days, then about 20 mg to about 60 mg for about 4 to about 7 days, and then about 30 mg to 100 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg to about 30 mg for about 4 to about 7 days, then about 15 mg to about 30 mg for about 4 to about 7 days, and then about 20 mg to 120 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg to about 40 mg for about 4 to about 7 days, then about 20 mg to about 40 mg for about 4 to about 7 days, and then about 25 mg to 100 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg to about 20 mg for about 3 to about 10 days, then about 20 mg to about 40 mg for about 3 to about 10 days, and then about 30 mg to 120 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 10 mg for about 3 to about 10 days, then about 15 mg to about 20 mg for about 3 to about 10 days, and then about 25 mg to 120 mg for at least 1 day and optionally thereafter; or a dose of about 20 mg to about 40 mg for about 4 to about 7 days, then about 25 mg to about 60 mg for about 4 to about 7 days, and then about 65 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 30 mg to about 50 mg for about 4 to about 7 days, then about 40 mg to about 80 mg for about 4 to about 7 days, and then about 60 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 40 mg to about 80 mg for about 4 to about 7 days, then about 60 mg to about 100 mg for about 4 to about 7 days, and then about 70 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg for about 3 to about 10 days, then about 10 mg for about 3 to about 10 days, and then about 15 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg for about 3 to about 10 days, then about 15 mg for about 3 to about 10 days, and then about 20 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg for about 3 to about 10 days, then about 20 mg for about 3 to about 10 days, and then about 25 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 15 mg for about 3 to about 10 days, then about 30 mg for about 3 to about 10 days, and then about 40 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 20 mg for about 3 to about 10 days, then about 30 mg for about 3 to about 10 days, and then about 40 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 20 mg for about 3 to about 10 days, then about 40 mg for about 3 to about 10 days, and then about 50 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 20 mg for about 3 to about 10 days, then about 40 mg for about 3 to about 10 days, and then about 60 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg for about 3 to about 10 days, then about 20 mg for about 3 to about 10 days, and optionally thereafter; or a dose of about 20 mg for about 3 to about 10 days, then about 30 mg for about 3 to about 10

days, and optionally thereafter; or a dose of about 20 mg for about 3 to about 10 days, then about 40 mg for about 3 to about 10 days, and optionally thereafter; or a dose of about 30 mg for about 3 to about 10 days, then about 50 mg for about 3 to about 10 days, and optionally thereafter; or a dose of about 30 mg for about 3 to about 10 days, then about 60 mg for about 3 to about 10 days, and optionally thereafter; or a dose of about 40 mg for about 3 to about 10 days, then about 60 mg for about 3 to about 10 days, and optionally thereafter; or a dose of about 40 mg for about 3 to about 10 days, then about 80 mg for about 3 to about 10 days, and optionally thereafter; or a dose of about 50 mg for about 3 to about 10 days, then about 80 mg for about 3 to about 10 days, and optionally thereafter; or a dose of about 50 mg for about 3 to about 10 days, then about 100 mg for about 3 to about 10 days, and optionally thereafter; or a dose of about 60 mg for about 3 to about 10 days, then about 100 mg for about 3 to about 10 days, and optionally thereafter. In some embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are the total daily dose (e.g., “about 2 mg to about 10 mg for about 3 to about 10 days” is a total daily dose of about 2 mg to about 10 mg taken for about 3 to about 10 days). In some other embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are the doses (or unit doses) at individual drug administration times (e.g., “about 2 mg to about 10 mg for about 3 to about 10 days” is about 2 mg to about 10 mg at each dosing time [e.g., Q8H, or Q12H or Q24H], taken for about 3 to about 10 days). In some embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are given Q8H, Q8H PRN, Q12H, Q12H PRN, Q24H, Q24H PRN, TID, TID PRN, BID, BID PRN, QD, or QD PRN).

[402] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; an oral controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a levorphanol dose (expressed in mg of levorphanol tartrate) of about 2 mg to about 10 mg for about 5 to about 10 days, then about 2 mg to about 20 mg for about 5 to about 10 days, and then about 10 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 10 mg for about 5 to about 20 days, then about 10 mg to about 80 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 20 mg for about 2 to about 7 days, then about 10 mg to about 40 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 20 mg for about 5 to about 20 days, then about 10 mg to about 80 mg for about 5 to about 20 days, and then about 20 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 15 mg for about 5 to about 10 days, then about 2 mg to about 40 mg for about 5 to about 10 days, and then about 10 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg to about 15 mg for about 5 to about 20 days, then about 20 mg to about 60 mg for about 5 to about 20 days, and then about 30 mg to 600 mg for at least 1 day and optionally thereafter; or a dose

mg for about 5 to about 10 days, then about 50 mg for about 5 to about 10 days, and optionally thereafter; or a dose of about 30 mg for about 5 to about 10 days, then about 60 mg for about 5 to about 10 days, and optionally thereafter; or a dose of about 40 mg for about 5 to about 10 days, then about 60 mg for about 5 to about 10 days, and optionally thereafter; or a dose of about 40 mg for about 5 to about 10 days, then about 80 mg for about 5 to about 10 days, and optionally thereafter; or a dose of about 50 mg for about 5 to about 10 days, then about 80 mg for about 5 to about 10 days, and optionally thereafter; or a dose of about 50 mg for about 5 to about 10 days, then about 100 mg for about 5 to about 10 days, and optionally thereafter; or a dose of about 60 mg for about 5 to about 10 days, then about 100 mg for about 5 to about 10 days, and optionally thereafter. In some embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are the total daily dose (e.g., “about 2 mg to about 10 mg for about 3 to about 10 days” is a total daily dose of about 2 mg to about 10 mg taken for about 3 to about 10 days). In some other embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are the doses (or unit doses) at individual drug administration times (e.g., “about 2 mg to about 10 mg for about 3 to about 10 days” is about 2 mg to about 10 mg at each dosing time [e.g., Q8H, or Q12H or Q24H], taken for about 3 to about 10 days). In some embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are given Q8H, Q8H PRN, Q12H, Q12H PRN, Q24H, Q24H PRN, TID, TID PRN, BID, BID PRN, QD, or QD PRN).

In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; an oral controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a levorphanol dose (expressed in mg of levorphanol tartrate) of about 2 mg to about 10 mg for about 1 to about 7 days, then about 2 mg to about 20 mg for about 1 to about 7 days, and then about 10 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 10 mg for about 1 to about 7 days, then about 10 mg to about 80 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 20 mg for about 1 to about 7 days, then about 10 mg to about 40 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 20 mg for about 1 to about 7 days, then about 10 mg to about 80 mg for about 1 to about 7 days, and then about 20 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 15 mg for about 1 to about 7 days, then about 2 mg to about 40 mg for about 1 to about 7 days, and then about 10 mg to 200 mg for at least 1 day and optionally thereafter; or about 2 mg to about 20 mg for about 1 to about 7 days, then about 10 mg to about 120 mg for about 1 to about 7 days, and then about 40 mg to 180 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 80 mg for about 1 to about 7 days, then about 10 mg to about 120 mg for about 1 to about 7 days, and then about 20 mg to 180 mg for at least 1 day and optionally thereafter; or a dose of about

mg for at least 1 day and optionally thereafter; or a dose of about 20 mg for about 1 to about 7 days, then about 30 mg for about 1 to about 7 days, and then about 40 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 20 mg for about 1 to about 7 days, then about 40 mg for about 1 to about 7 days, and then about 50 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 20 mg for about 1 to about 7 days, then about 40 mg for about 1 to about 7 days, and then about 60 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg for about 1 to about 7 days, then about 20 mg for about 1 to about 7 days, and optionally thereafter; or a dose of about 20 mg for about 1 to about 7 days, then about 30 mg for about 1 to about 7 days, and optionally thereafter; or a dose of about 20 mg for about 1 to about 7 days, then about 40 mg for about 1 to about 7 days, and optionally thereafter; or a dose of about 30 mg for about 1 to about 7 days, then about 50 mg for about 1 to about 7 days, and optionally thereafter; or a dose of about 30 mg for about 1 to about 7 days, then about 60 mg for about 1 to about 7 days, and optionally thereafter; or a dose of about 40 mg for about 1 to about 7 days, then about 60 mg for about 1 to about 7 days, and optionally thereafter; or a dose of about 40 mg for about 1 to about 7 days, then about 80 mg for about 1 to about 7 days, and optionally thereafter; or a dose of about 50 mg for about 1 to about 7 days, then about 80 mg for about 1 to about 7 days, and optionally thereafter; or a dose of about 50 mg for about 1 to about 7 days, then about 100 mg for about 1 to about 7 days, and optionally thereafter; or a dose of about 60 mg for about 1 to about 7 days, then about 100 mg for about 1 to about 7 days, and optionally thereafter. In some embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are the total daily dose (e.g., “about 2 mg to about 10 mg for about 1 to about 7 days” is a total daily dose of about 2 mg to about 10 mg taken for about 1 to about 7 days). In some other embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are the doses (or unit doses) at individual drug administration times (e.g., “about 2 mg to about 10 mg for about 1 to about 7 days” is about 2 mg to about 10 mg at each dosing time [e.g., Q8H, or Q12H or Q24H], taken for about 1 to about 7 days). In some embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are given Q8H, Q8H PRN, Q12H, Q12H PRN, Q24H, Q24H PRN, TID, TID PRN, BID, BID PRN, QD, or QD PRN).

[403] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; an oral controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a levorphanol dose (expressed in mg of levorphanol tartrate) of about 2 mg to about 10 mg for about 1 to about 10 days, then about 2 mg to about 20 mg for about 1 to about 10 days, and then about 10 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 10 mg for about 1 to about 10 days, then about 10 mg to about 80 mg for at least 1 day and

optionally thereafter; or a dose of about 2 mg to about 20 mg for about 1 to about 10 days, then about 10 mg to about 40 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 20 mg for about 1 to about 10 days, then about 10 mg to about 80 mg for about 1 to about 10 days, and then about 20 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 15 mg for about 1 to about 10 days, then about 2 mg to about 40 mg for about 1 to about 10 days, and then about 10 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg to about 15 mg for about 1 to about 10 days, then about 20 mg to about 60 mg for about 1 to about 10 days, and then about 30 mg to 600 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 10 mg for about 1 to about 10 days, then about 10 mg to about 20 mg for about 1 to about 10 days, and then about 25 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 30 mg for about 1 to about 10 days, then about 20 mg to about 60 mg for about 1 to about 10 days, and then about 30 mg to 100 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg to about 30 mg for about 1 to about 10 days, then about 15 mg to about 30 mg for about 1 to about 10 days, and then about 20 mg to 120 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg to about 40 mg for about 1 to about 10 days, then about 20 mg to about 40 mg for about 1 to about 10 days, and then about 25 mg to 100 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg to about 20 mg for about 1 to about 10 days, then about 20 mg to about 40 mg for about 1 to about 10 days, and then about 30 mg to 120 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 10 mg for about 1 to about 10 days, then about 15 mg to about 20 mg for about 1 to about 10 days, and then about 25 mg to 120 mg for at least 1 day and optionally thereafter; or a dose of about 20 mg to about 40 mg for about 1 to about 10 days, then about 25 mg to about 60 mg for about 1 to about 10 days, and then about 65 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 30 mg to about 50 mg for about 1 to about 10 days, then about 40 mg to about 80 mg for about 1 to about 10 days, and then about 60 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 40 mg to about 80 mg for about 1 to about 10 days, then about 60 mg to about 100 mg for about 1 to about 10 days, and then about 70 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg for about 1 to about 10 days, then about 10 mg for about 1 to about 10 days, and then about 15 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg for about 1 to about 10 days, then about 15 mg for about 1 to about 10 days, and then about 20 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg for about 1 to about 10 days, then about 20 mg for about 1 to about 10 days, and then about 25 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 15 mg for about 1 to about 10 days, then about 30 mg for about 1 to about 10 days, and then about 40 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 20 mg for about 1 to about 10 days, then about 30 mg for about 1 to about 10 days, and then about 40 mg to

150 mg for at least 1 day and optionally thereafter; or a dose of about 20 mg for about 1 to about 10 days, then about 40 mg for about 1 to about 10 days, and then about 50 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 20 mg for about 1 to about 10 days, then about 40 mg for about 1 to about 10 days, and then about 60 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg for about 1 to about 10 days, then about 20 mg for about 1 to about 10 days, and optionally thereafter; or a dose of about 20 mg for about 1 to about 10 days, then about 30 mg for about 1 to about 10 days, and optionally thereafter; or a dose of about 20 mg for about 1 to about 10 days, then about 40 mg for about 1 to about 10 days, and optionally thereafter; or a dose of about 30 mg for about 1 to about 10 days, then about 50 mg for about 1 to about 10 days, and optionally thereafter; or a dose of about 30 mg for about 1 to about 10 days, then about 60 mg for about 1 to about 10 days, and optionally thereafter; or a dose of about 40 mg for about 1 to about 10 days, then about 60 mg for about 1 to about 10 days, and optionally thereafter; or a dose of about 40 mg for about 1 to about 10 days, then about 80 mg for about 1 to about 10 days, and optionally thereafter; or a dose of about 50 mg for about 1 to about 10 days, then about 80 mg for about 1 to about 10 days, and optionally thereafter; or a dose of about 50 mg for about 1 to about 10 days, then about 100 mg for about 1 to about 10 days, and optionally thereafter; or a dose of about 60 mg for about 1 to about 10 days, then about 100 mg for about 1 to about 10 days, and optionally thereafter. In some embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are the total daily dose (e.g., “about 2 mg to about 10 mg for about 1 to about 10 days” is a total daily dose of about 2 mg to about 10 mg taken for about 1 to about 10 days). In some other embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are the doses (or unit doses) at individual drug administration times (e.g., “about 2 mg to about 10 mg for about 1 to about 10 days” is about 2 mg to about 10 mg at each dosing time [e.g., Q8H, or Q12H or Q24H], taken for about 1 to about 10 days). In some embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are given Q8H, Q8H PRN, Q12H, Q12H PRN, Q24H, Q24H PRN, TID, TID PRN, BID, BID PRN, QD, or QD PRN).

[404] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; an oral controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a levorphanol dose (expressed in mg of levorphanol tartrate) of about 2 mg to about 10 mg for about 5 to about 40 days, then about 2 mg to about 20 mg for about 5 to about 40 days, and then about 10 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 10 mg for about 5 to about 40 days, then about 10 mg to about 80 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 20 mg for about 5 to about 40 days, then about 10 mg to about 40 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to

about 20 mg for about 5 to about 40 days, then about 10 mg to about 80 mg for about 5 to about 40 days, and then about 20 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 15 mg for about 5 to about 40 days, then about 2 mg to about 40 mg for about 5 to about 40 days, and then about 10 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg to about 15 mg for about 5 to about 40 days, then about 20 mg to about 60 mg for about 5 to about 40 days, and then about 30 mg to 600 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 10 mg for about 5 to about 40 days, then about 10 mg to about 20 mg for about 5 to about 40 days, and then about 25 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 30 mg for about 5 to about 40 days, then about 20 mg to about 60 mg for about 5 to about 40 days, and then about 30 mg to 100 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg to about 30 mg for about 5 to about 40 days, then about 15 mg to about 30 mg for about 5 to about 40 days, and then about 20 mg to 120 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg to about 40 mg for about 5 to about 40 days, then about 20 mg to about 40 mg for about 5 to about 40 days, and then about 25 mg to 100 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg to about 20 mg for about 5 to about 40 days, then about 20 mg to about 40 mg for about 5 to about 40 days, and then about 30 mg to 120 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg to about 10 mg for about 5 to about 40 days, then about 15 mg to about 20 mg for about 5 to about 40 days, and then about 25 mg to 120 mg for at least 1 day and optionally thereafter; or a dose of about 20 mg to about 40 mg for about 5 to about 40 days, then about 25 mg to about 60 mg for about 5 to about 40 days, and then about 65 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 30 mg to about 50 mg for about 5 to about 40 days, then about 40 mg to about 80 mg for about 5 to about 40 days, and then about 60 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 40 mg to about 80 mg for about 5 to about 40 days, then about 60 mg to about 100 mg for about 5 to about 40 days, and then about 70 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 2 mg for about 5 to about 40 days, then about 10 mg for about 5 to about 40 days, and then about 15 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg for about 5 to about 40 days, then about 15 mg for about 5 to about 40 days, and then about 20 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg for about 5 to about 40 days, then about 20 mg for about 5 to about 40 days, and then about 25 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 15 mg for about 5 to about 40 days, then about 30 mg for about 5 to about 40 days, and then about 40 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 20 mg for about 5 to about 40 days, then about 30 mg for about 5 to about 40 days, and then about 40 mg to 150 mg for at least 1 day and optionally thereafter; or a dose of about 20 mg for about 5 to about 40 days, then about 40 mg for about 5 to about 40 days, and then about 50 mg to 150 mg for at least 1

day and optionally thereafter; or a dose of about 20 mg for about 5 to about 40 days, then about 40 mg for about 5 to about 40 days, and then about 60 mg to 200 mg for at least 1 day and optionally thereafter; or a dose of about 10 mg for about 5 to about 40 days, then about 20 mg for about 5 to about 40 days, and optionally thereafter; or a dose of about 20 mg for about 5 to about 40 days, then about 30 mg for about 5 to about 40 days, and optionally thereafter; or a dose of about 20 mg for about 5 to about 40 days, then about 40 mg for about 5 to about 40 days, and optionally thereafter; or a dose of about 30 mg for about 5 to about 40 days, then about 50 mg for about 5 to about 40 days, and optionally thereafter; or a dose of about 30 mg for about 5 to about 40 days, then about 60 mg for about 5 to about 40 days, and optionally thereafter; or a dose of about 40 mg for about 5 to about 40 days, then about 60 mg for about 5 to about 40 days, and optionally thereafter; or a dose of about 40 mg for about 5 to about 40 days, then about 80 mg for about 5 to about 40 days, and optionally thereafter; or a dose of about 50 mg for about 5 to about 40 days, then about 80 mg for about 5 to about 40 days, and optionally thereafter; or a dose of about 50 mg for about 5 to about 40 days, then about 100 mg for about 5 to about 40 days, and optionally thereafter; or a dose of about 60 mg for about 5 to about 40 days, then about 100 mg for about 5 to about 40 days, and optionally thereafter. In some embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are the total daily dose (e.g., “about 2 mg to about 10 mg for about 5 to about 40 days” is a total daily dose of about 2 mg to about 10 mg taken for about 5 to about 40 days). In some other embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are the doses (or unit doses) at individual drug administration times (e.g., “about 2 mg to about 10 mg for about 5 to about 40 days” is about 2 mg to about 10 mg at each dosing time [e.g., Q8H, or Q12H or Q24H], taken for about 5 to about 40 days). In some embodiments, the foregoing doses and dose ranges of said prespecified dosing regimens are given Q8H, Q8H PRN, Q12H, Q12H PRN, Q24H, Q24H PRN, TID, TID PRN, BID, BID PRN, QD, or QD PRN).

[405] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; optionally; said dosage form intended to treat pediatric patients; said dosage form administered at a prespecified dosing regimen; said dosing regimen providing a mean levorphanol area under the plasma concentration time curve (AUC) as provided herein, except that the AUC is multiplied by the ratio obtained from the child's weight in kilograms divided by 70 kilograms.

[406] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; an oral controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose which provides a mean levorphanol area under the plasma concentration time curve to 24 hours post-dose (AUC₀₋₂₄) of about 2 ng.hr/mL to about 200 ng.hr/mL for about 4 to

700 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 180 ng.hr/mL for about 4 to about 10 days, then about 20 ng.hr/mL to about 240 ng.hr/mL for about 4 to about 10 days, and then about 40 ng.hr/mL to about 800 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 150 ng.hr/mL for about 4 to about 10 days, then about 20 ng.hr/mL to about 240 ng.hr/mL for about 4 to about 10 days, and then about 20 ng.hr/mL to about 600 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 120 ng.hr/mL for about 4 to about 10 days, then about 20 ng.hr/mL to about 200 ng.hr/mL for about 4 to about 10 days, and then about 30 ng.hr/mL to about 500 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 120 ng.hr/mL for about 4 to about 10 days, then about 30 ng.hr/mL to about 150 ng.hr/mL for about 4 to about 10 days, and then about 40 ng.hr/mL to about 400 ng.hr/mL for at least 1 day and optionally thereafter; or about 15 ng.hr/mL to about 60 ng.hr/mL for about 4 to about 10 days, then about 20 ng.hr/mL to about 100 ng.hr/mL for about 4 to about 10 days, and then about 30 ng.hr/mL to about 500 ng.hr/mL for at least 1 day and optionally thereafter; or about 15 ng.hr/mL to about 100 ng.hr/mL for about 4 to about 10 days, then about 30 ng.hr/mL to about 150 ng.hr/mL for about 4 to about 10 days, and then about 40 ng.hr/mL to about 650 ng.hr/mL for at least 1 day and optionally thereafter; or about 20 ng.hr/mL to about 60 ng.hr/mL for about 4 to about 10 days, then about 30 ng.hr/mL to about 200 ng.hr/mL for about 4 to about 10 days, and then about 40 ng.hr/mL to about 700 ng.hr/mL for at least 1 day and optionally thereafter; or about 20 ng.hr/mL to about 150 ng.hr/mL for about 4 to about 10 days, then about 30 ng.hr/mL to about 200 ng.hr/mL for about 4 to about 10 days, and then about 40 ng.hr/mL to about 600 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 80 ng.hr/mL for about 4 to about 10 days, then about 15 ng.hr/mL to about 200 ng.hr/mL for about 4 to about 10 days, and then about 20 ng.hr/mL to about 700 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 100 ng.hr/mL for about 4 to about 10 days, then about 15 ng.hr/mL to about 200 ng.hr/mL for about 4 to about 10 days, and then about 20 ng.hr/mL to about 800 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 120 ng.hr/mL for about 4 to about 10 days, then about 40 ng.hr/mL to about 180 ng.hr/mL for about 4 to about 10 days, and then about 40 ng.hr/mL to about 600 ng.hr/mL for at least 1 day and optionally thereafter; or about 20 ng.hr/mL to about 120 ng.hr/mL for about 4 to about 10 days, then about 40 ng.hr/mL to about 180 ng.hr/mL for about 4 to about 10 days, and then about 40 ng.hr/mL to about 640 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 150 ng.hr/mL for about 4 to about 10 days, then about 15 ng.hr/mL to about 180 ng.hr/mL for about 4 to about 10 days, and then about 20 ng.hr/mL to about 900 ng.hr/mL for at least 1 day and optionally thereafter.

[407] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; an oral

controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose which provides a mean levorphanol area under the plasma concentration time curve to 24 hours post-dose (AUC_{0-24}) of about 2 ng.hr/mL to about 200 ng.hr/mL for about 1 to about 7 days, then about 10 ng.hr/mL to about 400 ng.hr/mL for at least 1 day and optionally thereafter; or about 2 ng.hr/mL to about 400 ng.hr/mL for about 1 to about 7 days, then about 20 ng.hr/mL to about 600 ng.hr/mL for at least 1 day and optionally thereafter; or about 5 ng.hr/mL to about 200 ng.hr/mL for about 1 to about 7 days, then about 10 ng.hr/mL to about 400 ng.hr/mL for at least 1 day and optionally thereafter; or about 5 ng.hr/mL to about 200 ng.hr/mL for about 1 to about 7 days, then about 10 ng.hr/mL to about 600 ng.hr/mL for at least 1 day and optionally thereafter; or about 5 ng.hr/mL to about 400 ng.hr/mL for about 1 to about 7 days, then about 20 ng.hr/mL to about 600 ng.hr/mL for at least 1 day and optionally thereafter; or about 5 ng.hr/mL to about 600 ng.hr/mL for about 1 to about 7 days, then about 40 ng.hr/mL to about 600 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 200 ng.hr/mL for about 1 to about 7 days, then about 20 ng.hr/mL to about 600 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 150 ng.hr/mL for about 1 to about 7 days, then about 20 ng.hr/mL to about 200 ng.hr/mL for at least 1 day and optionally thereafter; or about 5 ng.hr/mL to about 120 ng.hr/mL for about 1 to about 7 days, then about 20 ng.hr/mL to about 400 ng.hr/mL for at least 1 day and optionally thereafter; about 5 ng.hr/mL to about 100 ng.hr/mL for about 1 to about 7 days, then about 30 ng.hr/mL to about 500 ng.hr/mL for at least 1 day and optionally thereafter; or about 5 ng.hr/mL to about 150 ng.hr/mL for about 1 to about 7 days, then about 20 ng.hr/mL to about 250 ng.hr/mL for at least 1 day and optionally thereafter; or about 2 ng.hr/mL to about 180 ng.hr/mL for about 1 to about 7 days, then about 15 ng.hr/mL to about 350 ng.hr/mL for at least 1 day and optionally thereafter; or about 7 ng.hr/mL to about 150 ng.hr/mL for about 1 to about 7 days, then about 20 ng.hr/mL to about 500 ng.hr/mL for at least 1 day and optionally thereafter; or about 2 ng.hr/mL to about 120 ng.hr/mL for about 1 to about 7 days, then about 40 ng.hr/mL to about 650 ng.hr/mL for at least 1 day and optionally thereafter; or about 5 ng.hr/mL to about 80 ng.hr/mL for about 1 to about 7 days, then about 20 ng.hr/mL to about 200 ng.hr/mL for at least 1 day and optionally thereafter; or about 5 ng.hr/mL to about 140 ng.hr/mL for about 1 to about 7 days, then about 40 ng.hr/mL to about 350 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 200 ng.hr/mL for about 1 to about 7 days, then about 20 ng.hr/mL to about 500 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 150 ng.hr/mL for about 1 to about 7 days, then about 30 ng.hr/mL to about 250 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 150 ng.hr/mL for about 1 to about 7 days, then about 40 ng.hr/mL to about 450 ng.hr/mL for at least 1 day and optionally thereafter; or about 10 ng.hr/mL to about 140 ng.hr/mL for about 1 to about 7 days, then about 25

about 30 days, and then about 20 ng.hr/mL to about 900 ng.hr/mL for at least 1 day and optionally thereafter.

[408] In some preferred embodiments, the oral pharmaceutical composition is used on a time contingent basis, a scheduled basis or around the clock.

[409] In some preferred embodiments, the oral pharmaceutical composition is used on an as needed or PRN basis.

[410] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 to 4 mg for 1 to 7 days, followed by about 3 to 7 mg for a subsequent period of 1 to 7 days, followed by > about 8 mg for the duration of treatment; or about 2 to 4 mg for 1 to 7 days, followed by about 4 to 9 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 to 5 mg for 1 to 7 days, followed by about 3 to 7 mg for a subsequent period of 1 to 7 days, followed by > about 8 mg for the duration of treatment; or about 2 to 5 mg for 1 to 7 days, followed by about 4 to 9 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 to 10 mg for 1 to 7 days, followed by about 5 to 10 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 4 to 10 mg for 1 to 7 days, followed by about 5 to 10 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 5 to 10 mg for 1 to 7 days, followed by about 6 to 15 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 5 to 10 mg for 1 to 7 days, followed by about 8 to 20 mg for a subsequent period of 1 to 7 days, followed by > about 15 mg for the duration of treatment; or about 5 to 10 mg for 1 to 7 days, followed by about 10 to 20 mg for a subsequent period of 1 to 7 days, followed by > about 20 mg for the duration of treatment; or about 2 to 4 mg for 1 to 7 days, followed by about 5 to 10 mg for a subsequent period of 1 to 7 days, followed by > about 9 mg for the duration of treatment; or about 2 to 4 mg for 1 to 7 days, followed by about 5 to 10 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 to 5 mg for 1 to 7 days, followed by about 6 to 10 mg for a subsequent period of 1 to 7 days, followed by > about 9 mg for the duration of treatment; or about 2 to 5 mg for 1 to 7 days, followed by about 6 to 10 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 4 to 10 mg for 1 to 7 days, followed by about 11 to 20 mg for a subsequent period of 1 to 7 days, followed by > about 14 mg for the duration of treatment; or about 2 to 5 mg for 1 to 7 days, followed by about 10 to 20 mg for a subsequent period of 1 to 7 days,

followed by > about 10 mg for the duration of treatment; or about 2 to 5 mg for 1 to 7 days, followed by about 11 to 20 mg for a subsequent period of 1 to 7 days, followed by > about 12 mg for the duration of treatment; or about 5 to 10 mg for 1 to 7 days, followed by about 11 to 20 mg for a subsequent period of 1 to 7 days, followed by > about 11 mg for the duration of treatment; or about 5 to 10 mg for 1 to 7 days, followed by about 11 to 20 mg for a subsequent period of 1 to 7 days, followed by > about 20 mg for the duration of treatment; or about 4 to 6 mg for 1 to 7 days, followed by about 7 to 15 mg for a subsequent period of 1 to 7 days, followed by > about 8 mg for the duration of treatment; or about 4 to 6 mg for 1 to 7 days, followed by about 10 to 15 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for the duration of treatment. In some preferred embodiments, the foregoing dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimens are administered every 24 hours or once-a-day.

[411] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 mg for 1 to 7 days, followed by about 5 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 mg for 1 to 7 days, followed by about 5 mg for a subsequent period of 1 to 7 days, followed by > about 15 mg for the duration of treatment; or about 2 mg for 1 to 7 days, followed by about 10 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 mg for 1 to 7 days, followed by about 10 mg for a subsequent period of 1 to 7 days, followed by > about 15 mg for the duration of treatment; or about 4 mg for 1 to 7 days, followed by about 6 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 4 mg for 1 to 7 days, followed by about 8 mg for a subsequent period of 1 to 7 days, followed by > about 8 mg for the duration of treatment; or about 4 mg for 1 to 7 days, followed by about 8 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 4 mg for 1 to 7 days, followed by about 10 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 4 mg for 1 to 7 days, followed by about 10 mg for a subsequent period of 1 to 7 days, followed by > about 11 mg for the duration of treatment; or about 4 mg for 1 to 7 days, followed by about 10 mg for a subsequent period of 1 to 7 days, followed by > about 15 mg for the duration of treatment; or about 2.5 mg for 1 to 7 days, followed by about 5 mg for a subsequent period of 1 to 7

> about 30 mg for the duration of treatment; or about 2 to 4 mg for 1 to 7 days, followed by > about 5 mg for the duration of treatment; or about 2 to 4 mg for 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 to 4 mg for 1 to 7 days, followed by > about 15 mg for the duration of treatment; or about 2 to 5 mg for 1 to 7 days, followed by > about 5 mg for the duration of treatment; or about 2 to 5 mg for 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 to 5 mg for 1 to 7 days, followed by > about 15 mg for the duration of treatment; or about 2 to 10 mg for 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 to 10 mg for 1 to 7 days, followed by > about 15 mg for the duration of treatment; or about 5 to 10 mg for 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 5 to 10 mg for 1 to 7 days, followed by > about 15 mg for the duration of treatment; or about 5 to 10 mg for 1 to 7 days, followed by > about 20 mg for the duration of treatment; or about 2 to 15 mg for 1 to 7 days, followed by > about 15 mg for the duration of treatment; or about 2 to 15 mg for 1 to 7 days, followed by > about 20 mg for the duration of treatment; or about 5 to 15 mg for 1 to 7 days, followed by > about 15 mg for the duration of treatment; or about 5 to 15 mg for 1 to 7 days, followed by > about 20 mg for the duration of treatment; or about 10 to 20 mg for 1 to 7 days, followed by > about 20 mg for the duration of treatment; or about 2.5 mg for 1 to 7 days, followed by > about 5 mg for the duration of treatment; or about 2.5 mg for 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 5 mg for 1 to 7 days, followed by > about 5 mg for the duration of treatment; or about 5 mg for 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 5 mg for 1 to 7 days, followed by > about 15 mg for the duration of treatment; or about 5 mg for 1 to 7 days, followed by > about 20 mg for the duration of treatment; or about 7.5 mg for 1 to 7 days, followed by > about 7.5 mg for the duration of treatment; or about 7.5 mg for 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 7.5 mg for 1 to 7 days, followed by > about 15 mg for the duration of treatment; or about 7.5 mg for 1 to 7 days, followed by > about 20 mg for the duration of treatment; or about 10 mg for 1 to 7 days, followed by > about 10 mg for the duration of treatment; or about 10 mg for 1 to 7 days, followed by > about 12 mg for the duration of treatment; or about 10 mg for 1 to 7 days, followed by > about 15 mg for the duration of treatment; or about 10 mg for 1 to 7 days, followed by > about 20 mg for the duration of treatment. In some preferred embodiments, the foregoing dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimens are administered every 24 hours or once-a-day.

[412] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol

disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 to 4 mg for 4 to 7 days, followed by about 3 to 7 mg for a subsequent period of 4 to 7 days, followed by > about 8 mg for the duration of treatment; or about 2 to 4 mg for 4 to 7 days, followed by about 4 to 9 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 to 5 mg for 4 to 7 days, followed by about 3 to 7 mg for a subsequent period of 4 to 7 days, followed by > about 8 mg for the duration of treatment; or about 2 to 5 mg for 4 to 7 days, followed by about 4 to 9 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 to 10 mg for 4 to 7 days, followed by about 5 to 10 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 4 to 10 mg for 4 to 7 days, followed by about 5 to 10 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 5 to 10 mg for 4 to 7 days, followed by about 6 to 15 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 5 to 10 mg for 4 to 7 days, followed by about 8 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 15 mg for the duration of treatment; or about 5 to 10 mg for 4 to 7 days, followed by about 10 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 20 mg for the duration of treatment; or about 2 to 4 mg for 4 to 7 days, followed by about 5 to 10 mg for a subsequent period of 4 to 7 days, followed by > about 9 mg for the duration of treatment; or about 2 to 4 mg for 4 to 7 days, followed by about 5 to 10 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 to 5 mg for 4 to 7 days, followed by about 6 to 10 mg for a subsequent period of 4 to 7 days, followed by > about 9 mg for the duration of treatment; or about 2 to 5 mg for 4 to 7 days, followed by about 6 to 10 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 4 to 10 mg for 4 to 7 days, followed by about 11 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 14 mg for the duration of treatment; or about 2 to 5 mg for 4 to 7 days, followed by about 10 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 to 5 mg for 4 to 7 days, followed by about 11 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 12 mg for the duration of treatment; or about 5 to 10 mg for 4 to 7 days, followed by about 11 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 11 mg for the duration of treatment; or about 5 to 10 mg for 4 to 7 days, followed by about 11 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 20 mg for the duration of treatment; or about 4 to 6 mg for 4 to 7 days, followed by about 7 to 15 mg for a subsequent period of 4 to 7 days, followed by > about 8 mg for the duration of treatment; or about 4 to 6 mg for 4 to 7 days, followed by about 10 to 15 mg for a

subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment. In some preferred embodiments, the foregoing dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimens are administered every 24 hours or once-a-day.

[413] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 mg for 4 to 7 days, followed by about 5 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 mg for 4 to 7 days, followed by about 5 mg for a subsequent period of 4 to 7 days, followed by > about 15 mg for the duration of treatment; or about 2 mg for 4 to 7 days, followed by about 10 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2 mg for 4 to 7 days, followed by about 10 mg for a subsequent period of 4 to 7 days, followed by > about 15 mg for the duration of treatment; or about 4 mg for 4 to 7 days, followed by about 6 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 4 mg for 4 to 7 days, followed by about 8 mg for a subsequent period of 4 to 7 days, followed by > about 8 mg for the duration of treatment; or about 4 mg for 4 to 7 days, followed by about 8 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 4 mg for 4 to 7 days, followed by about 10 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 4 mg for 4 to 7 days, followed by about 10 mg for a subsequent period of 4 to 7 days, followed by > about 11 mg for the duration of treatment; or about 4 mg for 4 to 7 days, followed by about 10 mg for a subsequent period of 4 to 7 days, followed by > about 15 mg for the duration of treatment; or about 2.5 mg for 4 to 7 days, followed by about 5 mg for a subsequent period of 4 to 7 days, followed by > about 5 mg for the duration of treatment; or about 2.5 mg for 4 to 7 days, followed by about 5 mg for a subsequent period of 4 to 7 days, followed by > about 7.5 mg for the duration of treatment; or about 2.5 mg for 4 to 7 days, followed by about 5 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2.5 mg for 4 to 7 days, followed by about 5 mg for a subsequent period of 4 to 7 days, followed by > about 15 mg for the duration of treatment; or about 2 mg for 4 to 7 days, followed by about 5 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 2.5 mg for 4 to 7 days, followed by about 10 mg for a subsequent period of 4 to 7 days, followed by

treatment; or about 5 to 10 mg for 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 5 to 10 mg for 4 to 7 days, followed by > about 15 mg for the duration of treatment; or about 5 to 10 mg for 4 to 7 days, followed by > about 20 mg for the duration of treatment; or about 2 to 15 mg for 4 to 7 days, followed by > about 15 mg for the duration of treatment; or about 2 to 15 mg for 4 to 7 days, followed by > about 20 mg for the duration of treatment; or about 5 to 15 mg for 4 to 7 days, followed by > about 15 mg for the duration of treatment; or about 5 to 15 mg for 4 to 7 days, followed by > about 20 mg for the duration of treatment; or about 10 to 20 mg for 4 to 7 days, followed by > about 20 mg for the duration of treatment; or about 2.5 mg for 4 to 7 days, followed by > about 5 mg for the duration of treatment; or about 2.5 mg for 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 5 mg for 4 to 7 days, followed by > about 5 mg for the duration of treatment; or about 5 mg for 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 5 mg for 4 to 7 days, followed by > about 15 mg for the duration of treatment; or about 5 mg for 4 to 7 days, followed by > about 20 mg for the duration of treatment; or about 7.5 mg for 4 to 7 days, followed by > about 7.5 mg for the duration of treatment; or about 7.5 mg for 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 7.5 mg for 4 to 7 days, followed by > about 15 mg for the duration of treatment; or about 7.5 mg for 4 to 7 days, followed by > about 20 mg for the duration of treatment; or about 10 mg for 4 to 7 days, followed by > about 10 mg for the duration of treatment; or about 10 mg for 4 to 7 days, followed by > about 12 mg for the duration of treatment; or about 10 mg for 4 to 7 days, followed by > about 15 mg for the duration of treatment; or about 10 mg for 4 to 7 days, followed by > about 20 mg for the duration of treatment. In some preferred embodiments, the foregoing dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimens are administered every 24 hours or once-a-day.

[414] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 to 4 mg for 1 to 30 days, followed by about 3 to 7 mg for a subsequent period of 1 to 30 days, followed by > about 8 mg for the duration of treatment; or about 2 to 4 mg for 1 to 30 days, followed by about 4 to 9 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2 to 5 mg for 1 to 30 days, followed by about 3 to 7 mg for a subsequent period

of 1 to 30 days, followed by > about 8 mg for the duration of treatment; or about 2 to 5 mg for 1 to 30 days, followed by about 4 to 9 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2 to 10 mg for 1 to 30 days, followed by about 5 to 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 4 to 10 mg for 1 to 30 days, followed by about 5 to 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 5 to 10 mg for 1 to 30 days, followed by about 6 to 15 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 5 to 10 mg for 1 to 30 days, followed by about 8 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 15 mg for the duration of treatment; or about 5 to 10 mg for 1 to 30 days, followed by about 10 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 20 mg for the duration of treatment; or about 2 to 4 mg for 1 to 30 days, followed by about 5 to 10 mg for a subsequent period of 1 to 30 days, followed by > about 9 mg for the duration of treatment; or about 2 to 4 mg for 1 to 30 days, followed by about 5 to 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2 to 5 mg for 1 to 30 days, followed by about 6 to 10 mg for a subsequent period of 1 to 30 days, followed by > about 9 mg for the duration of treatment; or about 2 to 5 mg for 1 to 30 days, followed by about 6 to 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 4 to 10 mg for 1 to 30 days, followed by about 11 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 14 mg for the duration of treatment; or about 2 to 5 mg for 1 to 30 days, followed by about 10 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2 to 5 mg for 1 to 30 days, followed by about 11 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 12 mg for the duration of treatment; or about 5 to 10 mg for 1 to 30 days, followed by about 11 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 11 mg for the duration of treatment; or about 5 to 10 mg for 1 to 30 days, followed by about 11 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 20 mg for the duration of treatment; or about 4 to 6 mg for 1 to 30 days, followed by about 7 to 15 mg for a subsequent period of 1 to 30 days, followed by > about 8 mg for the duration of treatment; or about 4 to 6 mg for 1 to 30 days, followed by about 10 to 15 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment. In some preferred embodiments, the foregoing dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimens are administered every 24 hours or once-a-day.

[415] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol

disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 15 mg for the duration of treatment; or about 2 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 15 mg for the duration of treatment; or about 4 mg for 1 to 30 days, followed by about 6 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 4 mg for 1 to 30 days, followed by about 8 mg for a subsequent period of 1 to 30 days, followed by > about 8 mg for the duration of treatment; or about 4 mg for 1 to 30 days, followed by about 8 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 4 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 4 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 11 mg for the duration of treatment; or about 4 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 15 mg for the duration of treatment; or about 2.5 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 5 mg for the duration of treatment; or about 2.5 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 7.5 mg for the duration of treatment; or about 2.5 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2.5 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 15 mg for the duration of treatment; or about 2 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2.5 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2.5 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 11 mg for the duration of treatment; or about 5 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 5 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 11 mg for the duration of treatment; or about 5 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 15 mg for the duration of treatment; or about 5 mg for 1 to 30 days, followed by about 10 mg for a subsequent

followed by > about 20 mg for the duration of treatment; or about 10 to 20 mg for 1 to 30 days, followed by > about 20 mg for the duration of treatment; or about 2.5 mg for 1 to 30 days, followed by > about 5 mg for the duration of treatment; or about 2.5 mg for 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 5 mg for 1 to 30 days, followed by > about 5 mg for the duration of treatment; or about 5 mg for 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 5 mg for 1 to 30 days, followed by > about 15 mg for the duration of treatment; or about 5 mg for 1 to 30 days, followed by > about 20 mg for the duration of treatment; or about 7.5 mg for 1 to 30 days, followed by > about 7.5 mg for the duration of treatment; or about 7.5 mg for 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 7.5 mg for 1 to 30 days, followed by > about 15 mg for the duration of treatment; or about 7.5 mg for 1 to 30 days, followed by > about 20 mg for the duration of treatment; or about 10 mg for 1 to 30 days, followed by > about 10 mg for the duration of treatment; or about 10 mg for 1 to 30 days, followed by > about 12 mg for the duration of treatment; or about 10 mg for 1 to 30 days, followed by > about 15 mg for the duration of treatment; or about 10 mg for 1 to 30 days, followed by > about 20 mg for the duration of treatment. In some preferred embodiments, the foregoing dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimens are administered every 24 hours or once-a-day.

[416] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 to 4 mg for 7 to 30 days, followed by about 3 to 7 mg for a subsequent period of 7 to 30 days, followed by > about 8 mg for the duration of treatment; or about 2 to 4 mg for 7 to 30 days, followed by about 4 to 9 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2 to 5 mg for 7 to 30 days, followed by about 3 to 7 mg for a subsequent period of 7 to 30 days, followed by > about 8 mg for the duration of treatment; or about 2 to 5 mg for 7 to 30 days, followed by about 4 to 9 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2 to 10 mg for 7 to 30 days, followed by about 5 to 10 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for the duration of treatment; or about 4 to 10 mg for 7 to 30 days, followed by about 5 to 10 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for the duration of treatment; or about 5 to 10 mg for 7 to 30 days, followed by about 6 to 15 mg for a subsequent period of 7 to 30 days, followed by

> about 10 mg for the duration of treatment; or about 5 to 10 mg for 7 to 30 days, followed by about 8 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 15 mg for the duration of treatment; or about 5 to 10 mg for 7 to 30 days, followed by about 10 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 20 mg for the duration of treatment; or about 2 to 4 mg for 7 to 30 days, followed by about 5 to 10 mg for a subsequent period of 7 to 30 days, followed by > about 9 mg for the duration of treatment; or about 2 to 4 mg for 7 to 30 days, followed by about 5 to 10 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2 to 5 mg for 7 to 30 days, followed by about 6 to 10 mg for a subsequent period of 7 to 30 days, followed by > about 9 mg for the duration of treatment; or about 2 to 5 mg for 7 to 30 days, followed by about 6 to 10 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for the duration of treatment; or about 4 to 10 mg for 7 to 30 days, followed by about 11 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 14 mg for the duration of treatment; or about 2 to 5 mg for 7 to 30 days, followed by about 10 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2 to 5 mg for 7 to 30 days, followed by about 11 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 12 mg for the duration of treatment; or about 5 to 10 mg for 7 to 30 days, followed by about 11 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 11 mg for the duration of treatment; or about 5 to 10 mg for 7 to 30 days, followed by about 11 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 20 mg for the duration of treatment; or about 4 to 6 mg for 7 to 30 days, followed by about 7 to 15 mg for a subsequent period of 7 to 30 days, followed by > about 8 mg for the duration of treatment; or about 4 to 6 mg for 7 to 30 days, followed by about 10 to 15 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for the duration of treatment. In some preferred embodiments, the foregoing dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimens are administered every 24 hours or once-a-day.

[417] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 mg for 7 to 30 days, followed by about 5 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for the duration of treatment; or about 2 mg for 7 to 30 days, followed by about 5 mg for a subsequent period of 7 to 30 days, followed by > about 15 mg for the duration of treatment; or

or about 7.5 mg for 7 to 30 days, followed by > about 7.5 mg for the duration of treatment; or about 7.5 mg for 7 to 30 days, followed by > about 10 mg for the duration of treatment; or about 7.5 mg for 7 to 30 days, followed by > about 15 mg for the duration of treatment; or about 7.5 mg for 7 to 30 days, followed by > about 20 mg for the duration of treatment; or about 10 mg for 7 to 30 days, followed by > about 10 mg for the duration of treatment; or about 10 mg for 7 to 30 days, followed by > about 12 mg for the duration of treatment; or about 10 mg for 7 to 30 days, followed by > about 15 mg for the duration of treatment; or about 10 mg for 7 to 30 days, followed by > about 20 mg for the duration of treatment. In some preferred embodiments, the foregoing dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimens are administered every 24 hours or once-a-day.

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2 to 5 mg for 1 to 7 days, followed by about 6 to 10 mg for a subsequent period of 1 to 7 days, followed by > about 9 mg for at least one day thereafter; or about 2 to 5 mg for 1 to 7 days, followed by about 6 to 10 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 4 to 10 mg for 1 to 7 days, followed by about 11 to 20 mg for a subsequent period of 1 to 7 days, followed by > about 14 mg for at least one day thereafter; or about 2 to 5 mg for 1 to 7 days, followed by about 10 to 20 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 5 mg for 1 to 7 days, followed by about 11 to 20 mg for a subsequent period of 1 to 7 days, followed by > about 12 mg for at least one day thereafter; or about 5 to 10 mg for 1 to 7 days, followed by about 11 to 20 mg for a subsequent period of 1 to 7 days, followed by > about 11 mg for at least one day thereafter; or about 5 to 10 mg for 1 to 7 days, followed by about 11 to 20 mg for a subsequent period of 1 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 4 to 6 mg for 1 to 7 days, followed by about 7 to 15 mg for a subsequent period of 1 to 7 days, followed by > about 8 mg for at least one day thereafter; or about 4 to 6 mg for 1 to 7 days, followed by about 10 to 15 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for at least one day thereafter. In some preferred embodiments, the foregoing dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimen is administered every 24 hours or once-a-day.

[419] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 mg for 1 to 7 days, followed by about 5 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 mg for 1 to 7 days, followed by about 5 mg for a subsequent period of 1 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 2 mg for 1 to 7 days, followed by about 10 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 mg for 1 to 7 days, followed by about 10 mg for a subsequent period of 1 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 4 mg for 1 to 7 days, followed by about 6 mg for a subsequent period of 1 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 4 mg for 1 to 7 days, followed by about 8 mg for a subsequent period of 1 to 7 days, followed by > about 8 mg for at least one day thereafter; or about 4 mg for 1 to 7 days, followed by about 8 mg for a subsequent period of 1 to 7 days, followed

> about 20 mg for at least one day thereafter; or about 10 mg for 1 to 7 days, followed by about 15 mg for a subsequent period of 1 to 7 days, followed by > about 25 mg for at least one day thereafter; or about 10 mg for 1 to 7 days, followed by about 15 mg for a subsequent period of 1 to 7 days, followed by > about 30 mg for at least one day thereafter; or about 10 mg for 1 to 7 days, followed by about 20 mg for a subsequent period of 1 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 10 mg for 1 to 7 days, followed by about 20 mg for a subsequent period of 1 to 7 days, followed by > about 30 mg for at least one day thereafter; or about 2 to 4 mg for 1 to 7 days, followed by > about 5 mg for at least one day thereafter; or about 2 to 4 mg for 1 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 4 mg for 1 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 2 to 5 mg for 1 to 7 days, followed by > about 5 mg for at least one day thereafter; or about 2 to 5 mg for 1 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 5 mg for 1 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 2 to 10 mg for 1 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 10 mg for 1 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 5 to 10 mg for 1 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 5 to 10 mg for 1 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 5 to 10 mg for 1 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 2 to 15 mg for 1 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 2 to 15 mg for 1 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 5 to 15 mg for 1 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 5 to 15 mg for 1 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 10 to 20 mg for 1 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 2.5 mg for 1 to 7 days, followed by > about 5 mg for at least one day thereafter; or about 2.5 mg for 1 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 5 mg for 1 to 7 days, followed by > about 5 mg for at least one day thereafter; or about 5 mg for 1 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 5 mg for 1 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 5 mg for 1 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 7.5 mg for 1 to 7 days, followed by > about 7.5 mg for at least one day thereafter; or about 7.5 mg for 1 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 7.5 mg for 1 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 7.5 mg for 1 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 10 mg for 1 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 10 mg for 1 to 7 days, followed by > about 12 mg for at least one day thereafter; or about 10 mg for 1 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 10 mg for 1 to 7 days, followed by > about 20 mg for at least one day thereafter. In some preferred embodiments, the foregoing dosing regimen is

associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimen is administered every 24 hours or once-a-day.

[420] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 to 4 mg for 4 to 7 days, followed by about 3 to 7 mg for a subsequent period of 4 to 7 days, followed by > about 8 mg for at least one day thereafter; or about 2 to 4 mg for 4 to 7 days, followed by about 4 to 9 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 5 mg for 4 to 7 days, followed by about 3 to 7 mg for a subsequent period of 4 to 7 days, followed by > about 8 mg for at least one day thereafter; or about 2 to 5 mg for 4 to 7 days, followed by about 4 to 9 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 10 mg for 4 to 7 days, followed by about 5 to 10 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 4 to 10 mg for 4 to 7 days, followed by about 5 to 10 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 5 to 10 mg for 4 to 7 days, followed by about 6 to 15 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 5 to 10 mg for 4 to 7 days, followed by about 8 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 5 to 10 mg for 4 to 7 days, followed by about 10 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 2 to 4 mg for 4 to 7 days, followed by about 5 to 10 mg for a subsequent period of 4 to 7 days, followed by > about 9 mg for at least one day thereafter; or about 2 to 4 mg for 4 to 7 days, followed by about 5 to 10 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 5 mg for 4 to 7 days, followed by about 6 to 10 mg for a subsequent period of 4 to 7 days, followed by > about 9 mg for at least one day thereafter; or about 2 to 5 mg for 4 to 7 days, followed by about 6 to 10 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 4 to 10 mg for 4 to 7 days, followed by about 11 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 14 mg for at least one day thereafter; or about 2 to 5 mg for 4 to 7 days, followed by about 10 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 5 mg for 4 to 7 days, followed by about 11 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 12 mg

for at least one day thereafter; or about 5 to 10 mg for 4 to 7 days, followed by about 11 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 11 mg for at least one day thereafter; or about 5 to 10 mg for 4 to 7 days, followed by about 11 to 20 mg for a subsequent period of 4 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 4 to 6 mg for 4 to 7 days, followed by about 7 to 15 mg for a subsequent period of 4 to 7 days, followed by > about 8 mg for at least one day thereafter; or about 4 to 6 mg for 4 to 7 days, followed by about 10 to 15 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter. In some preferred embodiments, the foregoing dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimens are administered every 24 hours or once-a-day.

[421] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 mg for 4 to 7 days, followed by about 5 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 mg for 4 to 7 days, followed by about 5 mg for a subsequent period of 4 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 2 mg for 4 to 7 days, followed by about 10 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 mg for 4 to 7 days, followed by about 10 mg for a subsequent period of 4 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 4 mg for 4 to 7 days, followed by about 6 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 4 mg for 4 to 7 days, followed by about 8 mg for a subsequent period of 4 to 7 days, followed by > about 8 mg for at least one day thereafter; or about 4 mg for 4 to 7 days, followed by about 8 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 4 mg for 4 to 7 days, followed by about 10 mg for a subsequent period of 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 4 mg for 4 to 7 days, followed by about 10 mg for a subsequent period of 4 to 7 days, followed by > about 11 mg for at least one day thereafter; or about 4 mg for 4 to 7 days, followed by about 10 mg for a subsequent period of 4 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 2.5 mg for 4 to 7 days, followed by about 5 mg for a subsequent period of 4 to 7 days, followed by > about 5 mg for at least one day thereafter; or about 2.5 mg for 4 to 7 days, followed by about 5 mg for a subsequent period of 4 to 7 days, followed by > about 7.5

7 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 4 mg for 4 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 2 to 5 mg for 4 to 7 days, followed by > about 5 mg for at least one day thereafter; or about 2 to 5 mg for 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 5 mg for 4 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 2 to 10 mg for 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 10 mg for 4 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 5 to 10 mg for 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 5 to 10 mg for 4 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 5 to 10 mg for 4 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 2 to 15 mg for 4 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 2 to 15 mg for 4 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 5 to 15 mg for 4 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 5 to 15 mg for 4 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 10 to 20 mg for 4 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 2.5 mg for 4 to 7 days, followed by > about 5 mg for at least one day thereafter; or about 2.5 mg for 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 5 mg for 4 to 7 days, followed by > about 5 mg for at least one day thereafter; or about 5 mg for 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 5 mg for 4 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 5 mg for 4 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 7.5 mg for 4 to 7 days, followed by > about 7.5 mg for at least one day thereafter; or about 7.5 mg for 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 7.5 mg for 4 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 7.5 mg for 4 to 7 days, followed by > about 20 mg for at least one day thereafter; or about 10 mg for 4 to 7 days, followed by > about 10 mg for at least one day thereafter; or about 10 mg for 4 to 7 days, followed by > about 12 mg for at least one day thereafter; or about 10 mg for 4 to 7 days, followed by > about 15 mg for at least one day thereafter; or about 10 mg for 4 to 7 days, followed by > about 20 mg for at least one day thereafter. In some preferred embodiments, the foregoing dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimens are administered every 24 hours or once-a-day.

[422] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said

dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 to 4 mg for 1 to 30 days, followed by about 3 to 7 mg for a subsequent period of 1 to 30 days, followed by > about 8 mg for at least one day thereafter; or about 2 to 4 mg for 1 to 30 days, followed by about 4 to 9 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 5 mg for 1 to 30 days, followed by about 3 to 7 mg for a subsequent period of 1 to 30 days, followed by > about 8 mg for at least one day thereafter; or about 2 to 5 mg for 1 to 30 days, followed by about 4 to 9 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 10 mg for 1 to 30 days, followed by about 5 to 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 4 to 10 mg for 1 to 30 days, followed by about 5 to 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 5 to 10 mg for 1 to 30 days, followed by about 6 to 15 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 5 to 10 mg for 1 to 30 days, followed by about 8 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 5 to 10 mg for 1 to 30 days, followed by about 10 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 20 mg for at least one day thereafter; or about 2 to 4 mg for 1 to 30 days, followed by about 5 to 10 mg for a subsequent period of 1 to 30 days, followed by > about 9 mg for at least one day thereafter; or about 2 to 4 mg for 1 to 30 days, followed by about 5 to 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 5 mg for 1 to 30 days, followed by about 6 to 10 mg for a subsequent period of 1 to 30 days, followed by > about 9 mg for at least one day thereafter; or about 2 to 5 mg for 1 to 30 days, followed by about 6 to 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 4 to 10 mg for 1 to 30 days, followed by about 11 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 14 mg for at least one day thereafter; or about 2 to 5 mg for 1 to 30 days, followed by about 10 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 5 mg for 1 to 30 days, followed by about 11 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 12 mg for at least one day thereafter; or about 5 to 10 mg for 1 to 30 days, followed by about 11 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 11 mg for at least one day thereafter; or about 5 to 10 mg for 1 to 30 days, followed by about 11 to 20 mg for a subsequent period of 1 to 30 days, followed by > about 20 mg for at least one day thereafter; or about 4 to 6 mg for 1 to 30 days, followed by about 7 to 15 mg for a subsequent period of 1 to 30 days, followed by > about 8 mg for at least one day thereafter; or about 4 to 6 mg for 1 to 30 days, followed by about 10 to 15 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter. In some preferred embodiments, the foregoing

dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimens are administered every 24 hours or once-a-day.

[423] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 2 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 4 mg for 1 to 30 days, followed by about 6 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 4 mg for 1 to 30 days, followed by about 8 mg for a subsequent period of 1 to 30 days, followed by > about 8 mg for at least one day thereafter; or about 4 mg for 1 to 30 days, followed by about 8 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 4 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 4 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 11 mg for at least one day thereafter; or about 4 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 2.5 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 5 mg for at least one day thereafter; or about 2.5 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 7.5 mg for at least one day thereafter; or about 2.5 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2.5 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 2 mg for 1 to 30 days, followed by about 5 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2.5 mg for 1 to 30 days, followed by about 10 mg for a subsequent period of 1 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2.5 mg for 1 to 30 days, followed by about 10 mg for a subsequent

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of 7 to 30 days, followed by > about 8 mg for at least one day thereafter; or about 2 to 5 mg for 7 to 30 days, followed by about 4 to 9 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 10 mg for 7 to 30 days, followed by about 5 to 10 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 4 to 10 mg for 7 to 30 days, followed by about 5 to 10 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 5 to 10 mg for 7 to 30 days, followed by about 6 to 15 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 5 to 10 mg for 7 to 30 days, followed by about 8 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 5 to 10 mg for 7 to 30 days, followed by about 10 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 20 mg for at least one day thereafter; or about 2 to 4 mg for 7 to 30 days, followed by about 5 to 10 mg for a subsequent period of 7 to 30 days, followed by > about 9 mg for at least one day thereafter; or about 2 to 4 mg for 7 to 30 days, followed by about 5 to 10 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 5 mg for 7 to 30 days, followed by about 6 to 10 mg for a subsequent period of 7 to 30 days, followed by > about 9 mg for at least one day thereafter; or about 2 to 5 mg for 7 to 30 days, followed by about 6 to 10 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 4 to 10 mg for 7 to 30 days, followed by about 11 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 14 mg for at least one day thereafter; or about 2 to 5 mg for 7 to 30 days, followed by about 10 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2 to 5 mg for 7 to 30 days, followed by about 11 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 12 mg for at least one day thereafter; or about 5 to 10 mg for 7 to 30 days, followed by about 11 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 11 mg for at least one day thereafter; or about 5 to 10 mg for 7 to 30 days, followed by about 11 to 20 mg for a subsequent period of 7 to 30 days, followed by > about 20 mg for at least one day thereafter; or about 4 to 6 mg for 7 to 30 days, followed by about 7 to 15 mg for a subsequent period of 7 to 30 days, followed by > about 8 mg for at least one day thereafter; or about 4 to 6 mg for 7 to 30 days, followed by about 10 to 15 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter. In some preferred embodiments, the foregoing dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimens are administered every 24 hours or once-a-day.

[425] In some preferred embodiments, the invention comprises an oral extended release pharmaceutical composition and method for the treatment of subjects in need of levorphanol

disorders comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; a controlled release material to render said dosage form suitable for extended release in a human patient; said dosage form administered at a prespecified dosing regimen; said regimen comprising administering a dose of about 2 mg for 7 to 30 days, followed by about 5 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2 mg for 7 to 30 days, followed by about 5 mg for a subsequent period of 7 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 2 mg for 7 to 30 days, followed by about 10 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2 mg for 7 to 30 days, followed by about 10 mg for a subsequent period of 7 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 4 mg for 7 to 30 days, followed by about 6 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 4 mg for 7 to 30 days, followed by about 8 mg for a subsequent period of 7 to 30 days, followed by > about 8 mg for at least one day thereafter; or about 4 mg for 7 to 30 days, followed by about 8 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 4 mg for 7 to 30 days, followed by about 10 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 4 mg for 7 to 30 days, followed by about 10 mg for a subsequent period of 7 to 30 days, followed by > about 11 mg for at least one day thereafter; or about 4 mg for 7 to 30 days, followed by about 10 mg for a subsequent period of 7 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 2.5 mg for 7 to 30 days, followed by about 5 mg for a subsequent period of 7 to 30 days, followed by > about 5 mg for at least one day thereafter; or about 2.5 mg for 7 to 30 days, followed by about 5 mg for a subsequent period of 7 to 30 days, followed by > about 7.5 mg for at least one day thereafter; or about 2.5 mg for 7 to 30 days, followed by about 5 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2.5 mg for 7 to 30 days, followed by about 5 mg for a subsequent period of 7 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 2 mg for 7 to 30 days, followed by about 5 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2.5 mg for 7 to 30 days, followed by about 10 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 2.5 mg for 7 to 30 days, followed by about 10 mg for a subsequent period of 7 to 30 days, followed by > about 11 mg for at least one day thereafter; or about 5 mg for 7 to 30 days, followed by about 10 mg for a subsequent period of 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 5 mg for 7 to 30 days, followed by about 10 mg for a subsequent period of 7 to 30 days, followed by > about 11 mg for at least one day thereafter; or about 5 mg for 7 to 30 days, followed by about 10 mg for a subsequent period of 7 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 5 mg for 7 to 30 days, followed

days, followed by > about 20 mg for at least one day thereafter; or about 10 to 20 mg for 7 to 30 days, followed by > about 20 mg for at least one day thereafter; or about 2.5 mg for 7 to 30 days, followed by > about 5 mg for at least one day thereafter; or about 2.5 mg for 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 5 mg for 7 to 30 days, followed by > about 5 mg for at least one day thereafter; or about 5 mg for 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 5 mg for 7 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 5 mg for 7 to 30 days, followed by > about 20 mg for at least one day thereafter; or about 7.5 mg for 7 to 30 days, followed by > about 7.5 mg for at least one day thereafter; or about 7.5 mg for 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 7.5 mg for 7 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 7.5 mg for 7 to 30 days, followed by > about 20 mg for at least one day thereafter; or about 10 mg for 7 to 30 days, followed by > about 10 mg for at least one day thereafter; or about 10 mg for 7 to 30 days, followed by > about 12 mg for at least one day thereafter; or about 10 mg for 7 to 30 days, followed by > about 15 mg for at least one day thereafter; or about 10 mg for 7 to 30 days, followed by > about 20 mg for at least one day thereafter. In some preferred embodiments, the foregoing dosing regimen is associated with reduced side effects, improved tolerability and reduced treatment discontinuation due to side effects. In some preferred embodiments, the foregoing dosing regimens are administered every 12 hours or twice-a-day. In other preferred embodiments, the foregoing dosing regimens are administered every 24 hours or once-a-day.

[426] Extended Release Levorphanol Dissolution Rate

[427] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form providing an in-vitro release rate by weight of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C from 0% to about 20% at 1 hour, from about 10% to about 40% at 4 hours, from about 10% to about 50% at 6 hours, from about 20% to about 60% at 9 hours, from about 45% to about 75% at 17 hours, from about 45% to about 80% at 21 hours, from about 50% to about 85% at 25 hours, from about 55% to about 90% at 29 hours, from about 55% to about 95% at 33 hours, from about 60% to about 100% at 41 hours, and from about 65% to about 100% at 45 hours; or from 0% to about 40% at 4 hours, from about 10% to about 60% at 9 hours, from about 30% to about 80% at 17 hours, from about 30% to about 85% at 21 hours, from about 40% to about 95% at 17 hours, from about 45% to about 95% at 25 hours, from about 50% to about 95% at 32 hours, from about 55% to about 95% at 41 hours, and from about 60% to about 98% at 45 hours; or from 0% to about 50% at 4

hours, from about 10% to about 90% at 8 hours, from about 20% to about 95% at 17 hours, from about 25% to about 95% at 25 hours, from about 30% to about 95% at 32 hours, from about 35% to about 100% at 45 hours; or from 2% to about 50% at 4 hours, from about 10% to about 70% at 8 hours, from about 30% to about 85% at 17 hours, from about 30% to about 90% at 24 hours, from about 50% to about 95% at 33 hours and greater than 60% at 45 hours; or from about 2% to about 40% at 4 hours, from about 5% to about 50% at 8 hours, from about 20% to about 85% at 16 hours, from about 25% to about 90% at 20 hours, from about 30% to about 95% at 24 hours, from about 50% to about 98% at 25 hours, and greater than 65% at 32 hours; or from about 5% to about 60% at 8 hours, from about 20% to about 80% at 16 hours, from about 25% to about 95% at 24 hours, from about 40% to about 95% at 32 hours, greater than about 60% at 40 hours, and greater than about 70% at 48 hours; or from 0% to about 10% at 1 hour, from about 5% to about 20% at 4 hours, from about 15% to about 50% at 8 hours, from about 30% to about 70% at 16 hours, from about 40% to about 90% at 24 hours, greater than about 60% at 32 hours, and greater than about 75% at 48 hours; or from 0% to about 20% at 2 hour, from about 15% to about 45% at 5 hours, from about 20% to about 60% at 8 hours, from about 40% to about 80% at 14 hours, from about 50% to about 95% at 18 hours, from about 60% to about 100% at 24 hours, and greater than 65% at 32 hours; or from 10% to about 60% at 5 hour, from about 15% to about 90% at 8 hours, from about 20% to about 100% at 18 hours, from about 30% to about 100% at 24 hours; or from 0% to about 20% at 2 hour, from about 10% to about 35% at 4 hours, from about 50% to about 75% at 8 hours, from about 65% to about 95% at 17 hours, from about 80% to about 100% at 21 hours, and greater than 85% at 24 hours; or about 0% to about 40% at 2 hour, from about 5% to about 60% at 4 hours, from about 10% to about 80% at 8 hours, from about 30% to about 100% at 17 hours, from about 50% to about 100% at 21 hours, from about 60% to about 100% at 24 hours, from about 70% to about 100% at 32 hours, and from about 75% to about 100% at 45 hours; or about 0% to about 40% at 2 hour, from about 5% to about 60% at 4 hours, from about 10% to about 80% at 8 hours, from about 30% to about 100% at 16 hours, greater than about 50% at 21 hours, greater than about 60% at 21 hours, greater than about 70% at 24 hours, greater than about 80% at 32 hours, and greater than about 90% at 45 hours; or not more than 70% at 24 hours; or not more than 75% at 24 hours; or not more than 80% at 24 hours; or less than 80% at 32 hours; or less than 85% at 32 hours; or less than 90% at 32 hours; or less than 90% at 45 hours; or less than 95% at 45 hours.

[428] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material to render said dosage form extended release suitable for administration up to once-a-day or up to once every 24 hours (e.g., every 12 hours or every 24 hours); said dosage form providing an in-vitro release rate by weight of levorphanol, when measured by the USP Paddle Method with a sinker at 75 rpm in 600 ml of Simulated Intestinal Fluid (SIF) USP, without the

inclusion of enzyme, at a pH of 6.8 at 37 °C from 0% to about 20% at 1 hour, from about 10% to about 40% at 4 hours, from about 10% to about 50% at 6 hours, from about 20% to about 60% at 9 hours, from about 45% to about 75% at 17 hours, from about 45% to about 80% at 21 hours, from about 50% to about 85% at 25 hours, from about 55% to about 90% at 29 hours, from about 55% to about 95% at 33 hours, from about 60% to about 100% at 41 hours, and from about 65% to about 100% at 45 hours; or from 0% to about 40% at 4 hours, from about 10% to about 60% at 9 hours, from about 30% to about 80% at 17 hours, from about 30% to about 85% at 21 hours, from about 40% to about 95% at 17 hours, from about 45% to about 95% at 25 hours, from about 50% to about 95% at 32 hours, from about 55% to about 95% at 41 hours, and from about 60% to about 98% at 45 hours; or from 0% to about 50% at 4 hours, from about 10% to about 90% at 8 hours, from about 20% to about 95% at 17 hours, from about 25% to about 95% at 25 hours, from about 30% to about 95% at 32 hours, from about 35% to about 100% at 45 hours; or from 2% to about 50% at 4 hours, from about 10% to about 70% at 8 hours, from about 30% to about 85% at 17 hours, from about 30% to about 90% at 24 hours, from about 50% to about 95% at 33 hours and greater than 60% at 45 hours; or from about 2% to about 40% at 4 hours, from about 5% to about 50% at 8 hours, from about 20% to about 85% at 16 hours, from about 25% to about 90% at 20 hours, from about 30% to about 95% at 24 hours, from about 50% to about 98% at 25 hours, and greater than 65% at 32 hours; or from about 5% to about 60% at 8 hours, from about 20% to about 80% at 16 hours, from about 25% to about 95% at 24 hours, from about 40% to about 95% at 32 hours, greater than about 60% at 40 hours, and greater than about 70% at 48 hours; or from 0% to about 10% at 1 hour, from about 5% to about 20% at 4 hours, from about 15% to about 50% at 8 hours, from about 30% to about 70% at 16 hours, from about 40% to about 90% at 24 hours, greater than about 60% at 32 hours, and greater than about 75% at 48 hours; or from 0% to about 20% at 2 hour, from about 15% to about 45% at 5 hours, from about 20% to about 60% at 8 hours, from about 40% to about 80% at 14 hours, from about 50% to about 95% at 18 hours, from about 60% to about 100% at 24 hours, and greater than 65% at 32 hours; or from 10% to about 60% at 5 hour, from about 15% to about 90% at 8 hours, from about 20% to about 100% at 18 hours, from about 30% to about 100% at 24 hours; or from 0% to about 20% at 2 hour, from about 10% to about 35% at 4 hours, from about 50% to about 75% at 8 hours, from about 65% to about 95% at 17 hours, from about 80% to about 100% at 21 hours, and greater than 85% at 24 hours; or about 0% to about 40% at 2 hour, from about 5% to about 60% at 4 hours, from about 10% to about 80% at 8 hours, from about 30% to about 100% at 17 hours, from about 50% to about 100% at 21 hours, from about 60% to about 100% at 24 hours, from about 70% to about 100% at 32 hours, and from about 75% to about 100% at 45 hours; or about 0% to about 40% at 2 hour, from about 5% to about 60% at 4 hours, from about 10% to about 80% at 8 hours, from about 30% to about 100% at 16 hours, greater than about 50% at 21 hours, greater than about 60% at 21 hours, greater than about 70% at 24 hours, greater

than about 80% at 32 hours, and greater than about 90% at 45 hours; or not more than 70% at 24 hours; or not more than 75% at 24 hours; or not more than 80% at 24 hours; or less than 80% at 32 hours; or less than 85% at 32 hours; or less than 90% at 32 hours; or less than 90% at 45 hours; or less than 95% at 45 hours.

[429] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition for the treatment of a levorphanol responsive medical condition comprising a therapeutically effective amount of levorphanol, and a controlled release material; said dosage form providing an in-vitro release rate by weight of levorphanol, when measured by the USP Basket and Paddle Methods at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C of: (1) between 0% to about 47.5% at 1 hour, between about 10% to about 65% at 2 hours, between about 15% to about 70% at 4 hours, between about 25% to about 77.5% at 6 hours, between about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours; or (2) between about 10% to about 65% at 4 hours, between about 20% to about 70% at 8 hours, between about 25% to about 80% at 12 hours, between about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours; or (3) between 0% to about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 3% and about 95% at 4 hours and between about 10% and about 100% at 8 hours; or (4) between about 10% and about 65% at 1 hour, between about 20% and about 75% at 2 hours, between about 30% and about 95% at 4 hours and between about 40% and about 100% at 8 hours; or (5) between about 10% to about 65% at 2 hours, between about 15% to about 70% at 4 hours, between about 25% to about 77.5% at 6 hours, between about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours; or (6) between about 5% and about 50% at 1 hour, between about 10% and about 75% at 2 hours, between about 20% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, greater than about 50% at 12 hours, greater than about 70% at 18 hours, and greater than about 80% at 24 hours; or (7) between about 5% and about 50% at 1 hour, between about 10% and about 75% at 2 hours, between about 20% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, greater than about 50% at 12 hours, greater than about 70% at 18 hours, and greater than about 80% at 24 hours; or (8) between 0% to about 30% at 1 hour, between about 10% to about 65% at 4 hours, between about 20% to about 70% at 8 hours, between about 25% to about 80% at 12 hours, between about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours; or (9) between 0% to about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 3% and about 95% at 4 hours, between about 10% and about 100% at 8 hours, between about 25% and about 100% at 12 hours, between about 30% and about 100% at 16 hours, between about 50% and about 100% at 24 hours, and greater than about 80% at 36 hours; or (10) between about 20% and about 50% at 1 hour, between about 40% and about 75% at 2 hours, between about 60% and about 95% at 4 hours, between about 80% and about 100% at 8 hours and between about 90% and about 100% at 12 hours; or (11) between 0% to about

50% at 1 hour, between about 0% and about 75% at 2 hours, between about 10% and about 95% at 4 hours, between about 35% and about 100% at 8 hours, between about 55% and about 100% at 12 hours, between about 70% to about 100% at 16 hours, and greater than about 90% at 24 hours; or (12) between 0% to about 30% at 1 hour, between about 0% and about 45% at 2 hours, between about 3% and about 55% at 4 hours, between about 10% and about 65% at 8 hours, between about 20% and about 75% at 12 hours, between about 30% to about 88% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours; or (13) between 0% to about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 3% and about 95% at 4 hours, between about 10% and about 100% at 8 hours, between about 20% and about 100% at 12 hours, between about 30% to about 100% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours; or (14) between about 15% and about 25% at 1 hour, between about 25% and about 35% at 2 hours, between about 30% and about 45% at 4 hours, between about 40% and about 60% at 8 hours, between about 55% and about 70% at 12 hours and between about 60% to about 75% at 16 hours; or (15) between 0% to about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 3% and about 95% at 4 hours and between about 10% and about 100% at 8 hours; or (16) between 0% and about 10% at 1 hour, between about 0% and about 20% at 2 hours, between about 2% and about 80% at 4 hours and between about 5% and about 100% at 8 hours; or (17) between 0% and about 20% at 1 hour, between about 0% and about 40% at 2 hours, between about 0% and about 80% at 4 hours and between about 2% and about 100% at 8 hours; or (18) between 0% and about 40% at 1 hour, between about 0% and about 60% at 2 hours, between about 5% and about 85% at 4 hours and between about 5% and about 90% at 8 hours and greater than 20% at 12 hours; or (19) between 0% and about 50% at 1 hour, between about 0% and about 50% at 2 hours, between about 10% and about 90% at 4 hours and between about 15% and about 90% at 8 hours and greater than 30% at 12 hours; or (20) between 0% and about 70% at 1 hour, between about 0% and about 70% at 2 hours, between about 10% and about 75% at 4 hours and between about 15% and about 90% at 8 hours and greater than 30% at 12 hours; or (21) between about 10% and about 65% at 1 hour, between about 20% and about 75% at 2 hours, between about 30% and about 95% at 4 hours and between about 40% and about 100% at 8 hours; or (22) between 2% and about 70% at 1 hour, between about 5% and about 80% at 2 hours, between about 10% and about 90% at 4 hours and between about 20% and about 100% at 8 hours; or (23) between 5% and about 60% at 1 hour, between about 10% and about 75% at 2 hours, between about 15% and about 85% at 4 hours and between about 30% and about 100% at 8 hours; or (24) between 20% and about 70% at 1 hour, between about 20% and about 75% at 2 hours, between about 20% and about 90% at 4 hours and between about 40% and about 100% at 8 hours; or (25) between 30% and about 80% at 1 hour, between about 40% and about 85% at 2 hours, between about 40% and about 90% at 4 hours and between about 60% and about 100% at 8 hours; or (26) between 1% and

about 20% at 1 hour, between about 5% and about 20% at 2 hours, between about 10% and about 40% at 4 hours and between about 20% and about 40% at 8 hours and greater than 40% at 12 hours; or (27) between 0% to about 47.5% at 1 hour, between about 10% to about 65% at 2 hours, between about 15% to about 70% at 4 hours, between about 25% to about 77.5% at 6 hours, between about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours; or (28) between 0% to about 30% at 1 hour, between about 5% to about 45% at 2 hours, between about 10% to about 60% at 4 hours, between about 15% to about 70% at 6 hours, between about 25% to about 80% at 9 hours, and greater than about 50% at 12 hours; or (29) between 0% to about 20% at 1 hour, between about 2% to about 35% at 2 hours, between about 5% to about 50% at 4 hours, between about 10% to about 60% at 6 hours, between about 15% to about 70% at 9 hours, and greater than about 40% at 12 hours; or (30) between 0% to about 10% at 1 hour, between about 1% to about 30% at 2 hours, between about 5% to about 40% at 4 hours, between about 10% to about 60% at 6 hours, between about 15% to about 70% at 9 hours, and greater than about 40% at 12 hours; or (31) between 0% to about 5% at 1 hour, between about 0% to about 10% at 2 hours, between about 2% to about 20% at 4 hours, between about 5% to about 30% at 6 hours, between about 10% to about 40% at 9 hours, and greater than about 30% at 12 hours; or (32) between 0% to about 50% at 1 hour, between about 15% to about 70% at 2 hours, between about 20% to about 75% at 4 hours, between about 30% to about 80% at 6 hours, between about 30% to about 90% at 9 hours, and greater than about 70% at 12 hours; or (33) between 0% to about 60% at 1 hour, between about 15% to about 80% at 2 hours, between about 25% to about 85% at 4 hours, between about 35% to about 90% at 6 hours, between about 40% to about 90% at 9 hours, and greater than about 80% at 12 hours; (34) between 0% to about 70% at 1 hour, between about 20% to about 80% at 2 hours, between about 25% to about 80% at 4 hours, between about 35% to about 80% at 6 hours, between about 40% to about 80% at 9 hours, and greater than about 60% at 12 hours; or (35) between 0% to about 75% at 1 hour, between about 30% to about 80% at 2 hours, between about 35% to about 90% at 4 hours, between about 50% to about 90% at 6 hours, between about 55% to about 95% at 9 hours, and greater than about 70% at 12 hours; or (36) between about 5% and about 50% at 1 hour, between about 10% and about 75% at 2 hours, between about 20% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, greater than about 50% at 12 hours, greater than about 70% at 18 hours, and greater than about 80% at 24 hours; or (37) between 2% and about 50% at 1 hour, between about 5% and about 75% at 2 hours, between about 15% and about 75% at 4 hours, between about 30% and about 90% at 8 hours, greater than about 40% at 12 hours, greater than about 60% at 18 hours, and greater than about 70% at 24 hours; or (38) between 1% and about 40% at 1 hour, between about 2% and about 60% at 2 hours, between about 10% and about 65% at 4 hours, between about 20% and about 80% at 8 hours, greater than about 30% at 12 hours, greater than about 40% at 18 hours, and greater than about 60% at 24 hours; or (39) between 5% and about 60% at 1 hour, between about 15% and about

80% at 2 hours, between about 25% and about 95% at 4 hours, between about 45% and about 100% at 8 hours, greater than about 60% at 12 hours, greater than about 80% at 18 hours, and greater than about 90% at 24 hours; or (40) between 10% and about 65% at 1 hour, between about 20% and about 85% at 2 hours, between about 30% and about 100% at 4 hours, between about 60% and about 100% at 8 hours, greater than about 70% at 12 hours, greater than about 90% at 18 hours, and greater than about 95% at 24 hours; or (41) between 0% to about 30% at 1 hour, between about 10% to about 65% at 4 hours, between about 20% to about 70% at 8 hours, between about 25% to about 80% at 12 hours, between about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours; or (42) between 0% to about 20% at 1 hour, between about 5% to about 50% at 4 hours, between about 10% to about 60% at 8 hours, between about 15% to about 70% at 12 hours, between about 25% to about 90% at 18 hours, and greater than about 55% at 24 hours; or (43) between 0% to about 10% at 1 hour, between about 5% to about 40% at 4 hours, between about 8% to about 50% at 8 hours, between about 10% to about 60% at 12 hours, between about 22% to about 80% at 18 hours, and greater than about 45% at 24 hours; or (44) between 0% to about 35% at 1 hour, between about 15% to about 70% at 4 hours, between about 25% to about 75% at 8 hours, between about 30% to about 85% at 12 hours, between about 40% to about 100% at 18 hours, and greater than about 75% at 24 hours; or (45) between 0% to about 40% at 1 hour, between about 20% to about 70% at 4 hours, between about 30% to about 80% at 8 hours, between about 35% to about 90% at 12 hours, between about 45% to about 100% at 18 hours, and greater than about 80% at 24 hours; or (46) between 0% to about 45% at 1 hour, between about 25% to about 75% at 4 hours, between about 35% to about 85% at 8 hours, between about 40% to about 90% at 12 hours, between about 50% to about 100% at 18 hours, and greater than about 90% at 24 hours; or (47) between 0% to about 50% at 1 hour, between about 30% to about 80% at 4 hours, between about 40% to about 90% at 8 hours, between about 45% to about 95% at 12 hours, between about 60% to about 100% at 18 hours, and greater than about 95% at 24 hours; or (48) between 0% to about 60% at 1 hour, between about 40% to about 80% at 4 hours, between about 45% to about 90% at 8 hours, between about 50% to about 100% at 12 hours, between about 70% to about 100% at 18 hours, and greater than about 80% at 24 hours; or (49) between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 3% and about 95% at 4 hours, between about 10% and about 100% at 8 hours, between about 25% and about 100% at 12 hours, between about 30% and about 100% at 16 hours, between about 50% and about 100% at 24 hours, and greater than about 80% at 36 hours; or (50) between 0% and about 40% at 1 hour, between about 0% and about 65% at 2 hours, between about 2% and about 85% at 4 hours, between about 8% and about 90% at 8 hours, between about 20% and about 95% at 12 hours, between about 25% and about 95% at 16 hours, between about 40% and about 90% at 24 hours, and greater than about 70% at 36 hours; or (51) between 0% and about 30% at 1 hour, between about 0% and about 50% at 2 hours, between about

1% and about 75% at 4 hours, between about 5% and about 80% at 8 hours, between about 10% and about 85% at 12 hours, between about 15% and about 90% at 16 hours, between about 30% and about 80% at 24 hours, and greater than about 70% at 36 hours; or (52) between 0% and about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 5% and about 100% at 4 hours, between about 15% and about 100% at 8 hours, between about 35% and about 100% at 12 hours, between about 40% and about 100% at 16 hours, between about 60% and about 100% at 24 hours, and greater than about 85% at 36 hours; or (53) between 0% and about 65% at 1 hour, between about 0% and about 85% at 2 hours, between about 10% and about 100% at 4 hours, between about 20% and about 100% at 8 hours, between about 40% and about 100% at 12 hours, between about 50% and about 100% at 16 hours, between about 70% and about 100% at 24 hours, and greater than about 90% at 36 hours; or (54) between 0% and about 70% at 1 hour, between about 0% and about 90% at 2 hours, between about 20% and about 100% at 4 hours, between about 30% and about 100% at 8 hours, between about 50% and about 100% at 12 hours, between about 60% and about 100% at 16 hours, between about 80% and about 100% at 24 hours, and greater than about 95% at 36 hours; or (55) between 20% and about 50% at 1 hour, between about 40% and about 75% at 2 hours, between about 60% and about 95% at 4 hours, between about 80% and about 100% at 8 hours and between about 90% and about 100% at 12 hours; or (56) between 15% and about 45% at 1 hour, between about 35% and about 70% at 2 hours, between about 55% and about 90% at 4 hours, between about 75% and about 90% at 8 hours and between about 80% and about 95% at 12 hours; or (57) between 10% and about 40% at 1 hour, between about 30% and about 65% at 2 hours, between about 50% and about 85% at 4 hours, between about 70% and about 85% at 8 hours and between about 75% and about 90% at 12 hours; or (58) between 5% and about 35% at 1 hour, between about 25% and about 60% at 2 hours, between about 45% and about 80% at 4 hours, between about 65% and about 80% at 8 hours and between about 70% and about 85% at 12 hours; or (59) between 25% and about 55% at 1 hour, between about 45% and about 80% at 2 hours, between about 65% and about 95% at 4 hours, between about 85% and about 100% at 8 hours and between about 95% and about 100% at 12 hours; or (60) between 30% and about 60% at 1 hour, between about 50% and about 80% at 2 hours, between about 70% and about 95% at 4 hours, between about 90% and about 100% at 8 hours and between about 95% and about 100% at 12 hours; or (61) between 35% and about 60% at 1 hour, between about 50% and about 80% at 2 hours, between about 80% and about 95% at 4 hours, between about 90% and about 100% at 8 hours and between about 95% and about 100% at 12 hours; or (62) between 20% and about 40% at 1 hour, between about 40% and about 65% at 2 hours, between about 60% and about 85% at 4 hours, between about 70% and about 90% at 8 hours and between about 80% and about 100% at 12 hours; or (63) between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 10% and about 95% at 4 hours, between about 35% and about 100% at 8 hours,

between about 55% and about 100% at 12 hours, between about 70% to about 100% at 16 hours, and greater than about 90% at 24 hours; or (64) between 0% and about 40% at 1 hour, between about 0% and about 65% at 2 hours, between about 8% and about 85% at 4 hours, between about 30% and about 90% at 8 hours, between about 45% and about 100% at 12 hours, between about 60% to about 100% at 16 hours, and greater than about 80% at 24 hours; or (66) between 0% and about 30% at 1 hour, between about 0% and about 55% at 2 hours, between about 5% and about 75% at 4 hours, between about 20% and about 80% at 8 hours, between about 35% and about 100% at 12 hours, between about 50% to about 100% at 16 hours, and greater than about 70% at 24 hours; or (67) between 0% and about 20% at 1 hour, between about 0% and about 45% at 2 hours, between about 5% and about 65% at 4 hours, between about 10% and about 70% at 8 hours, between about 25% and about 80% at 12 hours, between about 40% to about 100% at 16 hours, and greater than about 60% at 24 hours; or (68) between 0% and about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 15% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, between about 60% and about 100% at 12 hours, between about 75% to about 100% at 16 hours, and greater than about 90% at 24 hours; or (69) between 0% and about 65% at 1 hour, between about 0% and about 85% at 2 hours, between about 20% and about 90% at 4 hours, between about 45% and about 100% at 8 hours, between about 65% and about 100% at 12 hours, between about 80% to about 100% at 16 hours, and greater than about 90% at 24 hours; or (70) between 0% and about 40% at 1 hour, between about 0% and about 50% at 2 hours, between about 10% and about 80% at 4 hours, between about 25% and about 70% at 8 hours, between about 40% and about 80% at 12 hours, between about 60% to about 100% at 16 hours, and greater than about 90% at 24 hours; or (71) between 0% and about 30% at 1 hour, between about 0% and about 45% at 2 hours, between about 3% and about 55% at 4 hours, between about 10% and about 65% at 8 hours, between about 20% and about 75% at 12 hours, between about 30% to about 88% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours; or (72) between 0% and about 25% at 1 hour, between about 0% and about 40% at 2 hours, between about 2% and about 50% at 4 hours, between about 8% and about 60% at 8 hours, between about 10% and about 70% at 12 hours, between about 25% to about 80% at 16 hours, between about 45% and about 100% hours at 24 hours and greater than 75% at 36 hours; or (73) between 0% and about 20% at 1 hour, between about 0% and about 35% at 2 hours, between about 1% and about 45% at 4 hours, between about 5% and about 55% at 8 hours, between about 8% and about 65% at 12 hours, between about 20% to about 75% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 70% at 36 hours; or (74) between 0% and about 15% at 1 hour, between about 0% and about 30% at 2 hours, between about 0% and about 40% at 4 hours, between about 5% and about 50% at 8 hours, between about 8% and about 60% at 12 hours, between about 15% to about 70% at 16 hours, between about 35% and about 100% hours at 24 hours and greater than 60%

at 36 hours; or (75) between 0% and about 10% at 1 hour, between about 0% and about 25% at 2 hours, between about 0% and about 35% at 4 hours, between about 5% and about 45% at 8 hours, between about 10% and about 50% at 12 hours, between about 10% to about 60% at 16 hours, between about 30% and about 90% hours at 24 hours and greater than 70% at 36 hours; or (76) between 0% and about 35% at 1 hour, between about 0% and about 50% at 2 hours, between about 5% and about 60% at 4 hours, between about 15% and about 70% at 8 hours, between about 25% and about 80% at 12 hours, between about 35% to about 90% at 16 hours, between about 55% and about 100% hours at 24 hours and greater than 85% at 36 hours; or (77) between 0% and about 40% at 1 hour, between about 0% and about 55% at 2 hours, between about 10% and about 65% at 4 hours, between about 20% and about 75% at 8 hours, between about 30% and about 85% at 12 hours, between about 40% to about 100% at 16 hours, between about 55% and about 100% hours at 24 hours and greater than 90% at 36 hours; or (78) between 0% and about 45% at 1 hour, between about 0% and about 60% at 2 hours, between about 15% and about 70% at 4 hours, between about 25% and about 80% at 8 hours, between about 35% and about 90% at 12 hours, between about 45% to about 100% at 16 hours, between about 60% and about 100% hours at 24 hours and greater than 60% at 36 hours; or (79) between 0% and about 50% at 1 hour, between about 5% and about 65% at 2 hours, between about 20% and about 75% at 4 hours, between about 30% and about 85% at 8 hours, between about 40% and about 95% at 12 hours, between about 50% to about 100% at 16 hours, between about 70% and about 100% hours at 24 hours and greater than 70% at 36 hours; or (80) between 0% and about 30% at 1 hour, between about 5% and about 40% at 2 hours, between about 10% and about 60% at 4 hours, between about 20% and about 70% at 8 hours, between about 30% and about 100% at 12 hours, between about 40% to about 100% at 16 hours, between about 60% and about 100% hours at 24 hours and greater than 90% at 36 hours; or (81) between 0% and about 30% at 1 hour, between about 0% and about 30% at 2 hours, between about 0% and about 30% at 4 hours, between about 5% and about 70% at 8 hours, between about 10% and about 80% at 12 hours, between about 20% to about 100% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 50% at 36 hours; or (82) between 0% and about 20% at 1 hour, between about 0% and about 20% at 2 hours, between about 0% and about 20% at 4 hours, between about 0% and about 20% at 8 hours, between about 5% and about 40% at 12 hours, between about 10% to about 80% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 60% at 36 hours; or (83) between 0% and about 10% at 1 hour, between about 0% and about 20% at 2 hours, between about 0% and about 40% at 4 hours, between about 5% and about 60% at 8 hours, between about 10% and about 80% at 12 hours, between about 20% to about 100% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 50% at 36 hours; or (84) between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 3% and about 95% at 4 hours, between about 10% and about 100% at 8 hours, between about

20% and about 100% at 12 hours, between about 30% to about 100% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours; or (85) between 0% and about 45% at 1 hour, between about 0% and about 70% at 2 hours, between about 3% and about 90% at 4 hours, between about 8% and about 100% at 8 hours, between about 15% and about 100% at 12 hours, between about 25% to about 100% at 16 hours, between about 45% and about 100% hours at 24 hours and greater than 80% at 36 hours; or (86) between 0% and about 40% at 1 hour, between about 0% and about 65% at 2 hours, between about 0% and about 80% at 4 hours, between about 5% and about 80% at 8 hours, between about 10% and about 90% at 12 hours, between about 20% to about 100% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 70% at 36 hours; or (87) between 0% and about 35% at 1 hour, between about 0% and about 60% at 2 hours, between about 0% and about 70% at 4 hours, between about 3% and about 70% at 8 hours, between about 5% and about 80% at 12 hours, between about 15% to about 100% at 16 hours, between about 30% and about 100% hours at 24 hours and greater than 40% at 36 hours; or (88) between 0% and about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 5% and about 100% at 4 hours, between about 15% and about 100% at 8 hours, between about 30% and about 100% at 12 hours, between about 40% to about 100% at 16 hours, between about 60% and about 100% hours at 24 hours and greater than 70% at 36 hours; or (89) between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 5% and about 95% at 4 hours, between about 25% and about 80% at 8 hours, between about 30% and about 100% at 12 hours, between about 40% to about 100% at 16 hours, between about 60% and about 100% hours at 24 hours and greater than 60% at 36 hours; or (90) between 0% and about 60% at 1 hour, between about 0% and about 85% at 2 hours, between about 5% and about 100% at 4 hours, between about 10% and about 100% at 8 hours, between about 20% and about 100% at 12 hours, between about 30% to about 100% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours; or (91) between 15% and about 25% at 1 hour, between about 25% and about 35% at 2 hours, between about 30% and about 45% at 4 hours, between about 40% and about 60% at 8 hours, between about 55% and about 70% at 12 hours and between about 60% to about 75% at 16 hours; or (92) between 10% and about 20% at 1 hour, between about 20% and about 30% at 2 hours, between about 25% and about 40% at 4 hours, between about 30% and about 50% at 8 hours, between about 50% and about 65% at 12 hours and between about 55% to about 65% at 16 hours; or (93) between 5% and about 15% at 1 hour, between about 15% and about 25% at 2 hours, between about 20% and about 35% at 4 hours, between about 25% and about 45% at 8 hours, between about 45% and about 60% at 12 hours and between about 50% to about 60% at 16 hours; or (94) between 15% and about 30% at 1 hour, between about 20% and about 40% at 2 hours, between about 20% and about 50% at 4 hours, between about 30% and about 70% at 8 hours, between about 60% and about 80% at 12 hours and between about 70% to about 90% at 16 hours;

or (95) between 0% and about 50% at 1 hour, between about 5% and about 50% at 2 hours, between about 5% and about 70% at 4 hours, between about 10% and about 80% at 8 hours, between about 20% and about 100% at 12 hours and between about 40% to about 100% at 16 hours; or (96) between 15% and about 40% at 1 hour, between about 15% and about 45% at 2 hours, between about 20% and about 60% at 4 hours, between about 20% and about 80% at 8 hours, between about 30% and about 90% at 12 hours and between about 40% to about 100% at 16 hours; or (97) between 0% to about 80% at 0.5 hours, and greater than about 40% at 1 hour; or (98) between 0% to about 40% at 0.5 hours, and greater than about 60% at 1 hour; or (98a) between 0% to about 20% at 0.5 hours, and greater than about 40% at 1 hour; or (99) between 0% to about 20% at 0.5 hours, and greater than about 20% at 1 hour; or (100) between 0% to about 90% at 0.5 hours, and greater than about 60% at 1 hour; or (101) between 0% to about 100% at 0.5 hours, and greater than about 60% at 1 hour; or (102) between 0% to about 90% at 1 hour, and greater than about 40% at 2 hours; or (103) between 0% to about 100% at 1 hour, and greater than about 60% at 2 hours; or (104) between 0% to about 60% at 1 hour, and greater than about 40% at 2 hours; or (105) between 0% to about 40% at 1 hour, and greater than about 30% at 2 hours; or (106) between 0% to about 50% at 1 hour, and greater than about 40% at 2 hours; or (107) between 0% to about 30% at 1 hour, and greater than about 20% at 2 hours; or (108) between 0% and about 50% at 1 hour, between about 0% and about 80% at 2 hours, between about 5% and about 100% at 4 hours and between about 10% and about 100% at 8 hours; or (109) between 10% and about 60% at 1 hour, between about 15% and about 75% at 2 hours, between about 20% and about 95% at 4 hours and between about 30% and about 100% at 8 hours; or (110) between 0% to about 80% at 0.25 hours, and greater than about 90 % at 1 hour; or (111) between 0% to about 100% at 0.25 hours, and greater than about 60 % at 1 hour. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 50 or 75 rpm instead of 100 rpm. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method in 100 ml, 250 or 500 mL of dissolution media instead of 900 mL. In some preferred embodiments, the foregoing release rate in (1) to (111) is measured with the aid of a sinker (e.g., a nonreactive stainless steel wire helix, other inert material, cork borers, cylinders, see, for example, USP 32–NF 27). In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Paddle Method with a sinker at 100 rpm in 900 mL distilled water at a pH of about 7.4 at 37 °C. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Paddle Method with a sinker at 75 rpm in 600 ml of Simulated Intestinal Fluid (SIF) USP, without the inclusion of enzyme, at a pH of 6.8 at 37 °C.

[430] In some embodiments of the invention, pH adjustments of the dissolution media may be achieved by adjustment as required with hydrochloric acid or sodium hydroxide. In some

embodiments of the invention, pH adjustments of the dissolution media may be achieved with other pharmaceutical excipients, including acids, bases and buffers known in the art.

[431] Delayed Onset, Extended Release Levorphanol Dissolution Rate

[432] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition comprising a therapeutically effective amount of levorphanol; said dosage form providing an in-vitro levorphanol release rate, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water at 37 °C which is substantially pH dependent in that a difference, at 1, or 1.5, or 2, or 2.5, or 3 hours, between the amount of levorphanol released at a pH of ≤ 0.5 , or ≤ 1 , or ≤ 1.5 , or ≤ 2 , or ≤ 2.5 , or ≤ 3 , or ≤ 3.5 , or ≤ 4 , or ≤ 4.5 , or ≤ 5 , or ≤ 5.5 and an amount released at a pH of or ≥ 5.8 , or ≥ 6 , or ≥ 6.2 , or ≥ 6.4 , or ≥ 6.6 , or ≥ 6.8 , or ≥ 7 , or ≥ 7.1 , or ≥ 7.2 , or ≥ 7.3 , or ≥ 7.4 , or ≥ 7.5 , or ≥ 7.6 , or ≥ 7.7 , or ≥ 7.8 , or ≥ 7.9 , or ≥ 8 , is greater than about 20%, 25%, 35%, 50%, 60%, 75%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, 1000%, or 1200%, 1500%, 2000%, 3000%, 4000%, 5000%, or 6000%.

[433] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition comprising a therapeutically effective amount of levorphanol; said dosage form providing duodenal delivery, jejunal delivery, ileal delivery, ileo-colonic delivery or colonic delivery; said dosage form providing an in-vitro levorphanol release rate, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water at 37 °C which is substantially pH dependent in that a difference, at 1, or 1.5, or 2, or 2.5, or 3 hours, between the amount of levorphanol released at a pH of ≤ 0.5 , or ≤ 1 , or ≤ 1.5 , or ≤ 2 , or ≤ 2.5 , or ≤ 3 , or ≤ 3.5 , or ≤ 4 , or ≤ 4.5 , or ≤ 5 , or ≤ 5.5 and an amount released at a pH of ≥ 5.8 , or ≥ 6 , or ≥ 6.2 , or ≥ 6.4 , or ≥ 6.6 , or ≥ 6.8 , or ≥ 7 , or ≥ 7.1 , or ≥ 7.2 , or ≥ 7.3 , or ≥ 7.4 , or ≥ 7.5 , or ≥ 7.6 , or ≥ 7.7 , or ≥ 7.8 , or ≥ 7.9 , or ≥ 8 , is greater than about 20%, 25%, 35%, 50%, 60%, 75%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, 1000%, or 1200%, 1500%, 2000%, 3000%, 4000%, 5000%, or 6000%.

[434] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material; said dosage form providing an in-vitro levorphanol release rate, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water at 37 °C which is substantially pH dependent in that a difference, at 1, or 1.5, or 2, or 2.5, or 3 hours, between the amount of levorphanol released at a pH of ≤ 0.5 , or ≤ 1 , or ≤ 1.5 , or ≤ 2 , or ≤ 2.5 , or ≤ 3 , or ≤ 3.5 , or ≤ 4 , or ≤ 4.5 , or ≤ 5 , or ≤ 5.5 and an amount released at a pH of ≥ 5.8 , or ≥ 6 , or ≥ 6.2 , or ≥ 6.4 , or ≥ 6.6 , or ≥ 6.8 , or ≥ 7 , or ≥ 7.1 , or ≥ 7.2 , or ≥ 7.3 , or ≥ 7.4 , or ≥ 7.5 , or ≥ 7.6 , or ≥ 7.7 , or ≥ 7.8 , or ≥ 7.9 , or ≥ 8 , is greater than about 25%, 35%, 50%, 60%, 75%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, 1000%,

or 1200%, 1500%, 2000%, 3000%, 4000%, 5000%, or 6000%.

[435] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition comprising a therapeutically effective amount of levorphanol, and a controlled release material; said dosage form providing duodenal delivery, jejunal delivery, ileal delivery, ileo-colonic delivery or colonic delivery; said dosage form providing an in-vitro levorphanol release rate, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water at 37 °C which is substantially pH dependent in that a difference, at 1, or 1.5, or 2, or 2.5, or 3 hours, between the amount of levorphanol released at a pH of ≤ 0.5 , or ≤ 1 , or ≤ 1.5 , or ≤ 2 , or ≤ 2.5 , or ≤ 3 , or ≤ 3.5 , or ≤ 4 , or ≤ 4.5 , or ≤ 5 , or ≤ 5.5 and an amount released at a pH of ≥ 5.8 , or ≥ 6 , or ≥ 6.2 , or ≥ 6.4 , or ≥ 6.6 , or ≥ 6.8 , or ≥ 7 , or ≥ 7.1 , or ≥ 7.2 , or ≥ 7.3 , or ≥ 7.4 , or ≥ 7.5 , or ≥ 7.6 , or ≥ 7.7 , or ≥ 7.8 , or ≥ 7.9 , or ≥ 8 , is greater than about 25%, 35%, 50%, 60%, 75%, 80%, 90%, 100%, 125%, 150%, 175%, 200%, 225%, 250%, 275%, 300%, 350%, 400%, 450%, 500%, 600%, 700%, 800%, 900%, 1000%, or 1200%, 1500%, 2000%, 3000%, 4000%, 5000%, or 6000%.

[436] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition for the treatment of a levorphanol responsive medical condition comprising a therapeutically effective amount of levorphanol, and a controlled release material; said dosage form, following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of 0.1N HCl for two hours at 37 °C, providing an in-vitro release rate of levorphanol by weight, when measured at about 2, 4, 8, 12 or 16 hours by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH between 4.5 and 8: (i) of less than about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70% or 80%; or (ii) of about 1% to about 20% or about 2% to about 20% or about 5% to about 20% or about 8% to about 20% or about 10% to about 20% or about 12% to about 20% or about 15% to about 20% or about 1% to about 50% or about 2% to about 50% or about 5% to about 50% or about 10% to about 50% or about 15% to about 50% or about 20% to about 50% or about 30% to about 50% or about 40% to about 50% or about 1% to about 60% or about 2% to about 60% or about 5% to about 60% or about 10% to about 60% or about 15% to about 60% or about 20% to about 60% or about 30% to about 60% or about 40% to about 60% or about 1% to about 70% or about 2% to about 70% or about 5% to about 70% or about 10% to about 70% or about 15% to about 70% or about 20% to about 70% or about 30% to about 70% or about 50% to about 70% or about 1% to about 80% or about 2% to about 80% or about 5% to about 80% or about 10% to about 80% or about 15% to about 80% or about 20% to about 80% or about 30% to about 80% or about 40% to about 80% or about 1% to about 90% or about 2% to about 90% or about 5% to about 90% or about 10% to about 90% or about 15% to about 90% or about 20% to about 90% or about 30% to about 90% or about 40% to about 90% or about 60% to about 90% or about 70% to about 90% or about 80% to about 90%, or more than about 1%, or more than about 5%, or more than about 10%, or more than about 15%, or

more than about 20%, or more than about 30%, or more than about 40%, or more than about 50%, or more than about 55%, or more than about 60%, or more than about 70%, or more than about 80%, or more than about 85%, or more than about 90%, or more than about 95%, or more than 99%; or (iii) of $\geq 0.1\%$, or $\geq 0.5\%$, or $\geq 1\%$, or $\geq 5\%$, $\geq 10\%$, or $\geq 20\%$, or $\geq 30\%$, or $\geq 40\%$, or $\geq 50\%$, or $\geq 60\%$, or $\geq 70\%$, or $\geq 80\%$, or $\geq 90\%$, or about 100%.

[437] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition for the treatment of a levorphanol responsive medical condition comprising a therapeutically effective amount of levorphanol, and a controlled release material; said dosage form, following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of 0.1N HCl for two hours at 37 °C, and then following further dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL distilled water at any pH of between 2 and 4 for a further time of up to two hours at 37 °C, providing an in-vitro release rate by weight of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH between 4.5 and 8 at 37 °C (measured at about 1, 3, 6 or 12 hours): (i) of about 1% to about 20% or about 2% to about 20% or about 5% to about 20% or about 8% to about 20% or about 10% to about 20% or about 12% to about 20% or about 15% to about 20% or about 1% to about 50% or about 2% to about 50% or about 5% to about 50% or about 10% to about 50% or about 15% to about 50% or about 20% to about 50% or about 30% to about 50% or about 40% to about 50% or about 1% to about 60% or about 2% to about 60% or about 5% to about 60% or about 10% to about 60% or about 15% to about 60% or about 20% to about 60% or about 30% to about 60% or about 40% to about 60% or about 1% to about 70% or about 2% to about 70% or about 5% to about 70% or about 10% to about 70% or about 15% to about 70% or about 20% to about 70% or about 30% to about 70% or about 50% to about 70% or about 1% to about 80% or about 2% to about 80% or about 5% to about 80% or about 10% to about 80% or about 15% to about 80% or about 20% to about 80% or about 30% to about 80% or about 40% to about 80% or about 1% to about 90% or about 2% to about 90% or about 5% to about 90% or about 10% to about 90% or about 15% to about 90% or about 20% to about 90% or about 30% to about 90% or about 40% to about 90% or about 60% to about 90% or about 70% to about 90% or about 80% to about 90%, or more than about 1%, or more than about 5%, or more than about 10%, or more than about 15%, or more than about 20%, or more than about 30%, or more than about 40%, or more than about 50%, or more than about 55%, or more than about 60%, or more than about 70%, or more than about 80%, or more than about 85%, or more than about 90%, or more than about 95%, or more than 99%, or about 100%; or (ii) of $\geq 0.1\%$, or $\geq 0.5\%$, or $\geq 1\%$, or $\geq 5\%$, $\geq 10\%$, or $\geq 20\%$, or $\geq 30\%$, or $\geq 40\%$, or $\geq 50\%$, or $\geq 60\%$, or $\geq 70\%$, or $\geq 80\%$, or $\geq 90\%$, or about 100%.

[438] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition for the treatment of a levorphanol responsive medical condition comprising a

therapeutically effective amount of levorphanol, and a controlled release material; said dosage form providing an in-vitro release rate by weight of levorphanol, when measured by the USP Basket and Paddle Methods at about 2, 4, 8, 12 or 16 hours at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C: (i) of less than about 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70% or 80%; or (ii) of about 1% to about 20% or about 2% to about 20% or about 5% to about 20% or about 8% to about 20% or about 10% to about 20% or about 12% to about 20% or about 15% to about 20% or about 1% to about 50% or about 2% to about 50% or about 5% to about 50% or about 10% to about 50% or about 15% to about 50% or about 20% to about 50% or about 30% to about 50% or about 40% to about 50% or about 1% to about 60% or about 2% to about 60% or about 5% to about 60% or about 10% to about 60% or about 15% to about 60% or about 20% to about 60% or about 30% to about 60% or about 40% to about 60% or about 1% to about 70% or about 2% to about 70% or about 5% to about 70% or about 10% to about 70% or about 15% to about 70% or about 20% to about 70% or about 30% to about 70% or about 50% to about 70% or about 1% to about 80% or about 2% to about 80% or about 5% to about 80% or about 10% to about 80% or about 15% to about 80% or about 20% to about 80% or about 30% to about 80% or about 40% to about 80% or about 1% to about 90% or about 2% to about 90% or about 5% to about 90% or about 10% to about 90% or about 15% to about 90% or about 20% to about 90% or about 30% to about 90% or about 40% to about 90% or about 60% to about 90% or about 70% to about 90% or about 80% to about 90%, or more than about 1%, or more than about 5%, or more than about 10%, or more than about 15%, or more than about 20%, or more than about 30%, or more than about 40%, or more than about 50%, or more than about 55%, or more than about 60%, or more than about 70%, or more than about 80%, or more than about 85%, or more than about 90%, or more than about 95%, or more than 99%; or (iii) of $\geq 0.1\%$, or $\geq 0.5\%$, or $\geq 1\%$, or $\geq 5\%$, $\geq 10\%$, or $\geq 20\%$, or $\geq 30\%$, or $\geq 40\%$, or $\geq 50\%$, or $\geq 60\%$, or $\geq 70\%$, or $\geq 80\%$, or $\geq 90\%$, or about 100%.

[439] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition for the treatment of a levorphanol responsive medical condition comprising a therapeutically effective amount of levorphanol, and a controlled release material; said dosage form, following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of 0.1N HCl for two hours at 37 °C, and then following further dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL distilled water at any pH of between 2 and 4 for a further time of up to two hours at 37 °C, providing an in-vitro release rate by weight of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at any pH between 4.5 and 8 at 37 °C: (i) from 1% to about 47.5% at 1 hour, from about 5% to about 65% at 2 hours, from about 15% to about 70% at 4 hours, from about 25% to about 77.5% at 6 hours, from about 35% to about 87.5% at 9 hours, and greater than about

65% at 12 hours; or (ii) from 0% to about 40% at 1 hour, from about 5% to about 55% at 2 hours, from about 10% to about 60% at 4 hours, from about 15% to about 70% at 6 hours, from about 25% to about 80% at 9 hours, and greater than about 50% at 12 hours.

[440] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition for the treatment of a levorphanol responsive medical condition comprising a therapeutically effective amount of levorphanol, and a controlled release material; said dosage form, following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of 0.1N HCl for two hours at 37 °C, providing an in-vitro release rate by weight of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH between 4.5 and 8 at 37 °C: (1) between 0% to about 47.5% at 1 hour, between about 10% to about 65% at 2 hours, between about 15% to about 70% at 4 hours, between about 25% to about 77.5% at 6 hours, between about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours; or (2) between about 10% to about 65% at 4 hours, between about 20% to about 70% at 8 hours, between about 25% to about 80% at 12 hours, between about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours; or (3) between 0% to about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 3% and about 95% at 4 hours and between about 10% and about 100% at 8 hours; or (4) between about 10% and about 65% at 1 hour, between about 20% and about 75% at 2 hours, between about 30% and about 95% at 4 hours and between about 40% and about 100% at 8 hours; or (5) between about 10% to about 65% at 2 hours, between about 15% to about 70% at 4 hours, between about 25% to about 77.5% at 6 hours, between about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours; or (6) between about 5% and about 50% at 1 hour, between about 10% and about 75% at 2 hours, between about 20% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, greater than about 50% at 12 hours, greater than about 70% at 18 hours, and greater than about 80% at 24 hours; or (7) between about 5% and about 50% at 1 hour, between about 10% and about 75% at 2 hours, between about 20% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, greater than about 50% at 12 hours, greater than about 70% at 18 hours, and greater than about 80% at 24 hours; or (8) between 0% to about 30% at 1 hour, between about 10% to about 65% at 4 hours, between about 20% to about 70% at 8 hours, between about 25% to about 80% at 12 hours, between about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours; or (9) between 0% to about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 3% and about 95% at 4 hours, between about 10% and about 100% at 8 hours, between about 25% and about 100% at 12 hours, between about 30% and about 100% at 16 hours, between about 50% and about 100% at 24 hours, and greater than about 80% at 36 hours; or (10) between about 20% and about 50% at 1 hour, between about 40% and about 75% at 2 hours, between about 60% and about 95% at 4 hours, between about 80% and about 100% at 8 hours and between about 90% and

about 100% at 12 hours; or (11) between 0% to about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 10% and about 95% at 4 hours, between about 35% and about 100% at 8 hours, between about 55% and about 100% at 12 hours, between about 70% to about 100% at 16 hours, and greater than about 90% at 24 hours; or (12) between 0% to about 30% at 1 hour, between about 0% and about 45% at 2 hours, between about 3% and about 55% at 4 hours, between about 10% and about 65% at 8 hours, between about 20% and about 75% at 12 hours, between about 30% to about 88% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours; or (13) between 0% to about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 3% and about 95% at 4 hours, between about 10% and about 100% at 8 hours, between about 20% and about 100% at 12 hours, between about 30% to about 100% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours; or (14) between about 15% and about 25% at 1 hour, between about 25% and about 35% at 2 hours, between about 30% and about 45% at 4 hours, between about 40% and about 60% at 8 hours, between about 55% and about 70% at 12 hours and between about 60% to about 75% at 16 hours; or (15) between 0% to about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 3% and about 95% at 4 hours and between about 10% and about 100% at 8 hours; or (16) between 0% and about 10% at 1 hour, between about 0% and about 20% at 2 hours, between about 2% and about 80% at 4 hours and between about 5% and about 100% at 8 hours; or (17) between 0% and about 20% at 1 hour, between about 0% and about 40% at 2 hours, between about 0% and about 80% at 4 hours and between about 2% and about 100% at 8 hours; or (18) between 0% and about 40% at 1 hour, between about 0% and about 60% at 2 hours, between about 5% and about 85% at 4 hours and between about 5% and about 90% at 8 hours and greater than 20% at 12 hours; or (19) between 0% and about 50% at 1 hour, between about 0% and about 50% at 2 hours, between about 10% and about 90% at 4 hours and between about 15% and about 90% at 8 hours and greater than 30% at 12 hours; or (20) between 0% and about 70% at 1 hour, between about 0% and about 70% at 2 hours, between about 10% and about 75% at 4 hours and between about 15% and about 90% at 8 hours and greater than 30% at 12 hours; or (21) between about 10% and about 65% at 1 hour, between about 20% and about 75% at 2 hours, between about 30% and about 95% at 4 hours and between about 40% and about 100% at 8 hours; or (22) between 2% and about 70% at 1 hour, between about 5% and about 80% at 2 hours, between about 10% and about 90% at 4 hours and between about 20% and about 100% at 8 hours; or (23) between 5% and about 60% at 1 hour, between about 10% and about 75% at 2 hours, between about 15% and about 85% at 4 hours and between about 30% and about 100% at 8 hours; or (24) between 20% and about 70% at 1 hour, between about 20% and about 75% at 2 hours, between about 20% and about 90% at 4 hours and between about 40% and about 100% at 8 hours; or (25) between 30% and about 80% at 1 hour, between about 40% and about 85% at 2 hours, between about 40% and about 90% at 4 hours and

between about 60% and about 100% at 8 hours; or (26) between 1% and about 20% at 1 hour, between about 5% and about 20% at 2 hours, between about 10% and about 40% at 4 hours and between about 20% and about 40% at 8 hours and greater than 40% at 12 hours; or (27) between 0% to about 47.5% at 1 hour, between about 10% to about 65% at 2 hours, between about 15% to about 70% at 4 hours, between about 25% to about 77.5% at 6 hours, between about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours; or (28) between 0% to about 30% at 1 hour, between about 5% to about 45% at 2 hours, between about 10% to about 60% at 4 hours, between about 15% to about 70% at 6 hours, between about 25% to about 80% at 9 hours, and greater than about 50% at 12 hours; or (29) between 0% to about 20% at 1 hour, between about 2% to about 35% at 2 hours, between about 5% to about 50% at 4 hours, between about 10% to about 60% at 6 hours, between about 15% to about 70% at 9 hours, and greater than about 40% at 12 hours; or (30) between 0% to about 10% at 1 hour, between about 1% to about 30% at 2 hours, between about 5% to about 40% at 4 hours, between about 10% to about 60% at 6 hours, between about 15% to about 70% at 9 hours, and greater than about 40% at 12 hours; or (31) between 0% to about 5% at 1 hour, between about 0% to about 10% at 2 hours, between about 2% to about 20% at 4 hours, between about 5% to about 30% at 6 hours, between about 10% to about 40% at 9 hours, and greater than about 30% at 12 hours; or (32) between 0% to about 50% at 1 hour, between about 15% to about 70% at 2 hours, between about 20% to about 75% at 4 hours, between about 30% to about 80% at 6 hours, between about 30% to about 90% at 9 hours, and greater than about 70% at 12 hours; or (33) between 0% to about 60% at 1 hour, between about 15% to about 80% at 2 hours, between about 25% to about 85% at 4 hours, between about 35% to about 90% at 6 hours, between about 40% to about 90% at 9 hours, and greater than about 80% at 12 hours; (34) between 0% to about 70% at 1 hour, between about 20% to about 80% at 2 hours, between about 25% to about 80% at 4 hours, between about 35% to about 80% at 6 hours, between about 40% to about 80% at 9 hours, and greater than about 60% at 12 hours; or (35) between 0% to about 75% at 1 hour, between about 30% to about 80% at 2 hours, between about 35% to about 90% at 4 hours, between about 50% to about 90% at 6 hours, between about 55% to about 95% at 9 hours, and greater than about 70% at 12 hours; or (36) between about 5% and about 50% at 1 hour, between about 10% and about 75% at 2 hours, between about 20% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, greater than about 50% at 12 hours, greater than about 70% at 18 hours, and greater than about 80% at 24 hours; or (37) between 2% and about 50% at 1 hour, between about 5% and about 75% at 2 hours, between about 15% and about 75% at 4 hours, between about 30% and about 90% at 8 hours, greater than about 40% at 12 hours, greater than about 60% at 18 hours, and greater than about 70% at 24 hours; or (38) between 1% and about 40% at 1 hour, between about 2% and about 60% at 2 hours, between about 10% and about 65% at 4 hours, between about 20% and about 80% at 8 hours, greater than about 30% at 12 hours, greater than about 40% at 18 hours, and greater than

about 60% at 24 hours; or (39) between 5% and about 60% at 1 hour, between about 15% and about 80% at 2 hours, between about 25% and about 95% at 4 hours, between about 45% and about 100% at 8 hours, greater than about 60% at 12 hours, greater than about 80% at 18 hours, and greater than about 90% at 24 hours; or (40) between 10% and about 65% at 1 hour, between about 20% and about 85% at 2 hours, between about 30% and about 100% at 4 hours, between about 60% and about 100% at 8 hours, greater than about 70% at 12 hours, greater than about 90% at 18 hours, and greater than about 95% at 24 hours; or (41) between 0% to about 30% at 1 hour, between about 10% to about 65% at 4 hours, between about 20% to about 70% at 8 hours, between about 25% to about 80% at 12 hours, between about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours; or (42) between 0% to about 20% at 1 hour, between about 5% to about 50% at 4 hours, between about 10% to about 60% at 8 hours, between about 15% to about 70% at 12 hours, between about 25% to about 90% at 18 hours, and greater than about 55% at 24 hours; or (43) between 0% to about 10% at 1 hour, between about 5% to about 40% at 4 hours, between about 8% to about 50% at 8 hours, between about 10% to about 60% at 12 hours, between about 22% to about 80% at 18 hours, and greater than about 45% at 24 hours; or (44) between 0% to about 35% at 1 hour, between about 15% to about 70% at 4 hours, between about 25% to about 75% at 8 hours, between about 30% to about 85% at 12 hours, between about 40% to about 100% at 18 hours, and greater than about 75% at 24 hours; or (45) between 0% to about 40% at 1 hour, between about 20% to about 70% at 4 hours, between about 30% to about 80% at 8 hours, between about 35% to about 90% at 12 hours, between about 45% to about 100% at 18 hours, and greater than about 80% at 24 hours; or (46) between 0% to about 45% at 1 hour, between about 25% to about 75% at 4 hours, between about 35% to about 85% at 8 hours, between about 40% to about 90% at 12 hours, between about 50% to about 100% at 18 hours, and greater than about 90% at 24 hours; or (47) between 0% to about 50% at 1 hour, between about 30% to about 80% at 4 hours, between about 40% to about 90% at 8 hours, between about 45% to about 95% at 12 hours, between about 60% to about 100% at 18 hours, and greater than about 95% at 24 hours; or (48) between 0% to about 60% at 1 hour, between about 40% to about 80% at 4 hours, between about 45% to about 90% at 8 hours, between about 50% to about 100% at 12 hours, between about 70% to about 100% at 18 hours, and greater than about 80% at 24 hours; or (49) between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 3% and about 95% at 4 hours, between about 10% and about 100% at 8 hours, between about 25% and about 100% at 12 hours, between about 30% and about 100% at 16 hours, between about 50% and about 100% at 24 hours, and greater than about 80% at 36 hours; or (50) between 0% and about 40% at 1 hour, between about 0% and about 65% at 2 hours, between about 2% and about 85% at 4 hours, between about 8% and about 90% at 8 hours, between about 20% and about 95% at 12 hours, between about 25% and about 95% at 16 hours, between about 40% and about 90% at 24 hours, and greater than about 70% at 36 hours; or (51)

between 0% and about 30% at 1 hour, between about 0% and about 50% at 2 hours, between about 1% and about 75% at 4 hours, between about 5% and about 80% at 8 hours, between about 10% and about 85% at 12 hours, between about 15% and about 90% at 16 hours, between about 30% and about 80% at 24 hours, and greater than about 70% at 36 hours; or (52) between 0% and about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 5% and about 100% at 4 hours, between about 15% and about 100% at 8 hours, between about 35% and about 100% at 12 hours, between about 40% and about 100% at 16 hours, between about 60% and about 100% at 24 hours, and greater than about 85% at 36 hours; or (53) between 0% and about 65% at 1 hour, between about 0% and about 85% at 2 hours, between about 10% and about 100% at 4 hours, between about 20% and about 100% at 8 hours, between about 40% and about 100% at 12 hours, between about 50% and about 100% at 16 hours, between about 70% and about 100% at 24 hours, and greater than about 90% at 36 hours; or (54) between 0% and about 70% at 1 hour, between about 0% and about 90% at 2 hours, between about 20% and about 100% at 4 hours, between about 30% and about 100% at 8 hours, between about 50% and about 100% at 12 hours, between about 60% and about 100% at 16 hours, between about 80% and about 100% at 24 hours, and greater than about 95% at 36 hours; or (55) between 20% and about 50% at 1 hour, between about 40% and about 75% at 2 hours, between about 60% and about 95% at 4 hours, between about 80% and about 100% at 8 hours and between about 90% and about 100% at 12 hours; or (56) between 15% and about 45% at 1 hour, between about 35% and about 70% at 2 hours, between about 55% and about 90% at 4 hours, between about 75% and about 90% at 8 hours and between about 80% and about 95% at 12 hours; or (57) between 10% and about 40% at 1 hour, between about 30% and about 65% at 2 hours, between about 50% and about 85% at 4 hours, between about 70% and about 85% at 8 hours and between about 75% and about 90% at 12 hours; or (58) between 5% and about 35% at 1 hour, between about 25% and about 60% at 2 hours, between about 45% and about 80% at 4 hours, between about 65% and about 80% at 8 hours and between about 70% and about 85% at 12 hours; or (59) between 25% and about 55% at 1 hour, between about 45% and about 80% at 2 hours, between about 65% and about 95% at 4 hours, between about 85% and about 100% at 8 hours and between about 95% and about 100% at 12 hours; or (60) between 30% and about 60% at 1 hour, between about 50% and about 80% at 2 hours, between about 70% and about 95% at 4 hours, between about 90% and about 100% at 8 hours and between about 95% and about 100% at 12 hours; or (61) between 35% and about 60% at 1 hour, between about 50% and about 80% at 2 hours, between about 80% and about 95% at 4 hours, between about 90% and about 100% at 8 hours and between about 95% and about 100% at 12 hours; or (62) between 20% and about 40% at 1 hour, between about 40% and about 65% at 2 hours, between about 60% and about 85% at 4 hours, between about 70% and about 90% at 8 hours and between about 80% and about 100% at 12 hours; or (63) between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours,

between about 10% and about 95% at 4 hours, between about 35% and about 100% at 8 hours, between about 55% and about 100% at 12 hours, between about 70% to about 100% at 16 hours, and greater than about 90% at 24 hours; or (64) between 0% and about 40% at 1 hour, between about 0% and about 65% at 2 hours, between about 8% and about 85% at 4 hours, between about 30% and about 90% at 8 hours, between about 45% and about 100% at 12 hours, between about 60% to about 100% at 16 hours, and greater than about 80% at 24 hours; or (66) between 0% and about 30% at 1 hour, between about 0% and about 55% at 2 hours, between about 5% and about 75% at 4 hours, between about 20% and about 80% at 8 hours, between about 35% and about 100% at 12 hours, between about 50% to about 100% at 16 hours, and greater than about 70% at 24 hours; or (67) between 0% and about 20% at 1 hour, between about 0% and about 45% at 2 hours, between about 5% and about 65% at 4 hours, between about 10% and about 70% at 8 hours, between about 25% and about 80% at 12 hours, between about 40% to about 100% at 16 hours, and greater than about 60% at 24 hours; or (68) between 0% and about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 15% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, between about 60% and about 100% at 12 hours, between about 75% to about 100% at 16 hours, and greater than about 90% at 24 hours; or (69) between 0% and about 65% at 1 hour, between about 0% and about 85% at 2 hours, between about 20% and about 90% at 4 hours, between about 45% and about 100% at 8 hours, between about 65% and about 100% at 12 hours, between about 80% to about 100% at 16 hours, and greater than about 90% at 24 hours; or (70) between 0% and about 40% at 1 hour, between about 0% and about 50% at 2 hours, between about 10% and about 80% at 4 hours, between about 25% and about 70% at 8 hours, between about 40% and about 80% at 12 hours, between about 60% to about 100% at 16 hours, and greater than about 90% at 24 hours; or (71) between 0% and about 30% at 1 hour, between about 0% and about 45% at 2 hours, between about 3% and about 55% at 4 hours, between about 10% and about 65% at 8 hours, between about 20% and about 75% at 12 hours, between about 30% to about 88% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours; or (72) between 0% and about 25% at 1 hour, between about 0% and about 40% at 2 hours, between about 2% and about 50% at 4 hours, between about 8% and about 60% at 8 hours, between about 10% and about 70% at 12 hours, between about 25% to about 80% at 16 hours, between about 45% and about 100% hours at 24 hours and greater than 75% at 36 hours; or (73) between 0% and about 20% at 1 hour, between about 0% and about 35% at 2 hours, between about 1% and about 45% at 4 hours, between about 5% and about 55% at 8 hours, between about 8% and about 65% at 12 hours, between about 20% to about 75% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 70% at 36 hours; or (74) between 0% and about 15% at 1 hour, between about 0% and about 30% at 2 hours, between about 0% and about 40% at 4 hours, between about 5% and about 50% at 8 hours, between about 8% and about 60% at 12 hours, between about 15% to

about 70% at 16 hours, between about 35% and about 100% hours at 24 hours and greater than 60% at 36 hours; or (75) between 0% and about 10% at 1 hour, between about 0% and about 25% at 2 hours, between about 0% and about 35% at 4 hours, between about 5% and about 45% at 8 hours, between about 10% and about 50% at 12 hours, between about 10% to about 60% at 16 hours, between about 30% and about 90% hours at 24 hours and greater than 70% at 36 hours; or (76) between 0% and about 35% at 1 hour, between about 0% and about 50% at 2 hours, between about 5% and about 60% at 4 hours, between about 15% and about 70% at 8 hours, between about 25% and about 80% at 12 hours, between about 35% to about 90% at 16 hours, between about 55% and about 100% hours at 24 hours and greater than 85% at 36 hours; or (77) between 0% and about 40% at 1 hour, between about 0% and about 55% at 2 hours, between about 10% and about 65% at 4 hours, between about 20% and about 75% at 8 hours, between about 30% and about 85% at 12 hours, between about 40% to about 100% at 16 hours, between about 55% and about 100% hours at 24 hours and greater than 90% at 36 hours; or (78) between 0% and about 45% at 1 hour, between about 0% and about 60% at 2 hours, between about 15% and about 70% at 4 hours, between about 25% and about 80% at 8 hours, between about 35% and about 90% at 12 hours, between about 45% to about 100% at 16 hours, between about 60% and about 100% hours at 24 hours and greater than 60% at 36 hours; or (79) between 0% and about 50% at 1 hour, between about 5% and about 65% at 2 hours, between about 20% and about 75% at 4 hours, between about 30% and about 85% at 8 hours, between about 40% and about 95% at 12 hours, between about 50% to about 100% at 16 hours, between about 70% and about 100% hours at 24 hours and greater than 70% at 36 hours; or (80) between 0% and about 30% at 1 hour, between about 5% and about 40% at 2 hours, between about 10% and about 60% at 4 hours, between about 20% and about 70% at 8 hours, between about 30% and about 100% at 12 hours, between about 40% to about 100% at 16 hours, between about 60% and about 100% hours at 24 hours and greater than 90% at 36 hours; or (81) between 0% and about 30% at 1 hour, between about 0% and about 30% at 2 hours, between about 0% and about 30% at 4 hours, between about 5% and about 70% at 8 hours, between about 10% and about 80% at 12 hours, between about 20% to about 100% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 50% at 36 hours; or (82) between 0% and about 20% at 1 hour, between about 0% and about 20% at 2 hours, between about 0% and about 20% at 4 hours, between about 0% and about 20% at 8 hours, between about 5% and about 40% at 12 hours, between about 10% to about 80% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 60% at 36 hours; or (83) between 0% and about 10% at 1 hour, between about 0% and about 20% at 2 hours, between about 0% and about 40% at 4 hours, between about 5% and about 60% at 8 hours, between about 10% and about 80% at 12 hours, between about 20% to about 100% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 50% at 36 hours; or (84) between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between

about 3% and about 95% at 4 hours, between about 10% and about 100% at 8 hours, between about 20% and about 100% at 12 hours, between about 30% to about 100% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours; or (85) between 0% and about 45% at 1 hour, between about 0% and about 70% at 2 hours, between about 3% and about 90% at 4 hours, between about 8% and about 100% at 8 hours, between about 15% and about 100% at 12 hours, between about 25% to about 100% at 16 hours, between about 45% and about 100% hours at 24 hours and greater than 80% at 36 hours; or (86) between 0% and about 40% at 1 hour, between about 0% and about 65% at 2 hours, between about 0% and about 80% at 4 hours, between about 5% and about 80% at 8 hours, between about 10% and about 90% at 12 hours, between about 20% to about 100% at 16 hours, between about 40% and about 100% hours at 24 hours and greater than 70% at 36 hours; or (87) between 0% and about 35% at 1 hour, between about 0% and about 60% at 2 hours, between about 0% and about 70% at 4 hours, between about 3% and about 70% at 8 hours, between about 5% and about 80% at 12 hours, between about 15% to about 100% at 16 hours, between about 30% and about 100% hours at 24 hours and greater than 40% at 36 hours; or (88) between 0% and about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 5% and about 100% at 4 hours, between about 15% and about 100% at 8 hours, between about 30% and about 100% at 12 hours, between about 40% to about 100% at 16 hours, between about 60% and about 100% hours at 24 hours and greater than 70% at 36 hours; or (89) between 0% and about 50% at 1 hour, between about 0% and about 75% at 2 hours, between about 5% and about 95% at 4 hours, between about 25% and about 80% at 8 hours, between about 30% and about 100% at 12 hours, between about 40% to about 100% at 16 hours, between about 60% and about 100% hours at 24 hours and greater than 60% at 36 hours; or (90) between 0% and about 60% at 1 hour, between about 0% and about 85% at 2 hours, between about 5% and about 100% at 4 hours, between about 10% and about 100% at 8 hours, between about 20% and about 100% at 12 hours, between about 30% to about 100% at 16 hours, between about 50% and about 100% hours at 24 hours and greater than 80% at 36 hours; or (91) between 15% and about 25% at 1 hour, between about 25% and about 35% at 2 hours, between about 30% and about 45% at 4 hours, between about 40% and about 60% at 8 hours, between about 55% and about 70% at 12 hours and between about 60% to about 75% at 16 hours; or (92) between 10% and about 20% at 1 hour, between about 20% and about 30% at 2 hours, between about 25% and about 40% at 4 hours, between about 30% and about 50% at 8 hours, between about 50% and about 65% at 12 hours and between about 55% to about 65% at 16 hours; or (93) between 5% and about 15% at 1 hour, between about 15% and about 25% at 2 hours, between about 20% and about 35% at 4 hours, between about 25% and about 45% at 8 hours, between about 45% and about 60% at 12 hours and between about 50% to about 60% at 16 hours; or (94) between 15% and about 30% at 1 hour, between about 20% and about 40% at 2 hours, between about 20% and about 50% at 4 hours, between about 30% and about 70% at 8 hours,

between about 60% and about 80% at 12 hours and between about 70% to about 90% at 16 hours; or (95) between 0% and about 50% at 1 hour, between about 5% and about 50% at 2 hours, between about 5% and about 70% at 4 hours, between about 10% and about 80% at 8 hours, between about 20% and about 100% at 12 hours and between about 40% to about 100% at 16 hours; or (96) between 15% and about 40% at 1 hour, between about 15% and about 45% at 2 hours, between about 20% and about 60% at 4 hours, between about 20% and about 80% at 8 hours, between about 30% and about 90% at 12 hours and between about 40% to about 100% at 16 hours; or (97) between 0% to about 80% at 0.5 hours, and greater than about 40% at 1 hour; or (98) between 0% to about 40% at 0.5 hours, and greater than about 60% at 1 hour; or (98a) between 0% to about 20% at 0.5 hours, and greater than about 40% at 1 hour; or (99) between 0% to about 20% at 0.5 hours, and greater than about 20% at 1 hour; or (100) between 0% to about 90% at 0.5 hours, and greater than about 60% at 1 hour; or (101) between 0% to about 100% at 0.5 hours, and greater than about 60% at 1 hour; or (102) between 0% to about 90% at 1 hour, and greater than about 40% at 2 hours; or (103) between 0% to about 100% at 1 hour, and greater than about 60% at 2 hours; or (104) between 0% to about 60% at 1 hour, and greater than about 40% at 2 hours; or (105) between 0% to about 40% at 1 hour, and greater than about 30% at 2 hours; or (106) between 0% to about 50% at 1 hour, and greater than about 40% at 2 hours; or (107) between 0% to about 30% at 1 hour, and greater than about 20% at 2 hours; or (108) between 0% and about 50% at 1 hour, between about 0% and about 80% at 2 hours, between about 5% and about 100% at 4 hours and between about 10% and about 100% at 8 hours; or (109) between 10% and about 60% at 1 hour, between about 15% and about 75% at 2 hours, between about 20% and about 95% at 4 hours and between about 30% and about 100% at 8 hours; or (110) between 0% to about 80% at 0.25 hours, and greater than about 90% at 1 hour; or (111) between 0% to about 100% at 0.25 hours, and greater than about 60% at 1 hour. In some preferred embodiments, the in-vitro release rate of levorphanol in the foregoing (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of between 4.5 and 8 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of 0.1N HCl for about 1, 1.5, 2, 2.5 or 3 hours at 37 °C. In some preferred embodiments, the in-vitro release rate of levorphanol in the foregoing (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at any pH between 4.5 and 8 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of 0.1N HCl for about 1, 1.5, 2, 2.5 or 3 hours at 37 °C. In some preferred embodiments, the in-vitro release rate of levorphanol in the foregoing (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of 5, 6, 6.5, 7 or 7.4 at 37 °C, said release rate measured following dissolution

(pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of 0.1N HCl for about 1, 2 or 3 hours at 37 °C. In some preferred embodiments, the foregoing in-vitro release rate of levorphanol in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of 5, 6, 6.5, 7 or 8 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of 0.1N HCl for about 1 or 2 hours at 37 °C, and then following further dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL distilled water at a pH of between 2 and 4 for up to two hours at 37 °C. In some preferred embodiments, the foregoing in-vitro release rate of levorphanol in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water at 37 °C at a pH of between 4.5 and 8 at 37 °C, without any pretreatment in 0.1N HCl. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at any pH between 4.5 and 8 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of 0.1N HCl for two hours at 37 °C, and then following further dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL distilled water at any pH of between 2 and 4 for up to two hours at 37 °C. In some preferred embodiments, the foregoing release rate in (1) to (111) provides duodenal delivery, jejunal delivery, ileal delivery, ileo-colonic delivery or colonic delivery of levorphanol. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of between 4.5 and 8 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of 0.1N HCl for about 1, 1.5, 2, 2.5 or 3 hours at 37 °C. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of between 4.5 and 8 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of 0.1N HCl for about 1, 1.5, 2, 2.5 or 3 hours at 37 °C, and then following further dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL distilled water at a pH of between 2 and 4 for a further time of up to two hours at 37 °C. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water at 37 °C at a pH of between 4.5 and 8 at 37 °C. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 5 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of

distilled water for about 2 hours at 37 °C at a pH of about 2. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 5.5 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 2. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 6 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 2. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 6.8 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 2. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 7.4 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 2. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 5 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 3. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 5.5 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 3. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 6 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 3. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 6.8 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 3. In some preferred

embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 7.4 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 3. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 5 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 4. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 5.5 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 4. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 6 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 4. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 6.8 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 4. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 7.4 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 4. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 6 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 5. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 6.8 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 5. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when

measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 7.4 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 5. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 6.8 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 5.5. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 7.4 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 5.5. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 7 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 6. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 7.4 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water for about 2 hours at 37 °C at a pH of about 6. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Paddle Method with a sinker at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at a pH of about 7.4 at 37 °C, said release rate measured following dissolution (pretreatment) with USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH between 1.6 and 7.2 at 37 °C. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Paddle Method with a sinker at 75 rpm in 600 mL of Simulated Intestinal Fluid (SIF) USP, without the inclusion of enzyme, at a pH of 6.8 at 37 °C, said release rate measured without prior dissolution (or pretreatment) in 0.1N HCl. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method at 50 or 75 rpm instead of 100 rpm. In some preferred embodiments, the foregoing release rate in (1) to (111) is achieved when measured by the USP Basket or Paddle Method in 100 mL, 250 or 500 mL of dissolution media instead of 900 mL. In some preferred embodiments, the foregoing release rate in (1) to (111) is measured with the aid of a sinker (e.g., a nonreactive stainless steel wire helix, other inert material, cork borers, cylinders, see, for example, USP 32–NF 27).

[441] Extended Release Levorphanol Dosage Forms

[442] In some embodiments, the dosage form of the invention is an oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form therapeutically effective for up to 24 hours.

[443] In some embodiments, the dosage form of the invention is an oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form therapeutically effective for up to 12 hours.

[444] In some embodiments, the dosage form of the invention is an oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form therapeutically effective for at least about 10 hours.

[445] In some embodiments, the dosage form of the invention is an oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form therapeutically effective for at least about 12 hours.

[446] In some embodiments, the dosage form of the invention is an oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form therapeutically effective for at least about 16 hours.

[447] In some embodiments, the dosage form of the invention is an oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form therapeutically effective for at least about 18 hours.

[448] In some embodiments, the dosage form of the invention is an oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form therapeutically effective for at least about 24 hours.

[449] In some embodiments, the dosage form of the invention is an oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form suitable for dosing up to every 24 hours.

[450] In some embodiments, the dosage form of the invention is an oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form suitable for dosing every 12 hours.

- [451] In some embodiments, the dosage form of the invention is an oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form suitable for dosing every 24 hours.
- [452] In some preferred embodiments, the oral dosage form comprises a plurality of pharmaceutically acceptable beads coated with drug and overcoated with controlled release material.
- [453] In one embodiment of the invention, the dosage form includes a capsule within a capsule, each capsule containing a different drug or the same drug intended for treating the same or a different malady. In some preferred embodiments, the outer capsule may be an enteric coated capsule or a capsule containing an immediate release formulation to provide rapid plasma concentrations or a rapid onset of effect or a loading dose and the inner capsule contains an extended release formulation. In some preferred embodiments, up to 3 capsules within a capsule are contemplated as part of the invention. In one embodiment of the invention, the dosage form involves one or more tablets within a capsule, wherein the levorphanol is either in the tablet and/or in one of the capsules.
- [454] In one embodiment of the invention, the formulation is ingested orally as a tablet or capsule, preferably as a capsule. In another embodiment of the invention, the formulation is administered buccally.
- [455] In some preferred embodiments, the oral dosage form comprises (i) a drug layer; and (ii) a displacement layer comprising an osmopolymer; and (b) a semipermeable wall surrounding the bilayer core having a passageway disposed therein for the release of said drug.
- [456] In some preferred embodiments, the oral dosage form comprises a compressed tablet, compressed capsule or uncompressed capsule. In some preferred embodiments, the oral dosage form comprises a liquid fill capsule.
- [457] In some preferred embodiments, the pharmacokinetic and pharmacodynamic parameters of the specifications and claims are determined under fed conditions. In other preferred embodiments, the pharmacokinetic and pharmacodynamic parameters of the specifications and claims are determined under fasted conditions.
- [458] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; said dosage form intended solely for the treatment of pain.
- [459] In some preferred embodiments, the invention comprises an oral pharmaceutical composition for the treatment of diseases and disorders comprising a therapeutically effective amount of levorphanol.
- [460] In some preferred embodiments, the invention comprises an oral pharmaceutical composition for the treatment of pain comprising a therapeutically effective amount of levorphanol.

- [461] It is an object of certain embodiments of the present invention to provide oral levorphanol formulations with both immediate release and extended release forms.
- [462] It is an object of certain embodiments of the present invention to provide oral levorphanol wherein the levorphanol is dispersed within a matrix.
- [463] In certain preferred embodiments the oral dosage form of the present invention comprises a matrix which includes a controlled release material and levorphanol or a pharmaceutically acceptable salt thereof. In certain preferred embodiments, the matrix is compressed into a tablet and may be optionally overcoated with a coating that in addition to the controlled release material of the matrix may control the release of the levorphanol or pharmaceutically acceptable salt thereof from the formulation, such that blood levels of active ingredient are maintained within the therapeutic range over an extended period of time. In certain alternate embodiments, the matrix is encapsulated.
- [464] In certain preferred embodiments, the extended release oral dosage form of the present invention comprises a plurality of pharmaceutically acceptable extended release matrices comprising levorphanol, the dosage form maintaining the blood plasma levels of levorphanol within the therapeutic range over an extended period of time when administered to patients.
- [465] In some preferred embodiments, the dosage form of the invention comprises oral levorphanol formulated to release the levorphanol from the dosage form or to initiate the release of the levorphanol from the dosage form after a certain specific amount of time post-oral ingestion, or at an approximately specific anatomic location in the gastrointestinal tract, or when the dosage form is in contact with specific gastrointestinal conditions (e.g., pH range, osmolarity, electrolyte content, food content, pressure, time since first ingestion, osmotic pressure in the dosage form, osmotic pressure in the gastrointestinal tract, hydration, etc), said dosage form suitable for providing an orally effective therapeutic for a short, intermediate or extended duration of effect, said dosage form providing a rapid or delayed onset of clinical effect.
- [466] In certain preferred embodiments the extended release oral dosage form of the present invention is an osmotic dosage form which comprises a single layer or bilayer core comprising levorphanol; an expandable polymer; a semipermeable membrane surrounding the core; and a passageway disposed in the semipermeable membrane for extended release of the levorphanol or pharmaceutically acceptable salt thereof, such that blood levels of active ingredient are maintained within the therapeutic range over an extended period of time when administered to patients. Other oral osmotic delivery systems may be used for the oral administration of levorphanol, including elementary osmotic pump, multi-chamber osmotic pumps, push-pull osmotic pump, osmotic pumps with nonexpanding second chamber, controlled oral drug delivery systems, controlled porosity osmotic pump, modified osmotic pump for insoluble drugs, multiparticulate delayed-release system, monolithic osmotic systems [see Verma et al, Osmotically Controlled Oral Drug Delivery. Drug Dev Ind Pharm, 2000;26:695-708; Verma et al, Formulation aspects in the development of

osmotically controlled oral drug delivery systems. J Controlled Rel. 2002;79:7-27; Xiaoling Li, Design of Controlled Release Drug Delivery Systems (page 1-430), McGraw-Hill Professional; 1 edition (November 3, 2005); Colonic Drug Delivery (page 287-294), Wilson CG, In: Modified-Release Drug Delivery Technology, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008; Biopolymers and Colonic Delivery, Wilson CG, Mukherji G, Shah HK (pages 295-309), In: Modified-Release Drug Delivery Technology, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008; Enteric Coating for Colonic Delivery, Shah HK, Mukherji G, Brogmann B, Wilson CG (pages 311-324), In: Modified-Release Drug Delivery Technology, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008; Programmed Drug Delivery Systems and the Colon, Wilson CG, Shah HK, Lee WW, Brogmann B, Mukherji G (pages 325-335), In: Modified-Release Drug Delivery Technology, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008; Targeting the Colon Using COLAL™ : A Novel Bacteria-Sensitive Drug Delivery System, McConnell EL, Basit AW (pages 343-348), In: Modified-Release Drug Delivery Technology, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008, which are hereby incorporated in their entirety by reference for all purposes].

- [467] Other oral osmotic delivery systems may be used for the oral administration of levorphanol.
- [468] In some preferred embodiments of the invention, the oral levorphanol is interdispersed and are not isolated from each other in two distinct layers.
- [469] In some preferred embodiments of the invention, the oral levorphanol is in the form of multiparticulates.
- [470] In some preferred embodiments of the invention, the oral levorphanol is dispersed in a matrix
- [471] In some preferred embodiments of the invention, the oral levorphanol is in the form of multiparticulates can be dispersed in a matrix or contained in a capsule.
- [472] In some preferred embodiments of the invention, the oral levorphanol is in the form of multiparticulates can be dispersed in a matrix and compressed into a tablet.
- [473] In some preferred embodiments of the invention, the oral levorphanol is in a matrix that is in the form of pellets.
- [474] In some preferred embodiments of the invention, the oral levorphanol is in coated beads.
- [475] In some preferred embodiments, the dosage form of the invention comprises a compressed tablet, compressed capsule or uncompressed capsule. In other embodiments, the dosage form comprises a liquid fill capsule.
- [476] In some preferred embodiments, the dosage form of the invention comprises an oral formulation (e.g., tablet or capsule) which is coated to prevent substantial direct contact of

levorphanol with oral cavity (e.g. tongue, oral mucosa), oropharyngeal mucosal surface, esophagus or stomach.

- [477] In some preferred embodiments, the dosage form of the invention comprises an oral formulation which is coated with a film or polymer. In some preferred embodiments, the dosage form of the invention comprises levorphanol in an enteric coating.
- [478] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a therapeutically effective amount of levorphanol; said therapeutically effective amount in a reservoir comprising: (i) levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; (ii) a membrane layer, said membrane being substantially permeable to levorphanol; wherein the dosage form substantially releases the levorphanol from the dosage form to render said dosage form suitable for extended release to a human patient.
- [479] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising a plurality of pharmaceutically acceptable beads coated with a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; and overcoated with controlled release material to render said dosage form suitable for extended release oral administration to a human patient.
- [480] In some preferred embodiments, the dosage form provides an oral extended release pharmaceutical composition comprising (i) a drug layer comprising a therapeutically effective amount of levorphanol; and (ii) a displacement layer comprising an osmopolymer; and (b) a semipermeable wall surrounding the bilayer core having a passageway disposed therein for the release of said levorphanol or a pharmaceutically acceptable salt thereof; said dosage form suitable for extended release oral administration to a human patient.
- [481] In some preferred embodiments, the oral dosage form is a controlled release material suitable for extended release in a human patient of the dosage form comprises a matrix. In some preferred embodiments, the said matrix is a plurality of multiparticulate matrices. In some preferred embodiments, the multiparticulates are compressed into a tablet. In some preferred embodiments, the multiparticulates are disposed in a pharmaceutically acceptable capsule.
- [482] In some preferred embodiments, the extended release levorphanol dosage form of the invention is a solid dispersion. By reducing drug particle size and therefore improving drug wettability, the bioavailability may be substantially improved. Solid dispersions are usually presented as amorphous products, primarily made through two major different methods (e.g., melting and solvent evaporation). In addition, surfactants may be included to stabilize the dosage form in order to increase solubility and reduce recrystallization (see Vasconcelos et al, Drug Discovery Today, 2007; 12:1068-75, which is herein incorporated in its entirety by reference).
- [483] Some or all of the above objects and others are achieved by embodiments of the present

invention, which is directed in part to a dosage form of orally administered extended release levorphanol.

[484] Functional Excipients of the Dosage Form

[485] In some preferred embodiments, the extended release levorphanol dosage form is suitable for dosing a human subject about every 12 or 24 hours (Q12H, Q12H PRN, Q24H, Q24H PRN).

[486] In some preferred embodiments, the extended release levorphanol dosage form provides a therapeutic effect to a human subject for at least about 8, 10, 12, 14, 16, 18, 20, 22 or 24 hours.

[487] Applicant has now surprisingly discovered that extended release dosage forms of levorphanol suitable for dosing up to once-a-day (Q24H) provide robust bioavailability, comparable to immediate release levorphanol. This was previously believed to be unachievable with non-multiparticulate dosage forms of opioids for once-daily administration.

[488] Applicant has now also surprisingly discovered that extended release dosage forms of levorphanol suitable for dosing up to once-a-day (Q24H) can provide a robust extended release pharmacokinetic profile.

[489] Applicant has now also surprisingly discovered that extended release dosage forms of levorphanol comprising waxes and vegetable oils and their esters and derivatives, when treated by application of heat at least up to their melting point and admixed with a thixotrope and a release rate modifier provides robust bioavailability and excellent extended release profiles suitable for up to once-a-day (Q24H).

[490] Applicant has now also surprisingly discovered that extended release dosage forms of levorphanol comprising hydrogenated vegetable oils which are primarily lauric hard butter and lecithin, when treated by application of heat at least up to their melting point and admixed with a thixotrope and a release rate modifier provides robust bioavailability and excellent extended release profiles suitable for up to once-a-day (Q24H).

[491] Applicant has now also surprisingly discovered that extended release dosage forms of levorphanol comprising other hydrogenated vegetable oils, when treated by application of heat at least up to their melting point, and admixed with a thixotrope and a release rate modifier, and further admixed medium chain triglycerides provides robust bioavailability and excellent extended release profiles suitable for up to once-a-day (Q24H).

[492] Surprisingly, in some embodiment, oral levorphanol formulations of the invention containing Miglyol™ 812N, a fractionated coconut oil, provided more robust extended release formulations.

[493] Surprisingly, in some embodiment, oral levorphanol formulations of the invention containing Miglyol™ 812N, a fractionated coconut oil, provided more robust extended release formulations with reduced potential for physical manipulation of the dosage form (dosage form tampering) and hence reduced potential for abuse.

- [494] Surprisingly, in some embodiment, oral levorphanol formulations of the invention containing Miglyol™ 812N, a fractionated coconut oil, imparted softness and “stickiness” to formulations that contained waxes which were naturally hard and potentially subject to grinding into powders, and hence subject both to friability and product tampering.
- [495] Surprisingly, in some embodiment, oral levorphanol formulations of the invention containing Miglyol 812N, a fractionated coconut oil added to the difficulty of attempted extraction and isolation of levorphanol using materials such as alcohols, probably by virtue of the solubility of oils in organic solvents.
- [496] In one embodiment of the present invention, the dosage form contains hydrogenated palm kernel oil (e.g., Hydrokote™ 112) in an amount not more than about 600 mg, or not more than about 500 mg, or not more than about 400 mg, or not more than about 350 mg, or not more than about 325 mg, or not more than about 300 mg, or not more than about 290 mg, or not more than about 280 mg, or not more than about 270 mg, or not more than about 260 mg, or not more than about 250 mg, or not more than about 240 mg, or not more than about 230 mg, or not more than about 220 mg, or not more than about 210 mg, or not more than about 200 mg, or not more than about 190 mg, or not more than about 180 mg, or not more than about 170 mg, or not more than about 160 mg, or not more than about 150 mg, or not more than about 140 mg, or not more than about 130 mg, or not more than about 120 mg, or not more than about 120 mg, or not more than about 110 mg, or not more than about 100 mg, or not more than about 90 mg, or not more than about 80 mg, or not more than about 70 mg, or not more than about 60 mg, or not more than about 50 mg, or not more than about 40 mg, or not more than about 30 mg, or not more than about 20 mg, or not more than about 10 mg.
- [497] In one embodiment of the present invention, the dosage form contains glyceryl behenate hydrogenated (Compritol™ 888 ATO), in an amount not more than about 600 mg, or not more than about 500 mg, or not more than about 400 mg, or not more than about 350 mg, or not more than about 325 mg, or not more than about 300 mg, or not more than about 290 mg, or not more than about 280 mg, or not more than about 270 mg, or not more than about 260 mg, or not more than about 250 mg, or not more than about 240 mg, or not more than about 230 mg, or not more than about 220 mg, or not more than about 210 mg, or not more than about 200 mg, or not more than about 190 mg, or not more than about 180 mg, or not more than about 170 mg, or not more than about 160 mg, or not more than about 150 mg, or not more than about 140 mg, or not more than about 130 mg, or not more than about 120 mg, or not more than about 120 mg, or not more than about 110 mg, or not more than about 100 mg, or not more than about 90 mg, or not more than about 80 mg, or not more than about 70 mg, or not more than about 60 mg, or not more than about 50 mg, or not more than about 40 mg, or not more than about 30 mg, or not more than about 20 mg, or not more than about 10 mg.

[498] In one embodiment of the present invention, the dosage form contains hydrogenated cottonseed oil (e.g., Sterotex™ NF), in an amount not more than about 600 mg, or not more than about 500 mg, or not more than about 400 mg, or not more than about 350 mg, or not more than about 325 mg, or not more than about 300 mg, or not more than about 290 mg, or not more than about 280 mg, or not more than about 270 mg, or not more than about 260 mg, or not more than about 250 mg, or not more than about 240 mg, or not more than about 230 mg, or not more than about 220 mg, or not more than about 210 mg, or not more than about 200 mg, or not more than about 190 mg, or not more than about 180 mg, or not more than about 170 mg, or not more than about 160 mg, or not more than about 150 mg, or not more than about 140 mg, or not more than about 130 mg, or not more than about 120 mg, or not more than about 120 mg, or not more than about 110 mg, or not more than about 100 mg, or not more than about 90 mg, or not more than about 80 mg, or not more than about 70 mg, or not more than about 60 mg, or not more than about 50 mg, or not more than about 40 mg, or not more than about 30 mg, or not more than about 20 mg, or not more than about 10 mg.

[499] In one embodiment of the present invention, the dosage form contains a fractionated coconut oil (e.g., Miglyol™ 812N), in an amount not more than about 600 mg, or not more than about 500 mg, or not more than about 400 mg, or not more than about 350 mg, or not more than about 325 mg, or not more than about 300 mg, or not more than about 290 mg, or not more than about 280 mg, or not more than about 270 mg, or not more than about 260 mg, or not more than about 250 mg, or not more than about 240 mg, or not more than about 230 mg, or not more than about 220 mg, or not more than about 210 mg, or not more than about 200 mg, or not more than about 190 mg, or not more than about 180 mg, or not more than about 170 mg, or not more than about 160 mg, or not more than about 150 mg, or not more than about 140 mg, or not more than about 130 mg, or not more than about 120 mg, or not more than about 120 mg, or not more than about 110 mg, or not more than about 100 mg, or not more than about 90 mg, or not more than about 80 mg, or not more than about 70 mg, or not more than about 60 mg, or not more than about 50 mg, or not more than about 40 mg, or not more than about 30 mg, or not more than about 20 mg, or not more than about 10 mg, or not more than about 5 mg.

[500] In one embodiment of the present invention, the dosage form contains hydroxypropyl methyl cellulose (e.g., HPMC K15M), in an amount not more than about 600 mg, or not more than about 500 mg, or not more than about 400 mg, or not more than about 350 mg, or not more than about 325 mg, or not more than about 300 mg, or not more than about 290 mg, or not more than about 280 mg, or not more than about 270 mg, or not more than about 260 mg, or not more than about 250 mg, or not more than about 240 mg, or not more than about 230 mg, or not more than about 220 mg, or not more than about 210 mg, or not more than about 200 mg, or not more than about 190 mg, or not more than about 180 mg, or not more than about 170 mg, or not more than

about 160 mg, or not more than about 150 mg, or not more than about 140 mg, or not more than about 130 mg, or not more than about 120 mg, or not more than about 120 mg, or not more than about 110 mg, or not more than about 100 mg, or not more than about 90 mg, or not more than about 80 mg, or not more than about 70 mg, or not more than about 60 mg, or not more than about 50 mg, or not more than about 40 mg, or not more than about 30 mg, or not more than about 20 mg, or not more than about 10 mg, or not more than about 5 mg.

[501] In one embodiment of the present invention, the dosage form contains silicon dioxide (alone or in combination with Al₂O₃; e.g, Aerosil™, Aerosil™ 200, Aerosil™ COK84), in an amount not more than about 600 mg, or not more than about 500 mg, or not more than about 400 mg, or not more than about 350 mg, or not more than about 325 mg, or not more than about 300 mg, or not more than about 290 mg, or not more than about 280 mg, or not more than about 270 mg, or not more than about 260 mg, or not more than about 250 mg, or not more than about 240 mg, or not more than about 230 mg, or not more than about 220 mg, or not more than about 210 mg, or not more than about 200 mg, or not more than about 190 mg, or not more than about 180 mg, or not more than about 170 mg, or not more than about 160 mg, or not more than about 150 mg, or not more than about 140 mg, or not more than about 130 mg, or not more than about 120 mg, or not more than about 120 mg, or not more than about 110 mg, or not more than about 100 mg, or not more than about 90 mg, or not more than about 80 mg, or not more than about 70 mg, or not more than about 60 mg, or not more than about 50 mg, or not more than about 45 mg, or not more than about 40 mg, or not more than about 35 mg, or not more than about 30 mg, or not more than about 25 mg, or not more than about 20 mg, or not more than about 18 mg, or not more than about 15 mg, or not more than about 12 mg, or not more than about 10 mg, or not more than about 9 mg, or not more than about 8 mg, or not more than about 7 mg, or not more than about 6 mg, or not more than about 5 mg, or not more than about 4 mg, or not more than about 2 mg, or not more than about 1 mg.

[502] In one embodiment of the present invention, release rate modifiers, including hydroxypropyl methyl cellulose (e.g, HPMC K15M) may be incorporated. Release rate modifiers can also have additional useful properties that optimize the formulation.

[503] A variety of agents may be incorporated into the invention as thixotropes (e.g., fumed silicon dioxides, Aerosil™, Aerosil™ COK84, Aerosil™ 200, etc.). Thixotropes enhance the pharmaceutical formulations of the invention by increasing the viscosity of solutions complementing the action of HPMCs.

[504] In some preferred embodiments, the inclusion of silicon dioxide (alone or in combination with Al₂O₃; e.g, Aerosil™, Aerosil™ 200, Aerosil™ COK84) is essential to provide the desired pharmaceutical properties of the extended release dosage form of oral levorphanol. Without being bound by theory: in some embodiments, the inclusion of silicon dioxide (alone or in combination

with Al₂O₃; e.g, Aerosil™, Aerosil™ 200, Aerosil™ COK84) is essential to provide the desired pharmaceutical properties of the extended release dosage form of oral levorphanol, said silicon dioxide providing thixotropic properties, thereby providing extended release; in other embodiments, the inclusion of silicon dioxide (alone or in combination with Al₂O₃; e.g, Aerosil™, Aerosil™ 200, Aerosil™ COK84) is essential to provide the desired pharmaceutical properties of the extended release dosage form of oral levorphanol, said silicon dioxide providing thixotropic properties, said thixotrope providing a tamper or abuse deterrent dosage form; in other embodiments, the inclusion of silicon dioxide (alone or in combination with Al₂O₃; e.g, Aerosil™, Aerosil™ 200, Aerosil™ COK84) is essential to provide the desired pharmaceutical properties of the extended release dosage form of oral levorphanol, said silicon dioxide providing thixotropic properties, said thixotrope simultaneously providing a tamper or abuse deterrent dosage form and extended release; in some embodiments, the desired pharmaceutical properties of the extended release dosage form of oral levorphanol referred to in the foregoing requires the combination of hydroxypropyl methyl cellulose and silicon dioxide (alone or in combination with Al₂O₃; e.g, Aerosil™, Aerosil™ 200, Aerosil™ COK84).

[505] In some preferred embodiments, the composition is a liquid filled thermosoftening extended release dispersion systems which provides an alternative dosage form and method and process of manufacture of extended release levorphanol suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient. This dosage form is advantageously utilized to prepare a robust, cost effective formulation of the invention which (a) avoids one or more of the excipients in commercially available oral immediate-release levorphanol tartrate tablets and their associated adverse impact on the in vivo performance of the levorphanol; (b) substantially reduces or eliminates the need for pharmaceutical excipients generally recommended or considered necessary in a solid the dosage form (e.g. glidants, lubricants, diluents, fillers, binders, disintegrants and antioxidants), with associated cost, workplace safety and patient safety benefits; (c) is relatively easy to scale-up; and (d) requires a relatively simple manufacturing process, which may optionally be performed entirely in situ in a single heated mixing vessel prior to transfer to a filling machine for encapsulation.

[506] In some preferred embodiments, said liquid filled thermosoftening extended release levorphanol dosage form comprises, in addition to levorphanol, hydrogenated vegetable oils. In some preferred embodiments, said hydrogenated vegetable oil is selected from the group comprising hydrogenated cottonseed oil, hydrogenated palm oil, hydrogenated soybean oil and hydrogenated palm kernel oil, or derivatives thereof or mixture thereof.

[507] In some preferred embodiments, said liquid filled thermosoftening extended release levorphanol dosage form comprises, in addition to levorphanol, polyoxyethylene stearates and/or distearates. In some preferred embodiments, said polyoxyethylene stearates and/or distearates is

selected from the group comprising polyoxyl 2, 4, 6, 8, 12, 20, 30, 40, 50, 100 and 150 stearates and polyoxyl 4, 8, 12, 32 and 150 distearates, or derivatives thereof or mixture thereof.

[508] In some preferred embodiments, said liquid filled thermosoftening extended release levorphanol dosage form comprises, in addition to levorphanol, a wax. In some preferred embodiments, said wax is selected from the group comprising animal waxes, insect waxes, vegetable waxes, mineral waxes, petroleum waxes, synthetic waxes, nonionic emulsifying waxes, anionic emulsifying wax, carnauba wax, microcrystalline wax, yellow wax, white wax, cetyl esters wax, hydrogenated castor oil, lanolin alcohols, lanolin, glyceryl palmitostearate, cetostearyl alcohol, beeswax, stearyl macroglycerides, Hawaiian waxes, hydrogenated jojoba oil, hydroxyoctacosanyl hydroxystearate, Japan wax, paraffin waxes and rice bran wax, or the respective esters, derivatives or mixture thereof.

[509] In some preferred embodiments, said liquid filled thermosoftening extended release levorphanol dosage form comprises, in addition to levorphanol, a compound chosen from the group comprising glyceryl behenate, glyceryl palmitostearate and lauroyl macroglycerides, or mixtures thereof.

[510] In some preferred embodiments, said liquid filled thermosoftening extended release levorphanol dosage form comprises, in addition to levorphanol, a compound chosen from the group comprising coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof.

[511] In some preferred embodiments, said liquid filled thermosoftening extended release levorphanol dosage form comprises, in addition to levorphanol, a compound chosen from the group comprising glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, coconut oil, fractionated coconut oil, and beeswax, or the respective esters, derivatives or mixture thereof.

[512] As used herein, "hydrogenated palm kernel oil" includes the composition of Hydrokote™ 112, lauric hard butter and lecithin. Hydrokote™ 112 has an INCI name of "hydrogenated palm kernel oil" and a standard lauric hard butter and lecithin derived from edible vegetable oils, which has a CAS number of 84540-04-5 or 68334-28-1 and an EINECS number of 273-627-2 or 283-093-2.

[513] As used herein, "hydrogenated cottonseed oil" includes the composition of Sterotex™ and Sterotex™ NF. Sterotex™ are neutral organic esters (triglycerides) that conforms to the USP/NF monograph for Hydrogenated Vegetable Oil, Type I and the BP monograph for Hydrogenated Vegetable Oil, has a CAS number of 68334-00-9 and an EINECS number of 269-804-9 and goes by the synonym hydrogenated cottonseed oil and powdered vegetable stearine.

[514] As used herein, "hydrogenated soybean oil" includes the composition of Sterotex™ HM and Sterotex™ HM, NF. Sterotex™ HM has a CAS number of 8016-70-4 and an EINECS number of

232-410-2, goes by the synonyms hydrogenated soybean oil and powdered vegetable stearine, are neutral organic esters (triglycerides), and meets the requirements of the USP/NF monograph for Hydrogenated Vegetable Oil, Type 1 and the BP monograph for Hydrogenated Vegetable Oil.

[515] As used herein, “glycerol monostearate” includes all glyceryl monoesters, including the compositions of Cithrol™ GMS (glyceryl stearate), Cithrol™ GMS S/E (a self-emulsifying glyceryl monoester), Cithrol™ GMS N/E, Cithrol™ GMS A/S (an acid stable glyceryl monoester with PEG-100 Stearate) and Cithrol GMO (glyceryl oleate).

[516] As used herein, “glyceryl behenate” includes the composition of Compritol™ 888 and comprises is a mixture of glycerides of fatty acids, mainly behenic acid, with a 1-monoglycerides content between 12.0 and 18.0% (USP/NF-23) or a mixture of diacylglycerols, mainly dibehenoylglycerol, together with variable quantities of mono- and triacylglycerols (PhEur 2005 (Suppl. 5.1)).

[517] Fractionated coconut oil is a fraction in which the long-chain fatty acids are removed so that it consists substantially of medium chain saturated fatty acids. It is sometimes referred to as caprylic/capric, triglyceride oil or medium chain triglyceride oil because it is substantially comprised of the medium chain caprylic (C₈) and capric (C₁₀) acids.

[518] Unless specifically modified, as used herein, the terms “coconut oil” and “coconut oil derivative” comprise one or more of the following, regardless of the plant source or the synthetic source: (i) the compositions of Miglyol™ 810, Miglyol™ 812, Miglyol™ 818 and Miglyol™ 829; (ii) coconut oil, hydrogenated coconut oil, fractionated coconut oil, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, oleic acid, medium-chain triglycerides or related esters, triglycerides (Akomed™ E, Akomed™ R, Miglyol™ 810, and Captex™ 355, Labrafac™ CC), propylene glycol diester of caprylic and/or capric acid (Labrafac™ PG), propylene glycol monolaurate (Lauroglycol™ FCC), medium-chain diesters of propylene glycols (Miglyol™840), partial ester of diglycerides with natural fatty acids (Softisan™ 645), and linoleic acid; and (iii) oil of any source substantially comprising medium chain triglyceride (C₆ to C₁₂). Preferably, the coconut oil is substantially consists of medium chain triglycerides (C₆ to C₁₂), more (C₆ to C₁₀).

[519] In one preferred embodiment of the present invention, also included in the dosage form are coconut oil products, including without limitation and regardless of plant source or synthetic source, coconut oil, fractionated coconut oil, cetyl alcohol, lauric acid and medium chain triglycerides (e.g., Miglyol™ 810, Miglyol™ 812 are triglycerides of the fractionated plant fatty acids C₈ and C₁₀ which meet the requirements of the European Pharmacopeia (4.6) and USP/NF(22) as Medium Chain Triglycerides, the British Pharmacopoeia (1999) as Fractionated Coconut Oil and the Japanese Pharmaceutical Excipients (JPE) as Caprylic/Capric Triglyceride.

[520] Miglyol™ 818 is a triglyceride of the fractionated plant fatty acids C₈ and C₁₀ and contains

about 4 to 5 % linoleic acid.

- [521] Miglyol™ 829 is a glycerin ester of the fractionated plant fatty acids C₈ und C₁₀, combined with succinic acid.
- [522] Miglyol™ 840 is a propylene glycol diester of saturated plant fatty acids with chain lengths of C₈ and C₁₀.
- [523] In some preferred embodiments, the extended release levorphanol dosage form comprises, in addition to levorphanol, a vegetable oil or an esters or derivative of the vegetable oil, or mixture thereof. Any pharmaceutically acceptable ester of a vegetable oil may be used to practice the invention.
- [524] In some preferred embodiments, the extended release levorphanol dosage form comprises, in addition to levorphanol, a vegetable oil which is a hydrogenated vegetable oil, or an esters or derivative of the vegetable oil derived made from andiroba seed oil, apricot kernel oil, arachis oil, argane oil, artemisia oil, avocado butter, avocado oil, babassu oil, baobab oil, bitter cherry kernel oil, black cumin seed oil, black currant seed oil, black walnut oil, borage (starflower) oil, brazil nut oil, buriti oil, camellia oil, cape chestnut oil, cashew nut oil, castor oil, castor oil (sulfated), chaulmoogra oil, chia oil, chufa oil, cocoa butter, coconut oil, coffee bean oil, corn oil, cotton seed oil, cranberry seed oil, cupuacu butter, echium seed oil, evening primrose oil, gold of pleasure oil, grape seed oil, grapefruit seed oil, hazelnut oil, hemp oil, horseradish tree (Moringa) oil, illipe butter, kiwi seed oil, kokum butter, kukui nut oil, lime seed oil, linseed oil, london rocket oil, macadamia nut oil, mango butter, manketti nut oil, marigold seed oil, marula oil, meadowfoam seed oil, mobola plum oil, murumuru butter, neem oil, ngali nut oil, olive oil, palm kernel oil, palm oil, papaya seed oil, passion fruit, seed oil, peach kernel oil, peanut oil, pecan oil, pequi oil, perilla seed oil, pistachio nut oil, plum kernel oil, pomegranate seed oil, poppy seed oil, pumpkin seed oil, rape seed oil, raspberry seed oil, rice bran oil, rose hip oil (dog rose), rose hip oil (sweet brier), safflower oil, scarlet strawberry seed oil, sea buckthorn oil, seaside plum oil, sesame oil, shea butter, shorea robusta butter, soybean oil, sunflower oil, sweet almond oil, sweet cherry kernel oil, sweet orange seed oil, tamanu oil, walnut oil, watermelon seed oil (ootanga), wheatgerm oil and white mustard seed oil.
- [525] In some preferred embodiments, the extended release levorphanol dosage form comprises, in addition to levorphanol, a fatty acid derived from any vegetable or synthetic oil or fat, including caproic, caprylic, coconut, isostearic, lauric, myristic, oleic, palmitic and stearic acids.
- [526] In some preferred embodiments, the extended release levorphanol dosage form comprises, in addition to levorphanol, a fatty acid ester derived from any vegetable or synthetic oil or fat.
- [527] In some preferred embodiments, the extended release levorphanol dosage form comprises, in addition to levorphanol, a fat alcohol derived from any vegetable or synthetic fat, including behenyl, cetearyl, cetyl, isopropyl, isostearyl, lanolin, oleyl and stearyl alcohol.

[528] Any amount or combination of vegetable oil, hydrogenated vegetable oils, coconut oil, polyoxyethylene stearates and/or distearates, wax, or wax like compound may be included in the dosage form. Preferably, said compound represents about 0.001% to about 99% of the dosage form, more preferably, about 5% to about 95%, or about 10% to about 95%, or about 15% to about 95%, or about 20% to about 95%, or about 5% to about 85%, or about 5% to about 80%, or about 5% to about 70%, or about 10% to about 80%, or about 20% to about 80%, or about 30% to about 80%, or about 40% to about 80%, or about 50% to about 80%, each on on a %w/w basis. In one preferred embodiment of the present invention, also included in the dosage form are solubilizing agents, surfactants, emulsifying agents and other excipients selected from the group comprising Polyglycerol dioleate (Plurol Oleique™ CC 497), polyoxyethylene-polyoxypropylene copolymer (Poloxamer™ 124 and 188), partial glycerides of hydroxylated unsaturated fatty acids (Softigen™ 701), PEG-6 caprylic/capric glycerides (Softigen™ 767), polyoxyethylene glyceryl trioleate (Tagat™ TO), polyoxyethylene(20)sorbitan monooleate (Tween™ 80), propylene glycol monocaprylate (Capryol™ 90), polyglycolized glycerides (Gelucire™ 44/14 and 50/13), polyoxyl-40 hydrogenated castor oil (Cremophor™ RH 40), glycerol monostearate/di-triglycerides with glycerin(Imwitor™ 191), isosteryl diglyceryl succinate (Imwitor™ 780 K), glyceryl cocoate (Imwitor™ 928), glyceryl caprylate (Imwitor™ 988), oleoyl macrogol-8 glycerides (Labrafil™ M 1944 CS), linoleoyl macrogolglycerides (Labrafil™ M 2125 CS), PEG-8 caprylic/capric glycerides (Labrasol™), glyceryl monocaprylate (Imwitor® 308), glyceryl cocoate/citrate/lactate (Imwitor™ 380), glyceryl mono-di-caprylate/caprinate (Imwitor™ 742), lauric acid, propylene glycol laurate (Lauroglycol™ 90), oleic acid and PEG MW > 4000.

[529] In some embodiments, the invention comprises a liquid filled oral pharmaceutical composition comprising: (a) levorphanol; (b) one or more material selected from the group consisting of glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, hydrogenated coconut oil, fractionated coconut oil, and beeswax; (c) a thixotrope selected from the group consisting of amorphous anhydrous colloidal silicon dioxide, silicon dioxide, silica, fumed silicon dioxides, or a mixture of silicon dioxide and aluminum oxide, aluminum oxide, microcrystalline methylcellulose, bentonite clay, hectorite clay, magnesium aluminum silicate, lithium magnesium silicate, magnesium silicate, silicates, clays, metal oxides, aluminum hydroxide, magnesium hydroxide, carbon black, stearalkonium hectorite, kaolin, and montmorillonite; (d) a release rate modifier selected from the group consisting of hydroxypropyl methylcellulose, cellulose acetate, microcrystalline cellulose, powdered cellulose, cellulose acetate phthalate, hydroxyethyl cellulose, silicified microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, low-substituted hydroxypropyl cellulose, carboxymethylcellulose, carboxymethylcellulose calcium, hypromellose acetate succinate, hypromellose phthalate and ethylcellulose; and optionally, (e) one or more

pharmaceutically acceptable excipients; wherein (b) is dispensed into a mixer heated until fully melted, (d) is dispensed into the same heated mixer and mixed with (b) until dispersed, (c) is dispensed into the same heated mixer and mixed with (b) and (d) until dispersed, (e) is dispensed into the same heated mixer and mixed with (b), (c) and (d) until dispersed, (a) is dispensed into the same heated mixer with (b), (c), (d) and (e) and mixed thoroughly with a high shear mixer; wherein said mixture is substantially uniformly dispersed; wherein the mixed liquid mass comprising (a), (b), (c), (d) and (e) are transferred into a liquid filling machine and filled into capsules; wherein the liquid mass becomes a solid when allowed to cool to room temperature following encapsulation; wherein the liquid mass comprising (a), (b), (c), (d) and (e) is optionally prepared *in situ* in a single heated mixing vessel prior to transfer to a filling machine for encapsulation. In some embodiments, the capsule is coated with or incorporates controlled release material (e.g., a pH sensitive polymer) to render it delayed onset, extended release.

- [530] In some embodiments, said liquid filled thermosoftening extended release levorphanol dosage form comprises, in addition to levorphanol and hydrogenated vegetable oils, polyoxyethylene stearates and/or distearates, wax, or wax like compound, the coconut oil or a coconut oil derivative in amount of up to about 50%, or 40%, or 35%, or 30%, or 25%, or 20%, or 15%, or 10%, or 5% of the dosage form on a w/w basis. The benefit of incorporating a coconut oil or a coconut oil derivative as an additional compound are described herein.
- [531] In some embodiments of the present invention, a release rate modifier may be incorporated into the dosage form to impart optimized release rate properties. In some embodiments of the invention, the release rate modifiers is selected from the group comprising hydroxypropyl methylcellulose, cellulose acetate, powdered cellulose, cellulose acetate phthalate, hydroxyethyl cellulose, silicified microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, low-substituted hydroxypropyl cellulose, carboxymethylcellulose, carboxymethylcellulose calcium, hypromellose acetate succinate, hypromellose phthalate, and ethylcellulose, and mixture thereof. Release rate modifiers can also have additional useful properties that optimize the formulation, including the surprising property of tamper resistance.
- [532] In some embodiments, the release rate modifier is in an amount of up to 80%, or 70%, or 60%, or 50%, or 40%, or 30%, or 20%, or 10% on %w/w basis, preferably, up to 45%, or 40%, or 35%, or 30%, or 25%, or 20%, or 15% on %w/w basis.
- [533] In some embodiments, the release rate modifier is in an amount of up to about 200 mg, or 150 mg, or 120 mg, or 100 mg, or 80 mg, or 60 mg, or 40 mg or 20 mg.
- [534] In some embodiments, a preferred release rate modifier is hydroxypropyl methyl cellulose (e.g, HPMC K15M). Preferably, the HPMC is of a grade containing 16.5% to 30% methoxy and 4% to 32% hydroxypropyl groups. Preferably, a 2% (w/v) aqueous solutions of the hydroxypropyl methylcellulose has a viscosity of about 4 to about 300,000 Centipoise at 20 °C, said viscosity is

more preferably about 2000 to about 150,000 Centipoise, even more preferably, about 4000 to about 120,000 Centipoise, and most preferably, about 10000 to about 120,000 Centipoise.

[535] In some embodiments, the HPMC is in an amount of up to 80%, or 70%, or 60%, or 50%, or 40%, or 30%, or 20%, or 10% on %w/w basis, preferably, up to 45%, or 40%, or 35%, or 30%, or 25%, or 20%, or 15% on %w/w basis.

[536] In some embodiments, the HPMC is in an amount of up to about 200 mg, or 150 mg, or 120 mg, or 100 mg, or 80 mg, or 60 mg, or 40 mg or 20 mg.

[537] A variety of agents may be incorporated into the invention as thixotropes (e.g., amorphous anhydrous colloidal silicon dioxide, silicon dioxide, silica, fumed silicon dioxides, or a mixture of silicon dioxide and aluminum oxide, aluminum oxide, microcrystalline methylcellulose, bentonite clay, hectorite clay, magnesium aluminum silicate, lithium magnesium silicate, magnesium silicate, aluminum hydroxide, magnesium hydroxide, carbon black, stearylaluminum hectorite, kaolin, and montmorillonite which have silica, silicate or silicon dioxide groups on their surface.

[538] **Thixotropes**

[539] Fluids can generally be described as Newtonian or non-Newtonian. Liquid dispersions containing thixotropes or thixotropic material are a particular case of non-Newtonian fluids. Newtonian fluids are simple liquids that generally consist of small molecules and solutions where solute and solvent are show a linear relationship between the rate of flow or shear and the applied shear stress at a constant viscosity. In other words, the viscosity of Newtonian fluids depends only on composition, temperature and pressure. The viscosity increases moderately with increasing pressure and considerably with decreasing temperature. Fluids that deviate from Newton's law are called non-Newtonian fluids. Such fluids may be generally categorized as plastic, pseudoplastic or dilatant. Plastic fluids do not move until the applied shear stress exceeds a certain minimum value. Fluids are generally plastic due to the formation of a network structure throughout the fluid. This network needs to be disrupted before flow can begin. Pseudoplastic fluids (or shear thinning fluids) have flow immediately after application of shear stress and their apparent viscosity decreases with increased application of shear stress. Unlike fluids that exhibit Pseudoplastic flow, dilatant fluids are shear thickening, i.e., they show increased apparent viscosity with increasing shear stress. In the foregoing description of Newtonian and non-Newtonian fluids, repeated testing can be expected to produce the same results, i.e., the same rate of shear or viscosity with the same shear stress. In other words, the viscosity is independent of the prior history of the solution. In contrast, thixotropes do not follow this general rule. When mixed with fluids, thixotropes are material whose aqueous dispersions show non-Newtonian behavior but whose consistency depends on the duration of shear as well as on the rate of shear. Their apparent viscosity depends, in addition to temperature, composition and rate of shear stress, on the previous shear history and time under shear. For example, an aqueous dispersion containing an effective amount of a thixotropic material may set to

gel within three hours after it has been prepared when undisturbed, but may flow and be pourable within minutes after it has been stirred above a particular yield value. After a period of prolonged rest, the aqueous dispersion reverts to a gel as it rebuilds a three-dimensional gel-like structure. As used herein, a “thixotrope” is a non-toxic compound which when tested at one or more concentrations or in one or more amounts after incorporation into a fluid (e.g., a liquid dispersion) exhibits thixotropy, including, without limitation and without being bound by theory, compounds chosen from the group comprising a thixotrope selected from the group consisting of amorphous anhydrous colloidal silicon dioxide, silicon dioxide, silca, fumed silicon dioxides, or a mixture of silicon dioxide and aluminum oxide, aluminum oxide, microcrystalline methylcellulose, bentonite clay, hectorite clay, magnesium aluminum silicate, lithium magnesium silicate, magnesium silicate, silicates, clays, metal oxides, aluminum hydroxide, magnesium hydroxide, carbon black, stearylalkonium hectorite, kaolin, and montmorillonite. As used herein, “thixotropy” is a property exhibited by a liquid material if, when sheared at a constant rate, its apparent viscosity (or corresponding shear stress) decreases with time of shearing (see, Remington: The Science and Practice of Pharmacy, 21st ed, Lippincott Williams & Wilkins (2005); Kim C-J. Advanced Pharmaceutics: Physicochemical Principles, CRC Press (2004); Chhabra RP and Richardson JF, Non-Newtonian Flow and Applied Rheology: Engineering Applications, Butterworth-Heinemann (2008). Thixotropy may be measured using established equipment, software and methods, for example, certain viscometers such as R/S Plus™ Rheometers with a mounted spiral adapter running Rheo3000™ software from Brookfield Engineering Laboratories, Inc., Middleboro, MA.

- [540] A variety of agents may be incorporated into the invention as thixotropes (e.g., amorphous anhydrous colloidal silicon dioxide, silicon dioxide, silca, fumed silicon dioxides, or a mixture of silicon dioxide and aluminum oxide, aluminum oxide, microcrystalline methylcellulose, bentonite clay, hectorite clay, magnesium aluminum silicate, lithium magnesium silicate, magnesium silicate, silicates, clays, metal oxides, aluminum hydroxide, magnesium hydroxide, carbon black, stearylalkonium hectorite, kaolin, and montmorillonite which have silica, silicate or silicon dioxide groups on their surface.
- [541] Thixotropes enhance the pharmaceutical formulations of the invention by increasing the viscosity of solutions during attempted extraction, complementing the action of HPMCs. They may also provide a tamper resistance by helping to retain the structure of dosage units that have been heated to temperatures greater than the melting point of the base excipient (Aerosils™ are unaffected by heat). Preferably, the thixotrope is silicon dioxide, silca, fumed silicon dioxides, a mixture of silicon dioxide and aluminum oxide, or aluminum oxide.
- [542] In some embodiments, the thixotrope is in an amount of up to about 200 mg, or 150 mg, or 120 mg, or 100 mg, or 80 mg, or 60 mg, or 40 mg or 20 mg.
- [543] In some embodiments, the thixotrope is in an amount of up to about 40%, or 30%, or 20%,

or 15%, or 12%, or 10%, or 8%, or 6%, or 5%, or 4%, or 3%, or 2%, or 1%, or 0.1%, or 0.1% of the dosage form on a % w/w basis, preferably up to about 10% or 8% on a % w/w basis, more preferably, up to about 6%, or 5%, or 4%, or 3% on a % w/w basis.

[544] In some embodiments, the silicon dioxide, silica, fumed silicon dioxides, mixture of silicon dioxide and aluminum oxide, or aluminum oxide is in an amount of up to about 200 mg, or 150 mg, or 120 mg, or 100 mg, or 80 mg, or 60 mg, or 40 mg or 20 mg.

[545] In some embodiments, the silicon dioxide, silica, fumed silicon dioxides, mixture of silicon dioxide and aluminum oxide, or aluminum oxide is in an amount of up to about 40%, or 30%, or 20%, or 15%, or 12%, or 10%, or 8%, or 6%, or 5%, or 4%, or 3%, or 2%, or 1%, or 0.1%, or 0.1% of the dosage form on a % w/w basis, preferably up to about 10% or 8% on a % w/w basis, more preferably, up to about 6%, or 5%, or 4%, or 3% on a % w/w basis.

[546] In some embodiments, the thixotrope is in an amount of up to about 200 mg, or 150 mg, or 120 mg, or 100 mg, or 80 mg, or 60 mg, or 40 mg or 20 mg.

[547] **Liquid Filled Thermosoftening Extended Release Levorphanol Formulations**

[548] In some preferred embodiments, said liquid filled thermosoftening extended release levorphanol dosage form comprises the following material: (1) A and B; or (2) A and C; or (3) A and D; or (4) A and E; or (5) A, B and F; or (6) A, B and G; or (7) A, C and F; or (8) A, C and G; or (9) A, B, F and G; or (10) A, C, F and G, or (11) A, D and F, (12) A, D and G, or (13) A, E and F, or (14) A, E and G, or (15) A, D, F and G, or (16) A, E, F and G; wherein said material optionally includes (H); wherein said dosage form is rendered extended-release; wherein said dosage form is suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient; wherein, (A) = levorphanol; (B) = one or more compounds selected from each of the groups consisting of (i) glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (C) = one or more compounds selected from each of the groups consisting of (i) hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (D) = one or more compounds selected from the groups consisting of coconut oil, glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; (E) = one or more compounds selected from the groups consisting of coconut oil, hydrogenated vegetable oils, polyoxyethylene stearates,

polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macrogolglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; (F) = a thixotrope; (G) a release rate modifier; and (H) = one or more pharmaceutically acceptable excipients. In some preferred embodiments, the dosage form of the invention specifically excludes (H). In some preferred embodiments, the capsule is coated with or incorporates controlled release material (e.g., a pH sensitive polymer) to render it delayed onset, extended release.

- [549] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form comprises a dosage form wherein the combined total molar amount of the foregoing (B) to (E) in the dosage form is at least 15-fold greater than the molar amount of the levorphanol or its pharmaceutically acceptable salt in the dosage form.
- [550] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form comprises a pharmaceutical composition wherein the combined total molar amount of the foregoing (B) to (E) in the dosage form is at least 15-fold greater than the molar amount of the levorphanol or its pharmaceutically acceptable salt in the dosage form, inclusive of its water of hydration (e.g., anhydrous, monohydrate, dihydrate).
- [551] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form comprises levorphanol and excipients, wherein the levorphanol and the excipients are substantially uniformly dispersed within the dosage form.
- [552] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form is a liquid mass which becomes a solid when allowed to cool to room temperature following encapsulation.
- [553] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form is also rendered abuse-deterrent or tamper resistant.
- [554] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form is advantageously prepared in situ, where all active drug and all the excipients are mixed in a single heated mixing vessel prior to transfer to a filling machine for encapsulation.
- [555] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form comprises a monolithic dosage form.
- [556] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form comprises a compressed multiparticulate plug
- [557] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form is in the form of an encapsulated plug or a tablet with a diameter of more than 3 mm, 3.5 mm, 4 mm, 4.5 mm, 5 mm, 5.5 mm, or 6 mm. Preferably, the encapsulated plug is a single or solitary plug comprising the levorphanol, functional excipients, and optionally, processing

aids, including auxiliary agents and excipients.

- [558] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form is devoid of multiparticulates or microparticulates.
- [559] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form is the most water soluble salt or the most water soluble pharmaceutically acceptable salt of levorphanol.
- [560] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form is the most water soluble salt commercially available salt of levorphanol.
- [561] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form is the levorphanol in unsalified form or comprises levorphanol in unsalified form.
- [562] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form comprises a pharmaceutical composition which substantially forms a single phase in the dosage form.
- [563] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form comprises a pharmaceutical composition which substantially forms a single phase in the dosage form, wherein the dosage form is not in the form of an aggregate or composite of individual solid particulates.
- [564] In some preferred embodiments said liquid filled thermosoftening extended release levorphanol dosage form comprises a pharmaceutical composition is not in the form of an aggregate or composite of individual solid particulates.
- [565] In some preferred embodiments, the invention provides a method of preparing a oral extended release dosage form of the invention; said dosage form suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient.
- [566] In some preferred embodiments, the invention provides a method of preparing a oral levorphanol dosage form, comprising levorphanol and a controlled release material; said dosage form providing extended release; said dosage form suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient.
- [567] In some preferred embodiments, the invention provides a method of preparing a liquid filled oral capsule dosage form comprising the following material: (1) A and B; or (2) A and C; or (3) A and D; or (4) A and E; or (5) A, B and F; or (6) A, B and G; or (7) A, C and F; or (8) A, C and G; or (9) A, B, F and G; or (10) A, C, F and G, or (11) A,D and F, (12) A, D and G, or (13) A, E and F, or (14) A, E and G, or (15) A, D, F and G, or (16) A, E, F and G; wherein said material optionally includes (H); wherein said compound is heated at least up to its melting point; wherein said material is thoroughly mixed; wherein said material is substantially uniformly dispersed; wherein said material is a liquid mass which becomes a solid when allowed to cool to room temperature

following encapsulation; wherein said dosage form is rendered extended-release; wherein said dosage form is suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient; wherein, (A) = levorphanol; (B) = one or more compounds selected from each of the groups consisting of (i) glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (C) = one or more compounds selected from each of the groups consisting of (i) hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (D) = one or more compounds selected from the groups consisting of coconut oil, glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; (E) = one or more compounds selected from the groups consisting of coconut oil, hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; (F) = a thixotrope; (G) a release rate modifier; and (H) = one or more pharmaceutically acceptable excipients. In some preferred embodiments, the dosage form of the invention specifically excludes (H). In some preferred embodiments, the capsule is coated with or incorporates controlled release material (e.g., a pH sensitive polymer) to render it delayed onset, extended release.

[568] In some preferred embodiments, the invention provides a method of use of levorphanol in a population in need of said levorphanol, comprising administering an oral dosage form comprising levorphanol and a controlled release material; said dosage form providing extended release; said dosage form suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient.

[569] In some preferred embodiments, the invention provides a method of treating pain with levorphanol in a population in need of said levorphanol, comprising administering an oral dosage form comprising levorphanol and a controlled release material; said dosage form providing extended release; said dosage form suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient.

[570] In some preferred embodiments, the invention provides a method of use of levorphanol in a population in need of said levorphanol, comprising administering a liquid filled oral capsule dosage form comprising the following material: (1) A and B; or (2) A and C; or (3) A and D; or (4) A and

E; or (5) A, B and F; or (6) A, B and G; or (7) A, C and F; or (8) A, C and G; or (9) A, B, F and G; or (10) A, C, F and G, or (11) A,D and F, (12) A, D and G, or (13) A, E and F, or (14) A, E and G, or (15) A, D, F and G, or (16) A, E, F and G; wherein said material optionally includes (H); wherein said compound is heated at least up to its melting point; wherein said material is thoroughly mixed; wherein said material is substantially uniformly dispersed; wherein said material is a liquid mass which becomes a solid when allowed to cool to room temperature following encapsulation; wherein said dosage form is rendered extended-release; wherein said dosage form is suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient; wherein, (A) = levorphanol; (B) = one or more compounds selected from each of the groups consisting of (i) glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (C) = one or more compounds selected from each of the groups consisting of (i) hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (D) = one or more compounds selected from the groups consisting of coconut oil, glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; (E) = one or more compounds selected from the groups consisting of coconut oil, hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; (F) = a thixotrope; (G) a release rate modifier; and (H) = one or more pharmaceutically acceptable excipients. In some preferred embodiments, the dosage form of the invention specifically excludes (H). In some preferred embodiments, the capsule is coated with or incorporates controlled release material (e.g., a pH sensitive polymer) to render it delayed onset, extended release.

[571] In some preferred embodiments, the invention provides a method of protecting from ethanol induced dose-dumping, ethanol induced pharmacokinetic variability and ethanol induced toxicity in a population which includes subjects that can be expected to at least occasionally co-ingest the dosage form with ethanol comprising administering an oral dosage form comprising levorphanol and a controlled release material; said dosage form providing extended release; wherein said dosage form is suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient. Preferably, upon co-ingestion with 240 mL or 120 mL of a 40% solution of ethanol, said dosage form provides

a mean C_{max} ratio of from about 2:1 to about 1:2, or from about 1.5:1 to about 1:1.5, when compared with the same dose of said dosage given with an equal amount of water.

[572] In some preferred embodiments, the invention provides a method of protecting from ethanol induced dose-dumping, ethanol induced pharmacokinetic variability and ethanol induced toxicity in a population which includes subjects that can be expected to at least occasionally co-ingest the dosage form with ethanol comprising administering a liquid filled oral capsule dosage form comprising the following material: (1) A and B; or (2) A and C; or (3) A and D; or (4) A and E; or (5) A, B and F; or (6) A, B and G; or (7) A, C and F; or (8) A, C and G; or (9) A, B, F and G; or (10) A, C, F and G, or (11) A,D and F, (12) A, D and G, or (13) A, E and F, or (14) A, E and G, or (15) A, D, F and G, or (16) A, E, F and G; wherein said material optionally includes (H); wherein said compound is heated at least up to its melting point; wherein said material is thoroughly mixed; wherein said material is substantially uniformly dispersed; wherein said material is a liquid mass which becomes a solid when allowed to cool to room temperature following encapsulation; wherein said dosage form is rendered extended-release; wherein said dosage form is suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient; wherein, (A) = levorphanol; (B) = one or more compounds selected from each of the groups consisting of (i) glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (C) = one or more compounds selected from each of the groups consisting of (i) hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (D) = one or more compounds selected from the groups consisting of coconut oil, glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; (E) = one or more compounds selected from the groups consisting of coconut oil, hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; (F) = a thixotrope; (G) a release rate modifier; and (H) = one or more pharmaceutically acceptable excipients. In some preferred embodiments, the dosage form of the invention specifically excludes (H). In some preferred embodiments, the capsule is coated with or incorporates controlled release material (e.g., a pH sensitive polymer) to render it delayed onset, extended release. In some other preferred

embodiments, the foregoing method reduces the extent of ethanol induced dose-dumping, ethanol induced pharmacokinetic variability and ethanol induced toxicity.

[573] In some preferred embodiments, the invention provides a compositions and methods of reducing the variability in bioavailability when taken with food, compared with the fasted state, comprising administering to a human patient a oral dosage form comprising levorphanol and a controlled release material; said dosage form providing extended release; wherein said dosage form is suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient. Preferably, upon co-ingestion with food, said dosage form provides a mean C_{max} ratio from about 2:1 to about 1:2, or from about 1.5:1 to about 1:1.5, when compared with the same dose of said dosage given after an overnight fast.

[574] In some preferred embodiments, the invention provides compositions and methods of reducing the variability in bioavailability when taken with food, compared with the fasted state, comprising administering to a human patient a liquid filled oral capsule dosage form comprising the following material: (1) A and B; or (2) A and C; or (3) A and D; or (4) A and E; or (5) A, B and F; or (6) A, B and G; or (7) A, C and F; or (8) A, C and G; or (9) A, B, F and G; or (10) A, C, F and G, or (11) A,D and F, (12) A, D and G, or (13) A, E and F, or (14) A, E and G, or (15) A, D, F and G, or (16) A, E, F and G; wherein said material optionally includes (H); wherein said compound is heated at least up to its melting point; wherein said material is thoroughly mixed; wherein said material is substantially uniformly dispersed; wherein said material is a liquid mass which becomes a solid when allowed to cool to room temperature following encapsulation; wherein said dosage form is rendered extended-release; wherein said dosage form is suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient; wherein, (A) = levorphanol; (B) = one or more compounds selected from each of the groups consisting of (i) glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (C) = one or more compounds selected from each of the groups consisting of (i) hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (D) = one or more compounds selected from the groups consisting of coconut oil, glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; (E) = one or more compounds selected from the groups consisting of coconut oil, hydrogenated

vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; (F) = a thixotrope; (G) a release rate modifier; and (H) = one or more pharmaceutically acceptable excipients. In some preferred embodiments, the dosage form of the invention specifically excludes (H). In some preferred embodiments, the capsule is coated with or incorporates controlled release material (e.g., a pH sensitive polymer) to render it delayed onset, extended release. In some preferred embodiments, the capsule is coated with or incorporates controlled release material (e.g., a pH sensitive polymer) to render it delayed onset, extended release.

[575] In some preferred embodiments, the invention provides a method of rendering levorphanol extended release suitable for dosing every 12 or 24 hours, comprising administering to a human patient a liquid filled oral capsule dosage form comprising the following material: (1) A and B; or (2) A and C; or (3) A and D; or (4) A and E; or (5) A, B and F; or (6) A, B and G; or (7) A, C and F; or (8) A, C and G; or (9) A, B, F and G; or (10) A, C, F and G, or (11) A, D and F, (12) A, D and G, or (13) A, E and F, or (14) A, E and G, or (15) A, D, F and G, or (16) A, E, F and G; wherein said material optionally includes (H); wherein said compound is heated at least up to its melting point; wherein said material is thoroughly mixed; wherein said material is substantially uniformly dispersed; wherein said material is a liquid mass which becomes a solid when allowed to cool to room temperature following encapsulation; wherein said dosage form is rendered extended-release; wherein said dosage form is suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient; wherein, (A) = levorphanol; (B) = one or more compounds selected from each of the groups consisting of (i) glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (C) = one or more compounds selected from each of the groups consisting of (i) hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (D) = one or more compounds selected from the groups consisting of coconut oil, glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; (E) = one or more compounds selected from the groups consisting of coconut oil, hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate,

glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; (F) = a thixotrope; (G) a release rate modifier; and (H) = one or more pharmaceutically acceptable excipients. In some preferred embodiments, the dosage form of the invention specifically excludes (H). In some preferred embodiments, the capsule is coated with or incorporates controlled release material (e.g., a pH sensitive polymer) to render it delayed onset, extended release.

- [576] In some preferred embodiments, the invention provides a method of reducing the variability in bioavailability when taken with food, compared with the fasted state, comprising administering to a human patient a oral dosage form comprising levorphanol and a controlled release material; said dosage form providing extended release; wherein said dosage form is suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient; wherein, upon co-ingestion with food, said dosage form provides a mean $AUC_{0-\infty}$ ratio from about 2:1 to about 1:2, or from about 1.5:1 to about 1:1.5, when compared with the same dose of said dosage given after an overnight fast.
- [577] In some preferred embodiments, the extended release levorphanol dosage form comprises a material selected from the group comprising hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides or pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof, wherein the combined total molar amount of said material in the dosage form is at least 15-fold greater than the molar amount of the levorphanol or its pharmaceutically acceptable salt in the dosage form with or without its water of hydration (e.g., anhydrous, monohydrate, dihydrate)..
- [578] In some preferred embodiments, the extended release levorphanol dosage form comprises a monolithic dosage form.
- [579] In some preferred embodiments, the extended release levorphanol dosage form comprises a compressed multiparticulate plug
- [580] In some preferred embodiments, the extended release levorphanol dosage form is in the form of an encapsulated plug or a tablet with a diameter of more than 3 mm, 3.5 mm, 4 mm, 4.5 mm, 5 mm, 5.5 mm, or 6 mm. Preferably, the encapsulated plug is a single or solitary plug comprising the levorphanol, functional excipients, and optionally, processing aids, including auxiliary agents and excipients.
- [581] In some preferred embodiments, the extended release levorphanol dosage form is devoid of multiparticulates or microparticulates.
- [582] In some preferred embodiments, the extended release levorphanol dosage form comprises the most water soluble salt or the most water soluble pharmaceutically acceptable salt of levorphanol.
- [583] In some preferred embodiments, the extended release levorphanol dosage form comprises

the most water soluble salt commercially available salt of levorphanol.

- [584] In some preferred embodiments, the extended release levorphanol dosage form comprises the levorphanol in unsalified form or comprises levorphanol in unsalified form.
- [585] In some preferred embodiments, the extended release levorphanol dosage form is substantially single phase in the dosage form.
- [586] In some preferred embodiments, the extended release levorphanol dosage form is substantially a single phase in the dosage form, wherein the dosage form is not in the form of an aggregate or composite of individual solid particulates.
- [587] In some preferred embodiments, the extended release levorphanol dosage form is not in the form of an aggregate or composite of individual solid particulates.
- [588] In some preferred embodiments, the extended release levorphanol dosage form comprises a thixotrope, wherein the thixotrope renders said dosage form resistant to dose dumping when co-ingested with alcohol.
- [589] In some preferred embodiments, the extended release levorphanol dosage form comprises a release rate modifier, wherein the release rate modifier renders said dosage form resistant to dose dumping when co-ingested with alcohol.
- [590] In some preferred embodiments, the extended release levorphanol dosage form comprises a thixotrope and a release rate modifier, wherein both the thixotrope and release rate modifier render said dosage form resistant to dose dumping when co-ingested with alcohol.
- [591] In some preferred embodiments, the extended release levorphanol dosage form comprises a material selected from the group comprising hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides or pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof, wherein said material renders said dosage form resistant to dose dumping when co-ingested with alcohol. In other preferred embodiments, said material and the thixotrope, said material and release rate modifier or said material, the thixotrope and the release rate modifier render said dosage form resistant to dose dumping when co-ingested with alcohol
- [592] In some preferred embodiments, the extended release levorphanol dosage form comprises a material selected from the group comprising hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides or pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof, wherein said material in the dosage form is less than about 1400 mg, or 1000 mg, or 800 mg, or 600 mg, or 500 mg, or 450 mg, or 400 mg, or 350 mg, or 300 mg, or 275 mg, or 250 mg, or 225 mg, or 200 mg, or 175 mg, or 150 mg, or 125 mg.
- [593] A non-limiting list of suitable controlled-release materials which may be included in a

controlled-release matrix according to the invention include hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials, waxes, shellac, and oils such as hydrogenated castor oil, hydrogenated vegetable oil hydrogenated Type I or Type II vegetable oils, polyoxyethylene stearates and distearates, glycerol monostearate, and non-polymeric, non-water soluble liquids carbohydrate-based substances or poorly water soluble, high melting point (mp = 50 to 100° C) waxes and mixtures thereof.

[594] Representative examples of hydrogenated vegetable oils of the present invention include, without limitation, hydrogenated cottonseed oil (e.g., Akofine™; Lubritab™; Sterotex™ NF), hydrogenated palm oil (Dynasan™ P60; Softisan™ 154), hydrogenated soybean oil (Hydrocote™; Lipovol HS-K™; Sterotex™ HM) and hydrogenated palm kernel oil (e.g., Hydrokote™ 112).

[595] Representative examples of polyoxyethylene stearates and distearates of the present invention include, without limitation, Polyoxyl 2, 4, 6, 8, 12, 20, 30, 40, 50, 100 and 150 stearates (e.g., Hodag™ DGS; PEG-2 stearate; Acconon™ 200-MS; Hodag™ 20-S; PEG-4 stearate; Cerasynt™ 616; Kessco™ PEG 300 Monostearate; Acconon™ 400-MS; Cerasynt™ 660; Cithrol™ 4MS; Hodag™ 60-S; Kessco™ PEG 600 Monostearate; Cerasynt™ 840; Hodag 100-S; Myrj™ 51; PEG-30 stearate; polyoxyethylene (30) stearate; Crodet™ S40; E431; Emerest™ 2672; Atlas G-2153; Crodet™ S50) and polyoxyl 4, 8, 12, 32 and 150 distearates (e.g., Lipo-PEG™ 100-S; Myrj™ 59; Hodag™ 600-S; Ritox™ 59; Hodag™ 22-S; PEG-4 distearate; Hodag™ 42-S; Kessco™ PEG 400 DS; Hodag™ 62-S; Kessco™ PEG 600 Distearate; Hodag™ 154-S; Kessco™ PEG 1540 Distearate; Lipo-PEG™ 6000-DS; Protamate™ 6000-DS).

[596] Representative examples of poorly water soluble, high melting point (mp = 45 to 100° C) waxes of the present invention include, without limitation: (i) animal waxes; (ii) insect waxes; (iii) vegetable waxes; (iv) mineral waxes; (v) petroleum waxes; (vi) synthetic waxes; (vi) nonionic emulsifying waxes or cetomacrogol emulsifying wax (e.g., Collone NI™; Crodex N™; Emulgade 1000NI™; Permulin D™; Polawax™; Ritachol 2000; T-Wax™); (vii) anionic emulsifying wax (e.g., Collone HV™; Crodex A™; Cyclonette wax; Lanette wax SX™ BP); (viii) carnauba wax (also known as Brazil wax; caranda wax; E903); (ix) microcrystalline wax (also known as amorphous wax; E907; petroleum ceresin; petroleum wax (microcrystalline)); (x) yellow wax (e.g., yellow beeswax; Apifil™; E901; refined wax); (xi) white wax (bleached wax; E901); (xii) cetyl esters wax (e.g., cera cetyla; Crodamol SS™; Cutina CP™; Liponate SPS™; Protachem MST™; Ritaceti™; Ritachol SS™; spermaceti wax replacement; Starfol wax CG™; Synaceti 116™; synthetic spermaceti); (xiii) hydrogenated castor oil (e.g., Castorwax™; Castorwax MP 70™; Castorwax MP 80™; Croduret™; Cutina HR™; Fancol™; Simulsol 1293™); (xiv) lanolin alcohols (e.g., Cholesterol; lanolin; lanolin, hydrous; petrolatum and lanolin alcohols; mineral oils); (xv) lanolin (e.g., cera lanae; E913; lanolina; lanolin anhydrous; Protalan anhydrous; purified lanolin; refined wool fat); (xvi) glyceryl palmitostearate; (xvii) cetostearyl alcohol (e.g., cetearyl alcohol;

Crodacol CS90™; Lanette O™; Tego Alkanol 1618™; Tego Alkanol 6855™); (xviii) beeswax.

- [597] In one embodiment of the present invention, the levorphanol is combined with beeswax, hydroxypropyl methyl cellulose (e.g, HPMC K15M), silicon dioxide (alone or in combination with Al₂O₃; e.g, Aerosil™, Aerosil™ 200, Aerosil™ COK84).
- [598] In one embodiment of the present invention, the levorphanol is combined with hydrogenated cottonseed oil (e.g., Sterotex™ NF), hydroxypropyl methyl cellulose (e.g, HPMC K15M), coconut oil and silicon dioxide (alone or in combination with Al₂O₃; e.g, Aerosil™, Aerosil™ 200, Aerosil™ COK84).
- [599] In another embodiment of the present invention, the levorphanol is combined with glycerol monostearate (e.g., Cithrol™ GMS), hydroxypropyl methyl cellulose (e.g, HPMC K100M) and silicon dioxide (alone or in combination with Al₂O₃; e.g, Aerosil™, Aerosil™ 200, Aerosil™ COK84).
- [600] In yet another embodiment of the present invention, the levorphanol is combined with hydrogenated palm kernel oil (e.g., Hydrokote™ 112), hydroxypropyl methyl cellulose (e.g, HPMC K15M) and silicon dioxide (alone or in combination with Al₂O₃; e.g, Aerosil™, Aerosil™ 200, Aerosil™ COK84).
- [601] In one embodiment of the present invention, release rate modifiers, including hydroxypropyl methyl cellulose (e.g, HPMC K15M) may be incorporated. Release rate modifiers can also have additional useful properties that optimize the formulation.
- [602] In one embodiment of the present invention, the levorphanol is combined with hydrogenated palm kernel oil (e.g., Hydrokote™ 112), hydroxypropyl methyl cellulose (e.g, HPMC K15M), and silicon dioxide (alone or in combination with Al₂O₃; e.g, Aerosil™, Aerosil™ 200, Aerosil™ COK84).
- [603] In one embodiment of the present invention, the levorphanol is combined with glyceryl behenate (e.g., Compritol™ 888 ATO), fractionated coconut oil (e.g., Miglyol™ 812N), hydroxypropyl methyl cellulose (e.g, HPMC K15M) and silicon dioxide (alone or in combination with Al₂O₃; e.g, Aerosil™, Aerosil™ 200, Aerosil™ COK84).
- [604] In one embodiment of the present invention, the levorphanol is combined with hydrogenated cottonseed oil (e.g., Sterotex™ NF), fractionated coconut oil (e.g., Miglyol™ 812N), hydroxypropyl methyl cellulose (e.g, HPMC K15M) and silicon dioxide (alone or in combination with Al₂O₃; e.g, Aerosil™, Aerosil™ 200, Aerosil™ COK84).
- [605] Another method of producing the dosage form of the invention involves liquid fill compositions, including hydrogenated Type I or Type II vegetable oils (e.g., Hydrokote™ 112), polyoxyethylene stearates and distearates, glycerol monostearate (e.g., Cithrol™ GMS), non-polymeric, non-water soluble liquids carbohydrate-based substances, poorly water soluble, high melting point (mp = 40 to 100° C) waxes.

- [606] In one preferred embodiment of the present invention, also included are coconut oil products, including without limitation, coconut oil, fractionated coconut oil, cetyl alcohol, lauric acid and medium chain triglycerides (e.g., Bergabest; caprylic/capric triglyceride; Captex 300; Captex 355; Crodamol GTC/C; glyceryl tricaprylate/caprates; Labrafac CC; MCT oil; Miglyol™ 810™; Miglyol™ 812™; Myritol; Neobee M5™; Nesatol™; oleum neutrale; oleum vegetable tenue; thin vegetable oil; Waglinol 3/9280™). In a most preferred embodiment, the coconut oil is fractionated coconut oil.
- [607] A variety of agents may be incorporated into the dosage form of the invention as thixotropes (e.g., fumed silicon dioxides, Aerosil™, Aerosil™ COK84, Aerosil™ 200, etc.). Thixotropes can optimize the rate of release and also enhance the pharmaceutical formulations of the invention by increasing the viscosity of solutions during attempted tampering, complementing the action of HPMCs or other release rate modifiers. They may also provide a tamper resistance by helping to retain the structure of dosage units that have been heated to temperatures greater than the melting point of the base excipient (many thixotropes including Aerosils™ are unaffected by heat).
- [608] The dosage form of the invention may include any desired amount of the following functional excipients, but never to exceed 1500 mg of any one excipient or any combination of said excipients: glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, coconut oil, hydrogenated coconut oil, fractionated coconut oil, hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macroglycerides, waxes, thixotropes, release rate modifiers, silicon dioxide, silica, fumed silicon dioxides, a mixture of silicon dioxide and aluminum oxide microcrystalline methylcellulose, bentonite clay, hectorite clay, magnesium aluminum silicate, montmorillonite, lithium magnesium silicate, stearyl ammonium hectorite, hydroxypropyl methylcellulose, cellulose acetate, powdered cellulose, cellulose acetate phthalate, hydroxyethyl cellulose, silicified microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, low-substituted hydroxypropyl cellulose, carboxymethylcellulose, carboxymethylcellulose calcium, hypromellose acetate succinate, hypromellose phthalate, and ethylcellulose, or the respective esters, derivatives or mixture thereof. In some embodiments, the combined total amount of the foregoing functional excipients, expressed as a percentage of the total excipients, excluding the capsule shell, if applicable is about 0.0001% to about 99.8%, more preferably 0.001% to about 99%, even more preferably, 0.001% to about 98% on a dry weight basis. In some embodiments, the combined total amount of the foregoing functional excipients, excluding the capsule shell, if applicable, is less than 1300 mg, or less than 1000 mg, or less than 800 mg, or less than 600 mg, or less than 500 mg, or less than 400 mg or less than 200 mg, or less than 100 mg on a dry weight basis..

- [609] In some preferred embodiments, the controlled release material of the oral dosage form of the invention is selected from the group consisting of hydrophobic polymers, hydrophilic polymers, gums, protein derived materials, waxes, shellac, oils, fats and mixtures thereof.
- [610] In some preferred embodiments, the controlled release material of the oral dosage form of the invention is selected from the group consisting of polyethylene oxide, polyvinyl alcohol, hydroxypropyl methyl cellulose, a carbomer and mixtures thereof.
- [611] In some preferred embodiments, the controlled release material of the oral dosage form of the invention is selected from the group consisting of hydrogenated Type I or Type II vegetable oils, polyoxyethylene stearates and distearates, glycerol monostearate, and non-polymeric, non-water soluble liquids carbohydrate-based substances or poorly water soluble, high melting point (mp = 40 to 100° C) waxes and mixtures thereof.
- [612] In some preferred embodiments, the extended release levorphanol dosage form of the invention comprises the following material: (i) up to about 100 mg of levorphanol, a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; (ii) up to about 400 mg or up to about 800 mg of one or more hydrogenated vegetable oils, their respective esters or derivatives, or mixtures thereof, preferably selected from the group comprising Hydrokote™, Sterotex™ NF hydrogenated palm kernel oil, a mixture of lauric hard butter and lecithin, hydrogenated cottonseed oil, hydrogenated soybean oil, fractionated coconut oil, hydrogenated coconut oil and hydrogenated palm oil; (iii) up to about 100 mg or up to about 200 mg of a thixotrope, preferably selected from the group comprising amorphous anhydrous colloidal silicon dioxide, silicon dioxide and a mixture of silicon dioxide and aluminum oxide; (iv) up to about 150 mg or up to about 350 mg of a release rate modifier, preferably hydroxypropyl methylcellulose; and optionally, (v) one or more pharmaceutically acceptable excipients, wherein the material is substantially homogeneously mixed with the application of heat and filled into a capsule or compressed into a tablet.
- [613] In some preferred embodiments, the extended release levorphanol dosage form of the invention comprises the following material: (i) up to about 100 mg of levorphanol, a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; (ii) up to about 400 mg or up to about 800 mg of one or more hydrogenated vegetable oils, their respective esters or derivatives, or mixtures thereof, preferably selected from the group comprising Hydrokote™, Sterotex™ NF hydrogenated palm kernel oil, a mixture of lauric hard butter and lecithin, hydrogenated cottonseed oil, hydrogenated soybean oil and hydrogenated palm oil; (iii) up to about 200 mg or up to about 400 mg of coconut oil or a coconut oil derivative, preferably selected from the group comprising medium chain triglycerides, Miglyol™ 810, Miglyol™ 812, Miglyol™ 818, Miglyol™ 829, fractionated coconut oil, caproic acid, caprylic acid and capric acid; (iv) up to about 100 mg or up to about 200 mg of a thixotrope, preferably selected from the group comprising amorphous anhydrous colloidal silicon dioxide, silicon dioxide and a mixture of silicon dioxide and aluminum oxide; (v)

up to about 150 mg or up to about 350 mg of a release rate modifier, preferably hydroxypropyl methylcellulose; and optionally, (vi) one or more pharmaceutically acceptable excipients, wherein the material is substantially homogeneously mixed with the application of heat and filled into a capsule or compressed into a tablet.

[614] In some preferred embodiments, the extended release levorphanol dosage form of the invention comprises the following material: (i) up to about 100 mg of levorphanol, a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; (ii) up to about 400 mg or up to about 800 mg of glycerides of fatty acids, their respective derivatives, or mixtures thereof, preferably glyceryl behenate; (iii) up to about 100 mg or up to about 200 mg of a thixotrope, preferably selected from the group comprising amorphous anhydrous colloidal silicon dioxide, silicon dioxide and a mixture of silicon dioxide and aluminum oxide; (iv) up to about 150 mg or up to about 350 mg of a release rate modifier, preferably hydroxypropyl methylcellulose; and optionally, (v) one or more pharmaceutically acceptable excipients, wherein the material is substantially homogeneously mixed with the application of heat and filled into a capsule or compressed into a tablet.

[615] In some preferred embodiments, the extended release levorphanol dosage form of the invention comprises the following material: (i) up to about 100 mg of levorphanol, a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; (ii) up to about 400 mg or up to about 800 mg of glycerides of fatty acids, their respective derivatives, or mixtures thereof, preferably glyceryl behenate; (iii) up to about 200 mg or up to about 400 mg of coconut oil or a coconut oil derivative, preferably selected from the group comprising medium chain triglycerides, Miglyol™ 810, Miglyol™ 812, Miglyol™ 818, Miglyol™ 829, fractionated coconut oil, caproic acid, caprylic acid and capric acid; (iv) up to about 100 mg or up to about 200 mg of a thixotrope, preferably selected from the group comprising amorphous anhydrous colloidal silicon dioxide, silicon dioxide and a mixture of silicon dioxide and aluminum oxide; (v) up to about 150 mg or up to about 350 mg of a release rate modifier, preferably hydroxypropyl methylcellulose; and optionally, (vi) one or more pharmaceutically acceptable excipients, wherein the material is substantially homogeneously mixed with the application of heat and filled into a capsule or compressed into a tablet.

[616] In some preferred embodiments, the extended release levorphanol dosage form of the invention comprises the following material: (i) up to about 100 mg of levorphanol, a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; (ii) up to about 400 mg or up to about 800 mg of one or more glyceryl monoesters or derivatives, or mixtures thereof, preferably selected from the group comprising glycerol monostearate, Cithrol™, Cithrol™ GMS S/E, Cithrol™ GMS N/E, Cithrol™ GMS A/S and Cithrol™ GMO; (iii) up to about 100 mg or up to about 200 mg of a thixotrope, preferably selected from the group comprising amorphous anhydrous colloidal

silicon dioxide, silicon dioxide and a mixture of silicon dioxide and aluminum oxide; (iv) up to about 150 mg or up to about 350 mg of a release rate modifier, preferably hydroxypropyl methylcellulose; and optionally, (v) one or more pharmaceutically acceptable excipients, wherein the material is substantially homogeneously mixed with the application of heat and filled into a capsule or compressed into a tablet.

[617] In some preferred embodiments, the extended release levorphanol dosage form of the invention comprises the following material: (i) up to about 100 mg of levorphanol, a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; (ii) up to about 400 mg or up to about 800 mg of one or more glyceryl monoesters or derivatives, or mixtures thereof, preferably selected from the group comprising glycerol monostearate, Cithrol™, Cithrol™ GMS S/E, Cithrol™ GMS N/E, Cithrol™ GMS A/S and Cithrol™ GMO; (iii) up to about 200 mg or up to about 400 mg of coconut oil or a coconut oil derivative, preferably selected from the group comprising medium chain triglycerides, Miglyol™ 810, Miglyol™ 812, Miglyol™ 818, Miglyol™ 829, fractionated coconut oil, caproic acid, caprylic acid and capric acid; (iv) up to about 100 mg or up to about 200 mg of a thixotrope, preferably selected from the group comprising amorphous anhydrous colloidal silicon dioxide, silicon dioxide and a mixture of silicon dioxide and aluminum oxide; (v) up to about 150 mg or up to about 350 mg of a release rate modifier, preferably hydroxypropyl methylcellulose; and optionally, (vi) one or more pharmaceutically acceptable excipients, wherein the material is substantially homogeneously mixed with the application of heat and filled into a capsule or compressed into a tablet.

[618] In some preferred embodiments, the extended release levorphanol dosage form of the invention comprises the following material: (i) up to about 100 mg of levorphanol, a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; (ii) up to about 400 mg or up to about 800 mg of one or more waxes, preferably beeswax (yellow wax or white wax); (iii) up to about 100 mg or up to about 200 mg of a thixotrope, preferably selected from the group comprising amorphous anhydrous colloidal silicon dioxide, silicon dioxide and a mixture of silicon dioxide and aluminum oxide; (iv) up to about 150 mg or up to about 350 mg of a release rate modifier, preferably hydroxypropyl methylcellulose; and optionally, (v) one or more pharmaceutically acceptable excipients, wherein the material is substantially homogeneously mixed with the application of heat and filled into a capsule or compressed into a tablet.

[619] In some preferred embodiments, the extended release levorphanol dosage form of the invention comprises the following material: (i) up to about 100 mg of levorphanol, a pharmaceutically acceptable salt of levorphanol, or a mixture thereof; (ii) up to about 400 mg or up to about 800 mg of one or more waxes, preferably beeswax (yellow wax or white wax); (iii) up to about 200 mg or up to about 400 mg of coconut oil or a coconut oil derivative, preferably selected from the group comprising medium chain triglycerides, Miglyol™ 810, Miglyol™ 812, Miglyol™

818, Miglyol™ 829, fractionated coconut oil, caproic acid, caprylic acid and capric acid; (iv) up to about 100 mg or up to about 200 mg of a thixotrope, preferably selected from the group comprising amorphous anhydrous colloidal silicon dioxide, silicon dioxide and a mixture of silicon dioxide and aluminum oxide; (v) up to about 150 mg or up to about 350 mg of a release rate modifier, preferably hydroxypropyl methylcellulose; and optionally, (vi) one or more pharmaceutically acceptable excipients, wherein the material is substantially homogeneously mixed with the application of heat and filled into a capsule or compressed into a tablet.

[620] In some embodiments, a pore forming material in any desired amount is optionally added to the controlled-release material of the tablet or capsule coating or dispersed within the dosage form to promote release of the active agent from the core or to minimize any burst effect. The pore forming material is organic or inorganic; it is a material that can be dissolved, extracted or leached from the coating in the environment of use; or it can have a pH-dependent solubility property; and the like. Exemplary pore forming materials include hydrophilic polymers such as a hydroxy alkyl-alkyl cellulose (e.g., hydroxypropylmethyl cellulose, and the like), a hydroxyl alkyl cellulose (e.g., hydroxypropylcellulose, and the like), or a povidone; a saccharide (e.g., lactose, and the like); a metal stearate; an inorganic salt (e.g., dibasic calcium phosphate, sodium chloride, and the like); a polyethylene glycol (e.g., polyethylene glycol (PEG) 1450, and the like); a sugar alcohol (e.g., sorbitol, mannitol, and the like); an alkali alkyl sulfate (e.g., sodium lauryl sulfate); a polyoxyethylene sorbitan fatty acid ester (e.g., polysorbate); methacrylate copolymers (e.g., Eudragit™ RL); or a combination comprising at least one of the foregoing pore forming materials. Other suitable pore formers are known in the art (see for example, US patent No. 7,585,897). The pore-forming agent preferably comprises a water soluble polymer. Preferably, the pore forming agent is hypromellose. In some embodiments, when the controlled release coating is an ethylcellulose and polyvinyl acetate coating systems, preferably the pore forming agent is hypromellose and when when the controlled release coating is Eudragit™, preferably the pore forming agent is povidone (Kollidon™ K30).

[621] **Resistance to Alcohol Associated Dose Dumping**

[622] In some preferred embodiments, the invention provides a method of protecting from ethanol induced dose-dumping in a population which includes subjects that can be expected to at least occasionally co-ingest the dosage form with ethanol comprising administering a therapeutically effective amount of oral levorphanol and a controlled release material to render said dosage form extended release suitable for twice-a-day (Q12H or Q12H PRN) or once-a-day (QD, Q24H or Q24H PRN) administration to a human patient, wherein, upon co-ingestion with 120 mL of a 40% solution of ethanol, said dosage form provides a mean C_{max} difference of less than about 90% when compared with the same dose of said dosage given with 120 mL of water. In other embodiments,

the foregoing volume of ethanol and water is 180 mL or 240 mL. In other embodiments, the foregoing mean C_{\max} difference is less than about 80%, or less than about 70%, or less than about 60%, or less than about 50%, or less than about 45%, or less than about 40%, or less than about 35%, or less than about 30%, or less than about 25%, or less than about 20%, or less than about 15%.

[623] In some preferred embodiments, the invention provides a method of protecting from ethanol induced dose-dumping in a population which includes subjects that can be expected to at least occasionally co-ingest the dosage form with ethanol comprising administering a therapeutically effective amount of oral levorphanol and a controlled release material to render said dosage form extended release suitable for twice-a-day (Q12H or Q12H PRN) or once-a-day (QD, Q24H or Q24H PRN) administration to a human patient, wherein, upon co-ingestion with 120 mL of a 40% solution of ethanol, said dosage form provides a mean area under the plasma levorphanol concentration time curve from 0 to one hour after dosing ($AUC_{0-1\text{hour}}$) difference of less than about 90% when compared with the same dose of said dosage given with 120 mL of water. In other embodiments, the foregoing volume of ethanol and water is 180 mL or 240 mL. In other embodiments, the foregoing mean $AUC_{0-1\text{hour}}$ difference is less than about 80%, or less than about 70%, or less than about 60%, or less than about 50%, or less than about 45%, or less than about 40%, or less than about 35%, or less than about 30%, or less than about 25%, or less than about 20%, or less than about 15%. In other embodiments, the foregoing area under the plasma concentration time curve is from zero to two hours after dosing ($AUC_{0-2\text{hour}}$). In other embodiments, the foregoing area under the plasma concentration time curve is from zero to three hours after dosing ($AUC_{0-3\text{hour}}$).

[624] In some preferred embodiments, the dosage form comprises an oral pharmaceutical composition comprising a therapeutically effective amount of levorphanol a therapeutically effective amount of levorphanol and a controlled release material to render said dosage form extended release administration wherein the levorphanol C_{\max} is substantially independent of alcohol intake in that a difference, at any given time, between the mean C_{\max} of levorphanol administered with about 30 mL to about 240 mL of a 40% ethanol solution and the mean C_{\max} of levorphanol administered without concurrent alcohol (i.e., in an alcohol free state) is less than about 90%. In other preferred embodiments, said difference in mean C_{\max} of levorphanol is less than about 80%, or less than about 70%, or less than about 60%, or less than about 50%, or less than about 45%, or less than about 40%, or less than about 35%, or less than about 30%, or less than about 25%, or less than about 20%, or less than about 15%.

[625] In some preferred embodiments, the dosage form comprises an oral pharmaceutical composition comprising a therapeutically effective amount of levorphanol a therapeutically effective amount of levorphanol and a controlled release material to render said dosage form

extended release administration wherein the difference in mean area under the plasma levorphanol concentration time curve from 0 to one hour after dosing ($AUC_{0-1\text{hour}}$) is substantially independent of alcohol intake in that a difference between the mean levorphanol $AUC_{0-1\text{hour}}$ with about 30 mL to about 240 mL of a 40% ethanol solution and with an equal amount of water (i.e., in an alcohol free state) is less than about 90%. In other preferred embodiments, said difference in mean $AUC_{0-1\text{hour}}$ of levorphanol is less than about 80%, or less than about 70%, or less than about 60%, or less than about 50%, or less than about 45%, or less than about 40%, or less than about 35%, or less than about 30%, or less than about 25%, or less than about 20%, or less than about 15%. In other embodiments, the foregoing area under the plasma concentration time curve is from zero to two hours after dosing ($AUC_{0-2\text{hour}}$). In other embodiments, the foregoing area under the plasma concentration time curve is from zero to three hours after dosing ($AUC_{0-3\text{hour}}$).

[626] Resistance to Food Associated Dose Dumping

[627] In some preferred embodiments, the invention provides a method of reducing the variability in bioavailability when taken with food, compared with the fasted state, comprising administering a therapeutically effective amount of oral levorphanol and a controlled release material to render said dosage form extended release suitable for twice-a-day (Q12H or Q12H PRN) or once-a-day (QD, Q24H or Q24H PRN) administration to a human patient, wherein the mean levorphanol C_{max} is substantially independent of food intake in that a difference, at any given time, between the C_{max} of levorphanol administered in fasted state and the mean C_{max} of levorphanol administered in fed state (using a standardized meal) is less than about 90%. In other preferred embodiments, said difference in the mean C_{max} of levorphanol is less than about 80%, or less than about 70%, or less than about 60%, or less than about 50%, or less than about 45%, or less than about 40%, or less than about 35%, or less than about 30%, or less than about 25%, or less than about 20%, or less than about 15%.

[628] In some preferred embodiments, the invention provides a method of reducing the variability in bioavailability when taken with food, compared with the fasted state, comprising administering a therapeutically effective amount of oral levorphanol and a controlled release material to render said dosage form extended release suitable for twice-a-day (Q12H or Q12H PRN) or once-a-day (QD, Q24H or Q24H PRN) administration to a human patient, mean area under the plasma levorphanol concentration time curve from 0 to one hour after dosing ($AUC_{0-1\text{hour}}$) is substantially independent of food intake in that a difference, at any given time, between the $AUC_{0-1\text{hour}}$ of levorphanol administered in fasted state and the mean $AUC_{0-1\text{hour}}$ of levorphanol administered in fed state (using a standardized meal) is less than about 90%. In other preferred embodiments, said difference in the mean $AUC_{0-1\text{hour}}$ of levorphanol is less than about 80%, or less than about 70%, or less than about 60%, or less than about 50%, or less than about 45%, or less than about 40%, or less than about

35%, or less than about 30%, or less than about 25%, or less than about 20%, or less than about 15%. In other embodiments, the foregoing area under the plasma concentration time curve is from zero to two hours after dosing ($AUC_{0-2\text{hour}}$). In other embodiments, the foregoing area under the plasma concentration time curve is from zero to three hours after dosing ($AUC_{0-3\text{hour}}$).

[629] In some preferred embodiments, the invention provides a method of reducing the variability in bioavailability when taken with food, compared with the fasted state, comprising administering a therapeutically effective amount of oral levorphanol and a controlled release material to render said dosage form extended release suitable for twice-a-day (Q12H or Q12H PRN) or once-a-day (QD, Q24H or Q24H PRN) administration to a human patient, mean area under the plasma levorphanol concentration time (AUC_{0-12}) is substantially independent of food intake in that a difference, at any given time, between the AUC_{0-12} of levorphanol administered in fasted state and the mean AUC_{0-12} of levorphanol administered in fed state (using a standardized meal) is less than about 90%. In other preferred embodiments, said difference in the mean AUC_{0-12} of levorphanol is less than about 80%, or less than about 70%, or less than about 60%, or less than about 50%, or less than about 45%, or less than about 40%, or less than about 35%, or less than about 30%, or less than about 25%, or less than about 20%, or less than about 15%. In other embodiments, the foregoing area under the plasma concentration time curve is $AUC_{0-24\text{hours}}$. In other embodiments, the foregoing area under the plasma concentration time curve is $AUC_{0-\text{inf}}$.

[630] In some preferred embodiments, the dosage form comprises an oral pharmaceutical composition comprising a therapeutically effective amount of levorphanol a therapeutically effective amount of levorphanol and a controlled release material to render said dosage form extended release administration wherein the mean levorphanol C_{max} is substantially independent of food intake in that a difference, at any given time, between the C_{max} of levorphanol administered in fasted state and the mean C_{max} of levorphanol administered in fed state (using a standardized meal) is less than about 90%. In other preferred embodiments, said difference in the mean C_{max} of levorphanol is less than about 80%, or less than about 70%, or less than about 60%, or less than about 50%, or less than about 45%, or less than about 40%, or less than about 35%, or less than about 30%, or less than about 25%, or less than about 20%, or less than about 15%.

[631] In some preferred embodiments, the dosage form comprises an oral pharmaceutical composition comprising a therapeutically effective amount of levorphanol a therapeutically effective amount of levorphanol and a controlled release material to render said dosage form extended release administration wherein the mean area under the plasma levorphanol concentration time curve from 0 to one hour after dosing ($AUC_{0-1\text{hour}}$) is substantially independent wherein the mean levorphanol $AUC_{0-1\text{hour}}$ is substantially independent of food intake in that a difference, at any given time, between the $AUC_{0-1\text{hour}}$ of levorphanol administered in fasted state and the mean $AUC_{0-1\text{hour}}$ of levorphanol administered in fed state (using a standardized meal) is less than about 90%. In

other preferred embodiments, said difference in the mean $AUC_{0-1\text{hour}}$ of levorphanol is less than about 80%, or less than about 70%, or less than about 60%, or less than about 50%, or less than about 45%, or less than about 40%, or less than about 35%, or less than about 30%, or less than about 25%, or less than about 20%, or less than about 15%. In other embodiments, the foregoing area under the plasma concentration time curve is from zero to two hours after dosing ($AUC_{0-2\text{hour}}$). In other embodiments, the foregoing area under the plasma concentration time curve is from zero to three hours after dosing ($AUC_{0-3\text{hour}}$).

- [632] In some preferred embodiments, the dosage form comprises an oral pharmaceutical composition comprising a therapeutically effective amount of levorphanol a therapeutically effective amount of levorphanol and a controlled release material to render said dosage form extended release administration wherein the mean area under the plasma levorphanol concentration time curve (AUC_{0-12}) is substantially independent of food intake in that a difference, at any given time, between the AUC_{0-12} of levorphanol administered in fasted state and the mean AUC_{0-12} of levorphanol administered in fed state (using a standardized meal) is less than about 90%. In other preferred embodiments, said difference in the mean AUC_{0-12} of levorphanol is less than about 80%, or less than about 70%, or less than about 60%, or less than about 50%, or less than about 45%, or less than about 40%, or less than about 35%, or less than about 30%, or less than about 25%, or less than about 20%, or less than about 15%. In other embodiments, the foregoing area under the plasma concentration time curve is $AUC_{0-24\text{hours}}$. In other embodiments, the foregoing area under the plasma concentration time curve is $AUC_{0-\text{inf}}$.

[633] **Pharmacodynamic Effects**

- [634] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean drowsiness score in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than the mean drowsiness score after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally.

- [635] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean drowsiness score in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than the mean drowsiness score after an equal amount (or dose) or lower amount (or dose) of an oral immediate release dosage form, or an oral extended release dosage form of levorphanol which is not delayed onset, extended release.

- [636] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean dizziness score in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than the mean drowsiness score after an equal

amount or lower amount of an immediate release dosage form of levorphanol given orally.

- [637] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean nausea score which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than the mean nausea score after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally.
- [638] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean nausea score in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than the mean nausea score after an equal amount (or dose) or lower amount (or dose) of an oral immediate release dosage form, or an oral extended release dosage form of levorphanol which is not delayed onset, extended release.
- [639] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean driving simulation impairment score in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than the mean driving simulation impairment score after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally.
- [640] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean driving simulation impairment score in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than the mean driving simulation impairment score after an equal amount (or dose) or lower amount (or dose) of an oral immediate release dosage form, or an oral extended release dosage form of levorphanol which is not delayed onset, extended release.
- [641] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean “drug effects” score in opioid abusers or recreational opioid users which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally.
- [642] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean “drug effects” score in opioid abusers or recreational opioid users which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount (or dose) or lower amount (or dose) of an oral immediate release dosage form, or an oral extended release dosage form of levorphanol which is not delayed onset, extended release.

- [643] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean “drug liking” score in opioid abusers or recreational opioid users which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally.
- [644] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean “drug liking” score in opioid abusers or recreational opioid users which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount (or dose) or lower amount (or dose) of an oral immediate release dosage form, or an oral extended release dosage form of levorphanol which is not delayed onset, extended release.
- [645] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean “take again” score in opioid abusers or recreational opioid users which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally.
- [646] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean “take again” score in opioid abusers or recreational opioid users which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount (or dose) or lower amount (or dose) of an oral immediate release dosage form, or an oral extended release dosage form of levorphanol which is not delayed onset, extended release.
- [647] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean “coasting” score in opioid abusers or recreational opioid users which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally.
- [648] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean “coasting” score in opioid abusers or recreational opioid users which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount (or dose) or lower amount (or dose) of an oral immediate release dosage form, or an oral extended release dosage form of levorphanol which is not delayed onset, extended release.
- [649] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean “critical tracking task” impairment score in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%,

80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally.

[650] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean “critical tracking task” impairment score in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount (or dose) or lower amount (or dose) of an oral immediate release dosage form, or an oral extended release dosage form of levorphanol which is not delayed onset, extended release.

[651] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean “stop signal task” impairment score in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally.

[652] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean “stop signal task” impairment score in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount (or dose) or lower amount (or dose) of an oral immediate release dosage form, or an oral extended release dosage form of levorphanol which is not delayed onset, extended release.

[653] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean “Tower of London” (TOL) impairment score in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally.

[654] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean “Tower of London” (TOL) impairment score in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount (or dose) or lower amount (or dose) of an oral immediate release dosage form, or an oral extended release dosage form of levorphanol which is not delayed onset, extended release.

[655] In some preferred embodiments, the ratio of the foregoing mean scores for drowsiness,

dizziness score, nausea, driving simulation impairment, “drug effects”, “drug liking”, “take again”, “coasting”, “critical tracking task” impairment, “stop signal task” impairment and “Tower of London” (TOL) impairment after immediate release dosage form of levorphanol given orally, to the oral extended release levorphanol dosage form of the invention, is at least about 10:1, or 8:1, or 6:1, or 5:1, or 4:1, or 3:1, or 2.5:1, or 2:1, or 1.75:1, or 1.5:1, or 1.25:1, or 1.15:1, wherein the immediate release dosage form is given at an equal amount or lower amount.

[656] In some preferred embodiments, the ratio of the foregoing mean scores for drowsiness, dizziness score, nausea, driving simulation impairment, “drug effects”, “drug liking”, “take again”, “coasting”, “critical tracking task” impairment, “stop signal task” impairment and “Tower of London” (TOL) impairment after extended release dosage form of levorphanol given orally, to the delayed onset, extended release levorphanol dosage form, is at least about 10:1, or 8:1, or 6:1, or 5:1, or 4:1, or 3:1, or 2.5:1, or 2:1, or 1.75:1, or 1.5:1, or 1.25:1, or 1.15:1, wherein the extended release dosage form is given at an equal amount or lower amount.

[657] In some preferred embodiments, the foregoing mean scores for drowsiness, dizziness score, nausea, driving simulation impairment, “drug effects”, “drug liking”, “take again”, “coasting”, “critical tracking task” impairment, “stop signal task” impairment and “Tower of London” (TOL) impairment are measured after single administration or first administration. In some other preferred embodiments, the foregoing mean scores for drowsiness, dizziness score, nausea, driving simulation impairment, “drug effects”, “drug liking”, “take again”, “coasting”, “critical tracking task” impairment, “stop signal task” impairment and “Tower of London” (TOL) impairment are measured after repeated dose administration. In some preferred embodiments, the foregoing mean scores for drowsiness, dizziness score, nausea, driving simulation impairment, “drug effects”, “drug liking”, “take again”, “coasting”, “critical tracking task” impairment, “stop signal task” impairment and “Tower of London” (TOL) impairment are measured after administration to patients in need of treatment with levorphanol. Most preferably, the foregoing mean scores for drowsiness, dizziness score, nausea, driving simulation impairment, “drug effects”, “drug liking”, “take again”, “coasting”, “critical tracking task” impairment, “stop signal task” impairment and “Tower of London” (TOL) impairment are measured after first administration to opioid naïve subjects, between 0.5 to 6 hours after administration of the dosage form.

[658] In some preferred embodiments, the foregoing drowsiness, dizziness score, nausea, driving simulation impairment, “drug effects”, “drug liking”, “take again”, “coasting”, “critical tracking task” impairment, “stop signal task” impairment and “Tower of London” (TOL) impairment is assessed at a time 2.5 to 6 hours after administration of the dosage form, following alcohol (ethanol) administration sufficient to maintain a blood alcohol concentration of 0.04% to 0.08%, said ethanol administration 1.5 hours after said dosage form administration, said subjects only occasional or light consumers of alcohol.

- [659] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean number needed to harm (NNH) due to moderate to severe drowsiness in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally.
- [660] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean number needed to harm (NNH) due to drowsiness in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount (or dose) or lower amount (or dose) of an oral immediate release dosage form, or an oral extended release dosage form of levorphanol which is not delayed onset, extended release.
- [661] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean number needed to harm (NNH) due to moderate or severe nausea in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally.
- [662] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean number needed to harm (NNH) due to moderate to severe nausea in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount (or dose) or lower amount (or dose) of an oral immediate release dosage form, or an oral extended release dosage form of levorphanol which is not delayed onset, extended release.
- [663] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean number needed to harm (NNH) due to dizziness in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally.
- [664] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean number needed to harm (NNH) due to dizziness in opioid naïve or opioid inexperienced subjects which is at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 120%, 140%, 150%, 180%, 200%, 230%, 260%, or 300% lower than said score

after an equal amount (or dose) or lower amount (or dose) of an oral immediate release dosage form, or an oral extended release dosage form of levorphanol which is not delayed onset, extended release.

[665] In some preferred embodiments, the ratio of the foregoing NNH for drowsiness, nausea and dizziness after immediate release dosage form of levorphanol given orally, to the oral extended release levorphanol dosage form of the invention, is at least about 10:1, or 8:1, or 6:1, or 5:1, or 4:1, or 3:1, or 2.5:1, or 2:1, or 1.75:1, or 1.5:1, or 1.25:1, or 1.15:1, wherein the immediate release dosage form is given at an equal amount or lower amount.

[666] In some preferred embodiments, the ratio of the foregoing NNH for drowsiness, nausea and dizziness after extended release dosage form of levorphanol given orally, to the delayed onset, extended release levorphanol dosage form, is at least about 10:1, or 8:1, or 6:1, or 5:1, or 4:1, or 3:1, or 2.5:1, or 2:1, or 1.75:1, or 1.5:1, or 1.25:1, or 1.15:1, wherein the extended release dosage form is given at an equal amount or lower amount.

[667] In some preferred embodiments, the foregoing NNH for drowsiness, nausea and dizziness is assessed at a time 2.5 to 6 hours after administration of the dosage form, following alcohol (ethanol) administration sufficient to maintain a blood alcohol concentration of 0.04% to 0.08%, said ethanol administration 1.5 hours after said dosage form administration, said subjects only occasional or light consumers of alcohol.

[668] In some preferred embodiments, the foregoing NNH for drowsiness, nausea and dizziness are measured after single administration or first administration. In some other preferred embodiments, the foregoing NNH for drowsiness, nausea and dizziness are measured after repeated dose administration. In some preferred embodiments, the foregoing NNH for drowsiness, nausea and dizziness are measured after administration to patients in need of treatment with levorphanol. Most preferably, the foregoing NNH for drowsiness, nausea and dizziness are measured after first administration to opioid naïve subjects, between 0.5 to 6 hours after administration of the dosage form.

[669] As used herein, the phrase “after an equal amount or lower amount of an immediate release dosage form of levorphanol given orally” means an amount of oral immediate release levorphanol which is the equal to or at least up to about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% less than the dose or amount of extended release levorphanol in the dosage form of the invention, when said amounts are expressed in mass units of unsalified levorphanol.

[670] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean ratio of street price at about 1, or 2, or 3, or 4 or 5, or 6 hours post-dose, after administration of an equal amount or dose of an immediate release dosage form of levorphanol given orally to the dosage form of the invention which is ≥ 1.10 , ≥ 1.15 , or ≥ 1.25 , or ≥ 1.5 , or \geq

1.75, or ≥ 2 , or ≥ 2.5 , or ≥ 3 , or ≥ 3.5 , or ≥ 4 , or ≥ 4.5 , or ≥ 5 , or ≥ 5.5 , or ≥ 6 , or ≥ 6.5 , or ≥ 7 , or ≥ 7.5 , or ≥ 8 , or ≥ 8.5 , or ≥ 9 , or ≥ 9.5 , or ≥ 10 , where “street price” is based the price recreational drug users or drug addicts would be prepared to pay after consuming said levorphanol by the intended method of use or by any method of use.

[671] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean ratio of street price at about 1, or 2, or 3, or 4 or 5, or 6 hours post-dose, after administration of an equal amount of an oral immediate release dosage form or an oral extended release dosage form of levorphanol which is not delayed onset, extended release to the dosage form of the invention is ≥ 1.10 , ≥ 1.15 , or ≥ 1.25 , or ≥ 1.5 , or ≥ 1.75 , or ≥ 2 , or ≥ 2.5 , or ≥ 3 , or ≥ 3.5 , or ≥ 4 , or ≥ 4.5 , or ≥ 5 , or ≥ 5.5 , or ≥ 6 , or ≥ 6.5 , or ≥ 7 , or ≥ 7.5 , or ≥ 8 , or ≥ 8.5 , or ≥ 9 , or ≥ 9.5 , or ≥ 10 , where “street price” is based the price recreational drug users or drug addicts would be prepared to pay after consuming said levorphanol by the intended method of use or by any method of use.

[672] In some preferred embodiments, the oral extended release levorphanol dosage form of the invention provides a mean ratio of street price at about 1, or 2, or 3, or 4 or 5, or 6 hours post-dose, after administration of an equal amount or dose of an immediate release dosage form of levorphanol given orally to the dosage form of the invention is ≥ 1.10 , ≥ 1.15 , or ≥ 1.25 , or ≥ 1.5 , or ≥ 1.75 , or ≥ 2 , or ≥ 2.5 , or ≥ 3 , or ≥ 3.5 , or ≥ 4 , or ≥ 4.5 , or ≥ 5 , or ≥ 5.5 , or ≥ 6 , or ≥ 6.5 , or ≥ 7 , or ≥ 7.5 , or ≥ 8 , or ≥ 8.5 , or ≥ 9 , or ≥ 9.5 , or ≥ 10 , where “street price” is based the price recreational drug users or drug addicts would be prepared to pay after consuming said levorphanol by the intended method of use or by any method of use, and where said levorphanol use is followed about 0.5 to 1.5 hours later by alcohol (ethanol) administration sufficient to maintain a blood alcohol concentration of 0.04% to 0.08%.

[673] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form provides a mean ratio of street price at about 1, or 2, or 3, or 4 or 5, or 6 hours post-dose, after administration of an equal amount of an oral immediate release dosage form or an oral extended release dosage form of levorphanol which is not delayed onset, extended release to the dosage form of the invention is ≥ 1.10 , ≥ 1.15 , or ≥ 1.25 , or ≥ 1.5 , or ≥ 1.75 , or ≥ 2 , or ≥ 2.5 , or ≥ 3 , or ≥ 3.5 , or ≥ 4 , or ≥ 4.5 , or ≥ 5 , or ≥ 5.5 , or ≥ 6 , or ≥ 6.5 , or ≥ 7 , or ≥ 7.5 , or ≥ 8 , or ≥ 8.5 , or ≥ 9 , or ≥ 9.5 , or ≥ 10 , where “street price” is based the price recreational drug users or drug addicts would be prepared to pay after consuming said levorphanol by the intended method of use or by any method of use, and where said levorphanol use is followed about 0.5 to 1.5 hours later by alcohol (ethanol) administration sufficient to maintain a blood alcohol concentration of 0.04% to 0.08%.

[674] **Delayed Onset Extended Release Levorphanol Formulations**

[675] In some preferred embodiments, the dosage form provides a pharmaceutical dosage form comprising a therapeutically effective amount of levorphanol, said dosage form resistant or

substantially resistant to dissolution and/or absorption in the stomach, and/or in the duodenum, and/or in the jejunum, and/or in the ileum, or in the small intestine, or in the stomach and duodenum, or in the stomach, duodenum and jejunum, or in the stomach, duodenum, jejunum and terminal ileum, or in the stomach and small intestine, or before it reaches the ileo-cecal junction, or until it crosses the ileo-cecal junction, or until it reaches the colon; said levorphanol in the dosage form released rapidly or slowly upon reaching a the desired anatomic region of the GI tract (e.g., ileum or colon) or upon reaching the desired gastrointestinal conditions conducive to release from the dosage form (e.g., osmotic pressure, pH, time after ingestion, microbial flora); said dosage form in some embodiments providing immediate release of levorphanol following the expected lag time; said dosage form in some other embodiments providing sustained release of levorphanol following the expected lag time.

- [676] In embodiments, the delayed onset, extended release levorphanol dosage form provides abuse resistant properties in opioid abusers and in individuals with an opioid addiction disorder or a polysubstance addiction disorder.
- [677] In some embodiments, the delayed onset, extended release levorphanol dosage form is deters against PRN or as needed use of the drug by providing suboptimal efficacy upon PRN use but robust efficacy upon scheduled, around the clock of continuous use.
- [678] In embodiments, the delayed onset, extended release levorphanol dosage form provides resistance to alcohol associated dose dumping.
- [679] In embodiments, the delayed onset, extended release levorphanol dosage form provides minimizes pharmacokinetic when taken in the fed versus fasted state.
- [680] In some embodiments, the delayed onset, extended release levorphanol dosage form is substantially non-releasable until up to about 1, or 1.5, 2, or 2.25, or 2.5, or 2.75, or 3, or 3.25, or 3.5, or 3.75, or 4, or 4.25, or 4.5, or 4.75, or 5, or 5.25, or 5.5, or 5.75, or 6, or 6.25, or 6.5, or 7.75, or 7, or 7.25, or 7.5, or 7.75, or 8, or 8.25, or 8.5, or 8.75, or 9, or 9.25, or 9.5, or 9.75, or 10, or 10.25, or 10.5, or 10.75, or 11, or 11.25, or 1.5, or 11.75, or 12, or 14, or 16, or 18, or 20 hours after oral ingestion of the oral dosage form. In some particularly preferred embodiments, said dosage form is substantially non-releasable until up to about 2.5, or 2.75, or 3, or 3.25, or 3.5, or 3.75, or 4, or 4.25, or 4.5, or 4.75, or 5, or 5.25, or 5.5, or 5.75, or 6, or 6.25, or 6.5, or 7.75, or 7 hours after oral ingestion of the oral dosage form.
- [681] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form is a coated capsule or tablet wherein the coating comprises material which dissolves at a pH \geq 5, or \geq 5.5, or \geq 5.7, or \geq 6, or \geq 6.2, or \geq 6.4, or \geq 6.6, or \geq 6.8, \geq 7, or \geq 7.2. In some other preferred embodiments, the delayed onset, extended release levorphanol dosage form includes material incorporated in dosage form, wherein the material substantially resists dissolution for at least about 1, or 1.5, or 2, or 2.5, or 3, or 3.25, or 3.5, or 3.75, or 4, or 4.25, or 4.5, or 4.75, or 5, or

5.25, or 5.5, or 5.75, or 6, or 6.25, or 6.5, or 7.75, or 7 31 hours at a pH of about ≤ 5 , or ≤ 5.5 , or ≤ 5.7 , or ≤ 6 , or ≤ 6.2 , or ≤ 6.4 , or ≤ 6.6 , or ≤ 6.8 , ≤ 7 , or ≤ 7.2 .

[682] In some embodiments, the delayed onset, extended release levorphanol dosage form is coated with or includes incorporated one or more of the following: (i) cellulose acetate trimellitate (CAT); (ii) hydroxypropylmethyl cellulose phthalate (HPMCP); (iii) polyvinyl acetate phthalate (PVAP); (iv) shellac; (v) a copolymer of methacrylic acid and methylmethacrylate; (vi) a material which is redox-sensitive; (vii) an azopolymer or a disulphide polymer; (viii) a material which is degraded by enzymes or bacteria present in the colon; (ix) a copolymer of methacrylic acid and methylmethacrylate to which has been added during polymerization the monomer methyl acrylate; (x) a cellulose ester; (xi) polyvinyl acetate phthalate.

[683] In some embodiments, the dosage form consists of a coated capsule wherein the coating is applied separately to empty capsule body and cap. In some embodiments, the dosage form consists of a coated capsule filled with a caplet or tablet.

[684] In some embodiments, the dosage form is coated with a film or incorporates material which makes the delayed onset, extended release the dosage form: (i) is non-dissolving at $\text{pH} < 3$ to 4 and dissolving at $\text{pH} > 5$; or (ii) non-dissolving at $\text{pH} < 3$ to 4 and dissolving at $\text{pH} > 5.5$; or (iii) non-dissolving at $\text{pH} < 3$ to 4 and dissolving at $\text{pH} > 6$; or (iv) non-dissolving at $\text{pH} < 3$ to 4.5 and dissolving at $\text{pH} > 6$; or (v) non-dissolving at $\text{pH} < 3$ to 4 and dissolving at $\text{pH} > 6.5$; or (vi) non-dissolving at $\text{pH} < 3$ to 4.5, and dissolving at $\text{pH} > 6.5$; or (vii) non-dissolving at $\text{pH} < 3$ to 4 and dissolving at $\text{pH} > 7$; or (viii) non-dissolving at $\text{pH} < 3$ to 4.5 and dissolving at $\text{pH} > 7$; or (ix) is non-dissolving at $\text{pH} < 3$ to 5 and dissolving at $\text{pH} > 7$; or (x) non-dissolving at $\text{pH} < 3$ to 5.5 and dissolving at $\text{pH} > 7$.

[685] In some embodiments, the delayed onset, extended release levorphanol dosage form is non-dissolving or substantially non-dissolving at $\text{pH} < 5.5$, or at $\text{pH} < 6.0$, or at $\text{pH} < 6.2$, or at $\text{pH} < 6.5$, or at $\text{pH} < 6.8$, or at $\text{pH} < 7.0$, when measured by USP Basket Method or USP Paddle Method at 100 rpm in 900 mL of water at 37 °C (adjusted to the required pH with hydrochloric acid or sodium hydroxide) for up to about 2, 2.5, 3, 3.5, 4, 4.5, or 5.

[686] In some embodiments, the delayed onset, extended release levorphanol dosage form is non-releasing or substantially non-releasing at $\text{pH} < 5.5$, or at $\text{pH} < 6.0$, or at $\text{pH} < 6.2$, or at $\text{pH} < 6.5$, or at $\text{pH} < 6.8$, or at $\text{pH} < 7.0$, when measured by USP Basket Method or USP Paddle Method at 100 rpm in 900 mL of water at 37 °C (adjusted to the required pH with hydrochloric acid or sodium hydroxide) for up to about 2, 2.5, 3, 3.5, 4, 4.5, or 5.

[687] In some embodiments, the delayed onset, extended release levorphanol dosage form comprises material which is non-dissolving or substantially non-dissolving at a particular pH or range of pH and is dissolving or substantially dissolving at another pH or another range of pH, said material (i) commingled with the levorphanol API or with the granulation containing levorphanol

API; or (ii) commingled with the levorphanol API or with the granulation containing levorphanol API, in addition to being coated on the dosage form.

[688] In some embodiments, the specifications regarding coating of the delayed onset, extended release the dosage form of the invention with controlled release material or pH sensitive material are also applicable to dosage forms where said material is commingled with the levorphanol API or with the granulation containing levorphanol API, instead of or in addition to coating the dosage form.

[689] In some embodiments, the specifications regarding coating of the delayed onset, extended release the dosage form of the invention with controlled release material or pH sensitive material are also applicable to dosage forms where the coating is applied to multiparticulate matrices or to subunits of the dosage form e.g., beads incorporating drug), instead of or in addition to coating the dosage form.

[690] In some embodiments, the delayed onset, extended release the dosage form consists of a coated capsule wherein the coating is applied to capsules having a seal on the gap between capsule body and cap.

[691] In some embodiments, the delayed onset, extended release the dosage form consists of a coated capsule containing levorphanol, wherein the capsule is coated with a material selected from the group comprising cellulose acetate trimellitate, hydroxypropylmethyl cellulose phthalate, polyvinyl acetate phthalate, shellac, and a copolymer of methacrylic acid and ethyl acrylate, azopolymers, disulfide polymers and amylose.

[692] In some preferred embodiments, the delayed onset, extended release levorphanol dosage form has levorphanol T_{max} that exceeds its dosing frequency by about at least about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 or 5 hours.

[693] In some preferred embodiments, the levorphanol T_{max} ratio of the delayed onset, extended release levorphanol dosage form of the invention to levorphanol given orally as a conventional solution, suspension, immediate release tablet or capsule is ≥ 1.25 , or ≥ 1.5 , or ≥ 1.75 , or ≥ 2 , or ≥ 2.5 , or ≥ 3 , or ≥ 3.5 , or ≥ 4 , or ≥ 4.5 , or ≥ 5 , or ≥ 5.5 , or ≥ 6 , or ≥ 6.5 , or ≥ 7 , or ≥ 7.5 , or ≥ 8 , or ≥ 8.5 , or ≥ 9 , or ≥ 9.5 , or ≥ 10 , or ≥ 10.5 , or ≥ 12 , or ≥ 14 , or ≥ 16 , or ≥ 18 , or ≥ 20 .

[694] In some preferred embodiments, the levorphanol C_{max} ratio after levorphanol given orally as a conventional solution, suspension, immediate release tablet or capsule, to the delayed onset, extended release levorphanol dosage form of the invention given orally is ≥ 1.1 , or ≥ 1.2 , or ≥ 1.3 , or ≥ 1.5 , or ≥ 1.5 , or ≥ 1.6 , or ≥ 1.7 , or ≥ 1.8 , or ≥ 1.9 , or ≥ 2 , or ≥ 2.2 , or ≥ 2.5 , or ≥ 3 , or ≥ 3.5 , or ≥ 4 , or ≥ 4.5 , or ≥ 5 , or ≥ 5.5 , or ≥ 6 , or ≥ 6.5 , or ≥ 7 , or ≥ 7.5 , or ≥ 8 , or ≥ 8.5 , or ≥ 9 , or ≥ 9.5 , or ≥ 10 , or ≥ 10.5 , or ≥ 12 , or ≥ 14 , or ≥ 16 , or ≥ 18 , or ≥ 20 .

[695] In some embodiments, the delayed onset, extended release levorphanol dosage form releases less than about 0.1%, or 0.5%, or 1%, or 1.5%, or 2%, or 2.5%, or 3%, or 3.5%, or 4%, or 4.5%, or

5%, or 6%, or 7%, or 8%, or 9%, or 10%, or 12%, or 14%, or 15%, or 16%, or 17%, or 18%, or 20% of levorphanol in vitro from the dosage form when measured at about 1, 1.5, 2, 2.5, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 10.5, 11, 11.5, or 12 hours, said in vitro release measured by the USP Basket or Paddle Method at 100 rpm in 100 to 900 mL in one or more of the following: (a) water at 37 °C at a pH of 4.5, adjusted with HCl; (b) water at 37 °C at a pH of 5, adjusted with HCl; (c) water at 37 °C at a pH of 5.5, adjusted with HCl; (d) simulated gastric fluid at 37 °C; (e) simulated intestinal fluid at 37 °C; (f) simulated gastric fluid at 37 °C for one hour followed by a switch to simulated intestinal fluid; (g) Phosphate buffer 0.067M (pH 7.0) at 37 °C; and (h) Phosphate buffer 0.067M (pH 7.0) containing Tween 80 at 37 °C. In some embodiments, said in vitro dissolution is measured by the USP Apparatus III (Reciprocating Cylinder) Method instead of the Basket or Paddle Method. In some embodiments, most preferably, the dosage form releases less than about 0.1%, or 0.5%, or 1%, or 1.5%, or 2%, or 2.5%, or 3%, or 3.5%, or 4%, or 4.5%, or 5%, or 6%, or 7%, or 8%, or 9%, or 10% of levorphanol in vitro from the dosage form when measured at about 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, or 7 hours.

[696] In some embodiments, the delayed onset, extended release levorphanol dosage form releases 0%, or less than about 0.1%, or 0.5%, or 1%, or 1.5%, or 2%, or 2.5%, or 3%, or 3.5%, or 4%, or 4.5%, or 5%, or 6%, or 7%, or 8%, or 9%, or 10%, or 12%, or 14%, or 15%, or 16%, or 17%, or 18%, or 20% or 25% or 28% or 30% or 35% of levorphanol in vivo from the dosage form prior to reaching the duodenum, or jejunum, or ileum, or terminal ileum, or ileo-cecal junction, or ascending colon, or transverse colon, or descending colon, or colon

[697] In some embodiments, the delayed onset, extended release levorphanol dosage form releases 0%, or less than about 0.1%, or 0.5%, or 1%, or 1.5%, or 2%, or 2.5%, or 3%, or 3.5%, or 4%, or 4.5%, or 5%, or 6%, or 7%, or 8%, or 9%, or 10%, or 12%, or 14%, or 15%, or 16%, or 17%, or 18%, or 20% or 25% or 28% or 30% or 35% of levorphanol in vivo from the dosage form for at least about 1 hour, or at least about 1.5 hours, or at least about 2 hours, or at least about 2.5 hours, or at least about 3 hours, or at least about 3.25 hours, or at least about 3.5 hours, or at least about 3.75 hours, or at least about 4 hours, or at least about 4.25 hours, or at least about 4.5 hours, or at least about 4.75 hours, or at least about 5 hours, or at least about 5.25 hours, or at least about 5.5 hours, or at least about 5.75 hours, or at least about 6 hours, or at least about 6.25 hours, or at least about 6.5 hours, or at least about 6.75 hours, or at least about 7 hours, or at least about 7.25 hours, or at least about 7.5 hours, or at least about 7.75 hours, or at least about 8 hours, or at least about 8.25 hours, or at least about 8.5 hours, or at least about 8.75 hours, or at least about 9 hours, or at least about 9.25 hours, or at least about 9.5 hours, or at least about 9.75 hours, or at least about 10 hours, or at least about 10.25 hours, or at least about 10.5 hours, or at least about 10.75 hours, or at least about 11 hours, or at least about 11.5 hours, or at least about 12 hours after oral ingestion, said in vivo release from the dosage form measured by appearance of levorphanol in plasma, using

AUC_{0-n}/AUC_{0-inf}, or AUC_{0-n}/AUC_{0-τ}, where “n” is the time after oral ingestion. Most preferably, the time after oral ingestion is at least about 2 hours, or at least about 2.5 hours, or at least about 3 hours, or at least about 3.5 hours, or at least about 4 hours, or at least about 4.5 hours, or at least about 5 hours, or at least about 5.5 hours, or at least about 6 hours, or at least about 6.5 hours, or at least about 7 hours.

[698] In some embodiments, the delayed onset, extended release levorphanol dosage form releases 0%, or less than about 0.1%, or 0.5%, or 1%, or 1.5%, or 2%, or 2.5%, or 3%, or 3.5%, or 4%, or 4.5%, or 5%, or 6%, or 7%, or 8%, or 9%, or 10%, or 12%, or 14%, or 15%, or 16%, or 17%, or 18%, or 20% or 25% or 28% or 30% or 35% of levorphanol in vivo from the dosage form when the average measured or expected gastrointestinal pH is less than about 3.5, or is less than about 4, or is less than about 4.5, or is less than about 5, or less than about 5.2, or less than about 5.4, or less than about 5.6, or less than about 5.8, or less than about 6, or less than about 6.2, or less than about 6.4, or less than about 6.5, or less than about 6.6, or less than about 6.7, or less than about 6.8, or less than about 6.9, or less than about 7, or less than about 7.1, or less than about 7.2, or less than about 7.3, or less than about 7.4, or less than about 7.5, or less than about 7.6, or less than about 7.7, or less than about 7.8, or less than about 7.9, or less than about 8, or less than about 8.1, or less than about 8.2, or less than about 8.3, or less than about 8.4, or less than about 8.5, or less than about 8.6, or less than about 8.7, or less than about 8.8, or less than about 9, when measured up to about 1 hour, or up to about 1.5 hours, or up to about 2 hours, or up to about 2.5 hours, or up to about 2.75 hours, or up to about 3 hours, or up to about 3.25 hours, or up to about 3.5 hours, or up to about 3.75 hours, or up to about 4 hours, or up to about 4.25 hours, or up to about 4.5 hours, or up to about 4.75 hours, or up to about 5 hours, or up to about 5.25 hours, or up to about 5.5 hour, or up to about 5.75 hours, or up to about 6 hours, or up to about 6.5 hours, or up to about 6.75 hours, or up to about 7 hours, or up to about 7.25 hours, or up to about 7.5 hours, or up to about 7.5 hours, or up to about 7.75 hours, or up to about 8 hours, or up to about 8.25 hours, or up to about 8.5 hours, or up to about 8.75 hours, or up to about 9 hours, or up to about 9.25 hours, or up to about 9.5 hours, or up to about 9.75 hours, or up to about 10 hours, or up to about 10.5 hours, or up to about 11 hours, or up to about 12 hours, or up to about 12.5 hours after oral ingestion. Most preferably, the dosage form releases 0%, or less than about 0.1%, or 0.5%, or 1%, or 1.5%, or 2%, or 2.5%, or 3%, or 3.5%, or 4%, or 4.5%, or 5%, or 6%, or 7%, or 8%, or 9%, or 10%, or 12%, or 14%, or 15%, or 16%, or 17%, or 18%, or 20% or 25% or 28% or 30% or 35% of levorphanol in vivo when the measured or expected gastrointestinal pH is less than about 5, or less than about 5.5, or less than about 6, or less than about 6.5, or less than about 6.8, or less than about 7, or less than about 7.2, or less than about 7.5. Most preferably, said release is measured at about 2 hours, or about 2.5 hours, or about 3 hours, or 4 hours or 4.5 hours or 5 hours, or 5.5 hours or 6 hours or 6.5 hours or 7 hours.

[699] In some embodiments, the targeted gastrointestinal delivery of the levorphanol from the oral

extended release levorphanol dosage form into the lower segments of the gastrointestinal tract can be achieved through a variety of approaches, including but limited to incorporation of material or processes to achieve one or more of the following: time-controlled, pH-controlled, pressure-controlled, enzyme-controlled and hydration-controlled. Since the gastrointestinal tract is a complex, variable and highly dynamic environment and further complicated by the volume, content and location of food and beverages, in some embodiments, incorporation of material to achieve more than one of the above approaches is preferred.

[700] In some embodiments, the targeted gastrointestinal delivery of the levorphanol from the oral extended release levorphanol dosage form into the lower segments of the gastrointestinal tract can be achieved through encapsulation of the levorphanol, preferably with excipients or functional excipients, said capsule incorporating, coated with or overcoated with material or processes to achieve targeted gastrointestinal delivery.

[701] In some embodiments, the oral extended release levorphanol dosage form is coated with a material or incorporates material which is non-dissolving or substantially resistant to dissolution, each when measured by USP Basket Method or USP Paddle Method at 100 rpm in 900 mL of water at 37 °C (adjusted to the required pH with hydrochloric acid or sodium hydroxide) at about pH 2, pH 2.2, pH 2.4, pH 2.6, pH 2.8, pH 3, pH 3.2, pH 3.4, pH 3.6, pH 3.8, pH 4, pH 4.2, pH 4.4, pH 4.6, pH 4.8, pH 5, pH 5.2, pH 5.4, pH 5.6, pH 5.8, pH 6, pH 6.2, pH 6.4, pH 6.6, pH 6.8, pH 7, pH 7.2, pH 7.4, for up to about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 14, 16, 18, or 20 hours.

[702] In some embodiments, the oral extended release levorphanol dosage form is coated with a material or incorporates material which is non-releasing or substantially non-releasing, each when measured by USP Basket Method or USP Paddle Method at 100 rpm in 900 mL of water at 37 °C (adjusted to the required pH with hydrochloric acid or sodium hydroxide) at about pH 2, pH 2.2, pH 2.4, pH 2.6, pH 2.8, pH 3, pH 3.2, pH 3.4, pH 3.6, pH 3.8, pH 4, pH 4.2, pH 4.4, pH 4.6, pH 4.8, pH 5, pH 5.2, pH 5.4, pH 5.6, pH 5.8, pH 6, pH 6.2, pH 6.4, pH 6.6, pH 6.8, pH 7, pH 7.2, pH 7.4, for up to about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 14, 16, 18, or 20 hours.

[703] In some embodiments, the oral extended release levorphanol dosage form is coated with a material or incorporates material which is non-dissolving or substantially non-dissolving at one pH but dissolving or substantially dissolving at another pH for up to about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 14, 16, 18, or 20 hours; said one pH being ≤ 2 , or ≤ 2.1 , or ≤ 2.2 , or ≤ 2.3 , or ≤ 2.4 , or ≤ 2.5 , or ≤ 2.6 , or ≤ 2.7 , or ≤ 2.8 , or ≤ 2.9 , or ≤ 3 , or ≤ 3.1 , or ≤ 3.2 , or ≤ 3.3 , or ≤ 3.4 , or ≤ 3.5 , or ≤ 3.6 , or ≤ 3.7 , or ≤ 3.8 , or ≤ 3.9 , or ≤ 4 , or ≤ 4.1 , or ≤ 4.2 , or ≤ 4.3 , or ≤ 4.4 , or ≤ 4.5 , or ≤ 4.6 , or ≤ 4.7 , or ≤ 4.8 , or ≤ 4.9 , or ≤ 5 ; said another pH being ≥ 5.2 , or ≥ 5.3 , or ≥ 5.4 , or ≥ 5.5 , or ≥ 5.6 , or ≥ 5.7 , or ≥ 5.8 , or ≥ 5.9 , or ≥ 6 , or ≥ 6.1 , or \geq

6.2, or ≥ 6.3 , or ≥ 6.4 , or ≥ 6.5 , or ≥ 6.6 , or ≥ 6.7 , or ≥ 6.8 , or ≥ 6.9 , or ≥ 7 , or ≥ 7.1 , or ≥ 7.2 , or ≥ 7.3 , or ≥ 7.4 , or ≥ 7.5 , or ≥ 7.6 , or ≥ 7.7 , or ≥ 7.8 , or ≥ 7.9 , or ≥ 8.0 , or ≥ 8.1 , or ≥ 8.2 , or ≥ 8.3 , or ≥ 8.4 , or ≥ 8.5 , or ≥ 8.6 , or ≥ 8.7 , or ≥ 8.8 , or ≥ 8.9 , or ≥ 9.0 , each when measured when by USP Basket Method or USP Paddle Method at 100 rpm in 900 mL of water at 37 °C (adjusted to the required pH with hydrochloric acid or sodium hydroxide).

[704] In some embodiments, the oral extended release levorphanol dosage form is coated with a material or incorporates material which is non-releasing or substantially non-releasing at one pH but releasing or substantially releasing at another pH for up to about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 14, 16, 18, or 20 hours; said one pH being ≤ 2 , or ≤ 2.1 , or ≤ 2.2 , or ≤ 2.3 , or ≤ 2.4 , or ≤ 2.5 , or ≤ 2.6 , or ≤ 2.7 , or ≤ 2.8 , or ≤ 2.9 , or ≤ 3 , or ≤ 3.1 , or ≤ 3.2 , or ≤ 3.3 , or ≤ 3.4 , or ≤ 3.5 , or ≤ 3.6 , or ≤ 3.7 , or ≤ 3.8 , or ≤ 3.9 , or ≤ 4 , or ≤ 4.1 , or ≤ 4.2 , or ≤ 4.3 , or ≤ 4.4 , or ≤ 4.5 , or ≤ 4.6 , or ≤ 4.7 , or ≤ 4.8 , or ≤ 4.9 , or ≤ 5 ; said another pH being ≥ 5.2 , or ≥ 5.3 , or ≥ 5.4 , or ≥ 5.5 , or ≥ 5.6 , or ≥ 5.7 , or ≥ 5.8 , or ≥ 5.9 , or ≥ 6 , or ≥ 6.1 , or ≥ 6.2 , or ≥ 6.3 , or ≥ 6.4 , or ≥ 6.5 , or ≥ 6.6 , or ≥ 6.7 , or ≥ 6.8 , or ≥ 6.9 , or ≥ 7 , or ≥ 7.1 , or ≥ 7.2 , or ≥ 7.3 , or ≥ 7.4 , or ≥ 7.5 , or ≥ 7.6 , or ≥ 7.7 , or ≥ 7.8 , or ≥ 7.9 , or ≥ 8.0 , or ≥ 8.1 , or ≥ 8.2 , or ≥ 8.3 , or ≥ 8.4 , or ≥ 8.5 , or ≥ 8.6 , or ≥ 8.7 , or ≥ 8.8 , or ≥ 8.9 , or ≥ 9.0 , each when measured when by USP Basket Method or USP Paddle Method at 100 rpm in 900 mL of water at 37 °C (adjusted to the required pH with hydrochloric acid or sodium hydroxide).

[705] In some embodiments, the oral extended release levorphanol dosage form is non-bioavailable or substantially non-bioavailable for up to about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 14, 16, 18, or 20 hours after oral ingestion (e.g., the dosage form releases 0%, or less than about 0.1%, or 0.5%, or 1%, or 1.5%, or 2%, or 2.5%, or 3%, or 3.5%, or 4%, or 4.5%, or 5%, or 6%, or 7%, or 8%, or 9%, or 10%, or 12%, or 14%, or 15%, or 16%, or 17%, or 18%, or 20% or 25% or 28% or 30% or 35% of levorphanol in vivo when assessed up to the specified time). In some embodiments, the oral extended release levorphanol dosage form is coated with a material or incorporates material which renders the dosage form non-bioavailable or substantially non-bioavailable for up to about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 14, 16, 18, or 20 hours. Most preferably, said dosage form is non-bioavailable or substantially non-bioavailable for up to about 2 hours, or about 2.5 hours, or about 3 hours, or 4 hours or 4.5 hours or 5 hours, or 5.5 hours or 6 hours or 6.5 hours or 7 hours.

[706] In some embodiments, the invention provides a delayed onset, extended release oral pharmaceutical compositions of levorphanol, said compositions in extended release form, said dosage form releasing 0%, or less than about 0.1%, or 0.5%, or 1%, or 1.5%, or 2%, or 2.5%, or 3%, or 3.5%, or 4%, or 4.5%, or 5%, or 6%, or 7%, or 8%, or 9%, or 10%, or 12%, or 14%, or 15%, or 16%, or 17%, or 18%, or 20% or 25% or 28% or 30% or 35% of levorphanol in vivo from

the dosage form prior to reaching the duodenum, or jejunum, or ileum, or terminal ileum, or ileo-cecal junction, or ascending colon, or transverse colon, or descending colon, or colon.

[707] In some embodiments, the invention provides a delayed onset, extended release oral pharmaceutical compositions of levorphanol, said compositions in extended release form, said dosage form releasing most, substantially all or all of the releasable levorphanol in the lower segment of the gastrointestinal tract (e.g., distal to the duodenum, or jejunum, or ileum, or terminal ileum, or ileo-cecal junction, ascending colon, or transverse colon), said release occurring over about 4, 5, 6, 7, 8, 9, 10, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 30, 32, 36 or 40 hours.

[708] In some embodiments, the invention provides a delayed onset, extended release oral pharmaceutical compositions of levorphanol, said compositions in extended release form, said dosage form releasing most, substantially all or all of the releasable levorphanol in the lower segment of the gastrointestinal tract (e.g., distal to the duodenum, or jejunum, or ileum, or terminal ileum, or ileo-cecal junction, ascending colon, or transverse colon), said release occurring over about 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5 or 4 hours.

[709] In some embodiments, the invention provides a delayed onset, extended release oral pharmaceutical compositions of levorphanol, said composition in delayed onset, extended release form, said dosage form releasing 0%, or less than about 0.1%, or 0.5%, or 1%, or 1.5%, or 2%, or 2.5%, or 3%, or 3.5%, or 4%, or 4.5%, or 5%, or 6%, or 7%, or 8%, or 9%, or 10%, or 12%, or 14%, or 15%, or 16%, or 17%, or 18%, or 20% or 25% or 28% or 30% or 35% of levorphanol proximal to the duodenum, or jejunum, or ileum, or terminal ileum, or ileo-cecal junction.

[710] In some embodiments, the invention provides a delayed onset, extended release oral pharmaceutical compositions of levorphanol, said composition in delayed onset, extended release form, or for delivery distal to the duodenum, or jejunum, or ileum, or terminal ileum, or ileo-cecal junction, said dosage form containing up to about 50%, or up to about 45%, or up to about 40%, or up to about 35%, or up to about 30%, or up to about 25%, or up to about 20%, or up to about 15%, or up to about 10%, or up to about 5% of the levorphanol dose in immediate release form, said immediate release form released and/or available for absorption in the stomach, duodenum, jejunum and/or ileum, and said immediate release form released and/or available for absorption at a pH of less than about 1, or less than about 1.5, or less than about 2, or less than about 2.5, or less than about 3, or less than about 3.5, or less than about 4, or less than about 4.5, or less than about 5, or less than about 5.5, or less than about 6, or less than about 7.

[711] In some embodiments, the plasma T_{lag} of the delayed onset, extended release levorphanol dosage form is more than about 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5 or 12 hours, preferably at least about 2 hours, and more preferably at least about 3 hours and most preferably at least about 4 hours.

[712] In some embodiments, where the delayed onset, extended release levorphanol dosage form

provides duodenal delivery, jejunal delivery, ileal delivery, ileo-colonic delivery, or colonic delivery, the plasma T_{lag} of the delayed onset, extended release levorphanol dosage form is more than about 1.25, 1.5, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5 or 12 hours, preferably at least about 2 hours, and more preferably at least about 3 hours and most preferably at least about 4 hours.

[713] In some embodiments, the $T_{lagD(1.2)}$, $T_{lagD(2)}$, $T_{lagD(3)}$, $T_{lagD(4)}$, $T_{lagD(4.5)}$, $T_{lagD(5.0)}$, $T_{lagD(5.5)}$, $T_{lagD(6)}$, $T_{lagD(6.2)}$, $T_{lagD(6.8)}$, $T_{lagD(7.0)}$ and $T_{lagD(7.2)}$ of the delayed onset, extended release levorphanol dosage form is more than about 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, or 4 hours, preferably more than about 2, 2.25, 2.5, 2.75, or 3 hours.

[714] In some preferred embodiments where the delayed onset, extended release levorphanol dosage form incorporates a controlled release material to render it delayed onset suitable for dosing every 12 hours, said dosage form releases or delivers levorphanol at a controlled rate of release for a period of about 7, 8, 9, 10, 11, 12, 14, 16 or 18 hours.

[715] In some preferred embodiments where the delayed onset, extended release levorphanol dosage form incorporates a controlled release material to render it delayed onset suitable for dosing every 24 hours, said dosage form releases or delivers levorphanol at a controlled rate of release for a period of about 12, 14, 16, 18, 20, 22, 24, 26 or 30 hours.

[716] In some preferred embodiments, the dosage form maintains a plasma levorphanol concentration within 50% of C_{max} for about 1 to about 22 hours, or about 1 to about 18 hours or about 1 to about 16 hours, or about 1 to about 14 hours or about 1 to about 10 hours, or about 1 to about 8 hours or about 1 to about 6 hours, or about 1 to about 5 hours or about 2 to about 20 hours, or about 4 to about 20 hours or about 4 to about 18 hours, or about 5 to about 18 hours or about 6 to about 18 hours, or about 7 to about 18 hours or about 8 to about 18 hours, or about 10 to about 18 hours or about 12 to about 18 hours, or about 14 to about 18 hours or about 4 to about 16 hours, or about 4 to about 12 hours or about 4 to about 10 hours, or about 4 to about 8 hours or about 5 to about 15 hours, or about 5 to about 10 hours or about 6 to about 18 hours, or about 6 to about 12 hours or about 6 to about 10 hours, or about 8 to about 18 hours or about 8 to about 16 hours, or about 10 to about 20 hours during the dosing interval.

[717] Although dosage forms that provide pH independent in vitro dissolution and in vivo release are frequently sought after and viewed favorably, particularly many extended release dosage forms, in some embodiments, pH independent dissolution and release can work against the objectives of the some oral dosage forms of levorphanol (e.g., delayed onset, extended release) which are intended to provide delivery or release of the dosage form in the proximal to the stomach, duodenum, or ileum (i.e., duodenal release, jejunal release, ileal release, ileo-colonic release or colonic release). Indeed, certain controlled release material used to achieve delayed onset, duodenal release, jejunal release, ileal release, ileo-colonic release or colonic release exploit the pH difference

in the GI tract to achieve some or all of its objectives.

- [718] Therefore, in some preferred embodiments, where the oral levorphanol pharmaceutical composition is intended to provide delayed onset, extended release, through use of a pH sensitive controlled release material, the in-vitro release rate is substantially dependent on pH in that the amount of levorphanol released at an undesirable pH (e.g., pH 1.2) and the amount released at a desirable pH (e.g., depending on the controlled release material and delivery and release objectives, pH 5.5, 6, 6.5, 7, 7.2, 7.4), when measured in-vitro at 1.5 or 2 hours using the USP Basket or Paddle Method of USP Drug Release test of U.S. Pharmacopeia (2003) at 100 rpm in 900 ml aqueous buffer is significantly different. For example, in some preferred embodiments, the in-vitro release rate difference is greater than about 35%, or 40%, or 45%, or 50%, or 55%, or 60% or 70%, or 80%, with the release rate higher at the desirable pH compared with the undesirable pH.
- [719] In some preferred embodiments of the invention, the dosage form of the invention is a duodenal delivery, or jejunal delivery, or ileal delivery, or ileo-colonic delivery or colonic delivery dosage form.
- [720] In some preferred embodiments, the levorphanol in the dosage form is non-releasable or substantially non-releasable until (i) after a particular time following oral ingestion, when the dosage form can be anticipated to have reached the duodenum, jejunum, ileum, ileo-cecal junction, cecum, or colon; or (ii) the dosage form has come in contact or substantial contact or sustained contact with a desired gastrointestinal pH environment (e.g., pH > 3, or pH > 3.5, or pH > 4, or pH > 4.5, or pH, > 5, or pH > 5.5, or pH > 6, or pH > 7, or pH > 7.5, or pH > 7.8); or (iii) the dosage form has come in contact with desired microbial flora (e.g., colonic microbial flora).
- [721] In certain situations involving pharmacokinetic evaluations, it may not be possible to provide the same amount of drug by different routes of administration due to the lack of commercially available dosage strengths or because such administration would require testing outside the approved method of administration (e.g., oral administration of high doses of immediate release levorphanol). Under such circumstances, the term “after the same amount” of levorphanol or “after an equal amount” of levorphanol may be modified and different amounts of drug may be evaluated, provided the data are dose normalized using pharmacokinetic approaches well known in the art.
- [722] Also disclosed are methods for the treatment of a human patient suffering from a medical condition amenable to treatment with levorphanol comprising administering a therapeutically effective amount of oral levorphanol and a controlled release material to render said dosage form extended release.
- [723] Also disclosed are methods for the treatment of a human patient suffering from pain with levorphanol comprising administering a therapeutically effective amount of oral levorphanol, and a controlled release material to render said dosage form extended release.

- [724] Also disclosed are methods for the treatment of medical conditions amenable to treatment with levorphanol in patients who are at higher risk for nausea, vomiting, sedation or other opioid agonist side effects or who have a prior history of said side effects on other opioids comprising administering a therapeutically effective amount of oral levorphanol, and a controlled release material to render said dosage form extended release.
- [725] The treatment of all pain states is contemplated by this invention, regardless of etiology, mechanisms, duration, prior treatment response and anatomic location, including acute pain, inflammatory pain, chronic pain, cancer pain, visceral pain and neuropathic pain. Particularly preferable pain states are those requiring treatment for more than a few days, more than a few weeks or more than a few months, e.g., chronic (non-cancer) pain, chronic cancer pain and neuropathic pain.
- [726] Also disclosed are methods of providing relief in a human patient suffering from neuropathic pain and chronic. In some preferred embodiments, the dosage form of the invention is intended for the treatment of neuropathic pain, peripheral neuropathic pain, central neuropathic pain, chronic pain, osteoarthritis, back pain, cancer pain, and chronic inflammatory pain.
- [727] The invention is also directed to methods of preparing the dosage forms disclosed herein.
- [728] The invention is also directed to a process for the preparation and manufacture of the dosage form.
- [729] Also disclosed are methods of providing relief in a human patient suffering from acute pain.
- [730] All kinds of kits of the present invention are contemplated. In some preferred embodiments, also provided are kits for use in treating or preventing the pain with the oral administration of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof for a subject in need of such treatment, comprising: (i) a dosage form of the invention; (ii) a container for the dosage form; and optionally, any of (iii) to (vi): (iii) a container for individual units of the dosage form (e.g., individual tablets or capsules in blisters); (iv) educational instructions in any media about various medical conditions, their etiology, pathophysiology, consequences and treatment, including information on the potential for abuse and diversion and methods for prevention of same and information on the proper use and disposal of the medication; (v) containers or bags for the safe disposal of any used or remaining unused dosage form, preferably child proof and flushable; (vi) tamper evident and child proof packaging for the kit and its contents.

ACTIVE TREATMENTS

- [731] **Levorphanol**
- [732] The amount of levorphanol in the oral dosage form will vary depending on variety of physiologic, pharmacologic, pharmacokinetic, pharmaceutical and physicochemical factors, including, without limitation: (i) the choice of levorphanol as the base, pharmaceutically acceptable

salt or mixtures thereof; (ii) the nature of the oral dosage form (e.g, immediate release or extended release); (iii) the anatomical location of the pain relieving target; (iv) the intensity and intractability of the pain; (v) the contribution of different mechanism to the initiation, propagation, summation and maintenance of the pain; (vi) the absorption, metabolism, distribution and excretion of orally administered levorphanol in healthy subjects and in patients with various diseases and disorders, including renal and hepatic impairment; (vii) the presence of comorbid pathology; (viii) the patient's risk of iatrogenic side effects; (ix) the tolerability of the dose, including the patient's propensity for levorphanol associated CNS and gastrointestinal side effects; (x) use of concurrent analgesics; (xi) the efficiency of the dosage form; and (xii) prior opioid exposure, including the type of opioid, the dose, the duration and the recency of use.

[733] In certain embodiments, the amount of levorphanol in the oral dosage form of the invention for use in an adult is about 0.5 mg to about 5 grams. In other embodiments, the amount of levorphanol in the dosage form is about 1 mg to about 800 mg, or about 1 mg to about 600 mg, or about 1 mg to about 400 mg, or about 1 mg to about 300 mg, or about 1 mg to about 250 mg, or about 1 mg to about 200 mg, or about 1 mg to about 180 mg, or about 1 mg to about 160 mg, or about 1 mg to about 140 mg, or about 1 mg to about 120 mg, or about 1 mg to about 100 mg, or about 1 mg to about 90 mg, or about 1 mg to about 80 mg, or about 1 mg to about 70 mg, or about 1 mg to about 60 mg, or about 1 mg to about 55 mg, or about 1 mg to about 50 mg, or about 1 mg to about 45 mg, or about 1 mg to about 40 mg, or about 1 mg to about 38 mg, or about 1 mg to about 35 mg, or about 1 mg to about 32 mg, or about 1 mg to about 30 mg, or about 1 mg to about 28 mg, or about 1 mg to about 26 mg, or about 1 mg to about 25 mg, or about 1 mg to about 23 mg, or about 1 mg to about 20 mg, or about 2 mg to about 100 mg, or about 2 mg to about 80 mg, or about 2 mg to about 50 mg, or about 2 mg to about 40 mg, or about 2 mg to about 30 mg, or about 4 mg to about 100 mg, or about 4 mg to about 80 mg, or about 4 mg to about 50 mg, or about 4 mg to about 40 mg, or about 4 mg to about 30 mg, or about 5 mg to about 100 mg, or about 5 mg to about 80 mg, or about 5 mg to about 50 mg, or about 5 mg to about 40 mg, or about 5 mg to about 30 mg, or about 6 mg to about 100 mg, or about 6 mg to about 80 mg, or about 6 mg to about 50 mg, or about 6 mg to about 40 mg, or about 6 mg to about 30 mg, or about 8 mg to about 100 mg, or about 8 mg to about 80 mg, or about 8 mg to about 50 mg, or about 8 mg to about 40 mg, or about 8 mg to about 30 mg, or about 8 mg to about 100 mg, or about 8 mg to about 80 mg, or about 8 mg to about 50 mg, or about 8 mg to about 40 mg, or about 8 mg to about 30 mg. In more preferred embodiments, the amount of levorphanol in the dosage form is about 2 mg to about 80 mg, or about 2 mg to about 60 mg, or about 2 mg to about 40 mg, or about 4 mg to about 60 mg, or about 4 mg to about 50 mg, or about 5 mg to about 30 mg.

[734] In other embodiments, the amount of levorphanol in a single unit dose (e.g., one tablet or capsule) of the invention for use in an adult the exceeds the maximum unit dose of oral immediate

release levorphanol by at least about 20%, or 30%, or 40%, or 50%, or 60%, or 70%, or 80%, or 90%, or 100%, or 120%, or 140%, or 160%, or 180%, or 200%, or 220%, or 240%, or 260%, or 280%, or 300%, or 320%, or 340%, or 360%, or 380%, or 400%, or 450%, or 500%, or 550%, or 600%, or 650%, or 700%.

[735] Suitable pharmaceutically acceptable salts of levorphanol include levorphanol bitartrate, levorphanol bitartrate hydrate, levorphanol hydrochloride, levorphanol p-toluenesulfonate, levorphanol phosphate, levorphanol thiosemicarbazone, levorphanol sulfate, levorphanol trifluoroacetate, levorphanol hemipentahydrate, levorphanol pentafluoropropionate, levorphanol p-nitrophenylhydrazone, levorphanol o-methyloxime, levorphanol semicarbazone, levorphanol hydrobromide, levorphanol mucate, levorphanol oleate, levorphanol phosphate dibasic, levorphanol phosphate monobasic, levorphanol inorganic salt, levorphanol organic salt, levorphanol acetate trihydrate, levorphanol bis(heptafluorobutyrate), levorphanol bis(methylcarbamate), levorphanol bis(pentafluoropropionate), levorphanol bis(pyridine carboxylate), levorphanol bis(trifluoroacetate), levorphanol chlorhydrate, and levorphanol sulfate pentahydrate. Preferably, the levorphanol is present as the tartrate salt or the base.

[736] **Aversive Agents**

[737] In certain preferred embodiments of the present invention, the dosage form may include, in addition to the levorphanol, substances, process or technologies that impart abuse deterrent, abuse resistant or tamper resistant properties to the dosage form, including aversive agents; said dosage form reducing or preventing opioid abuse, drug abuse, drug misuse, recreational drug use, drug diversion and toxicity from intentional or accidental overdose.

[738] In some preferred dosage forms of the invention, the dosage form includes taste aversive agents (e.g., bittering agents) in sequestered or unsequestered form to deter sublingual, oromucosal, buccal or intranasal use of the dosage form. In some embodiments, the taste aversive agents (bittering agent) is coated on the oral dosage form and then overcoated with material which prevents or minimizes the bitter sensation upon normal oral ingestion but which does not protect against an aversive taste upon prolonged residence in the oral cavity (e.g., upon sublingual, oromucosal or buccal use) or upon intranasal use. In this manner the taste aversive agent is not sequestered in the sense that it is readily released in the GI tract upon oral ingestion, where it is devoid of taste aversive effects. A wide variety of pharmaceutical excipients known in the art may be used to provide the desired outer coating to the dosage form. In some embodiments, the taste aversive agents (e.g., bittering agent) is incorporated in the oral dosage form which prevents or minimizes the bitter sensation upon normal oral ingestion but which does not protect against an aversive taste upon prolonged residence in the oral cavity (e.g., upon sublingual, oromucosal or buccal use). In this manner the taste aversive agent may be sequestered or unsequestered. In some embodiments, the taste aversive agents (e.g., bittering agent) is incorporated into the inside walls of

the capsule shell which prevents or minimizes the bitter sensation upon normal oral ingestion but which does not protect against an aversive taste upon prolonged residence in the oral cavity (e.g., upon sublingual, oromucosal or buccal use).

[739] All kinds of abuse deterrent agents, excipients, dosage forms and technologies are contemplated, including, without limitation, excipients that deter or resist extraction of drug with the application of mechanical, chemical, or thermal energy, use of solvents, use of sequestered or unsequestered (releasable) antagonists to the drug or to a co-abused drug, use of sequestered or unsequestered (releasable) aversive agents, and use covalently bound moieties that modulate release of the levorphanol in vitro, in the GI tract and in the liver.

[740] In certain preferred embodiments of the present invention, the dosage form may include, in addition to levorphanol or a pharmaceutically acceptable salt thereof, abuse deterrent or abuse resistant substances, process or technologies known in the art, including one or more aversive agents. All kinds of aversive agents are contemplated, including, without limitation, antagonists of opioids and other abusable drugs, laxatives, cutaneous vasodilators, headache producing agents, emetics, emetogenic compound, nausea producing compounds, bittering agents, drugs that cause burning on irritation when in contact with tissue or mucous membranes (e.g., naso-mucosal irritants, oro-mucosal irritants, respiratory irritants), tissue irritants, gastrointestinal irritants, drugs that precipitate withdrawal effects, tissue dyes, lakes and colorants, beverage dyes, lakes and colorants, non-tissue staining beverage dyes, lakes and colorants (i.e., that do not stain or discolor the skin upon ingestion), fecal discolorants, urine discolorants, malodorous agents, opioid antagonists, benzodiazepine antagonists (e.g., flumazenil), cannabinoid antagonists and pharmacologic antagonists to co-abused drugs not contained in the dosage form. Such aversive agents may be in the dosage form in a releasable, partially releasable or a non-releasable form (i.e., sequestered), the latter being released on tampering the dosage form (e.g., mechanical, thermal, chemical, solvent tampering, ingestion in ways not recommended, and the like). Further, in some embodiments, such aversive agents may be in the dosage form in an amount that does not produce an aversive effect or aversion in any, many or substantially all patients when taken in accordance with the prescribing information or the manufacturer's instructions (for example, in small quantities), but which produce an aversive effect when taken in excess (e.g., higher dose or more frequently). In other embodiments, said aversive agent pharmacologically blocks the effects of the levorphanol and/or the effects of a co-abused drug, said co-abused drug in the same dosage form or in a different dosage form or not an approved or conventional pharmaceutical product. Various bittering agents can be employed including, for example and without limitation, T2R or TAS2R receptor agonists, phenylthiourea (phenylthiocarbamide), natural, artificial and synthetic flavor oils and flavoring aromatics and/or oils, oleoresins and extracts derived from plants, leaves, flowers, fruits, and so forth, and combinations thereof. Nonlimiting representative flavor oils include

spearmint oil, peppermint oil, eucalyptus oil, oil of nutmeg, allspice, mace, oil of bitter almonds, menthol and the like. Also useful bittering agents are artificial, natural and synthetic fruit flavors such as citrus oils including lemon, orange, lime, grapefruit, and fruit essences and so forth. Additional bittering agents include sucrose derivatives (e.g., sucrose octaacetate), chlorosucrose derivatives, quinine and quinine salts, quinidine and quinidine salts and the like. The preferred bittering agent for use in the present invention is denatonium, denatonium benzoate and denatonium saccharide. A dosage form including a bittering agent preferably discourages improper usage of the tampered dosage form by imparting a disagreeable taste to the tampered dosage form.

[741] Various emetic agents can be employed including, for example and without limitation, zinc and pharmaceutically acceptable salts thereof (e.g., zinc oxide, zinc gluconate, zinc acetate, zinc sulfate, zinc carbonate), dopamine agonists, apomorphine, ipecac, ipecacuanha, emetine, emetine (methylcephaline), cephaline, psychotrine, O-methylpsychotrine, ammonium chloride, potassium chloride, magnesium sulfate, ferrous gluconate, ferrous sulfate, aloin, algarot or antimonious oxychloride, antimony trichloride, folate, folic acid, niacin (niacin) and nicotinamide.

[742] In some embodiments, the aversive agent in the dosage form may be zinc in the form of elemental zinc or a pharmaceutically acceptable salt of zinc, in a quantity expressed as mg of elemental zinc, of about 1 mg to about 400 mg, or about 1 mg to about 300 mg, or about 1 mg to about 200 mg, or about 1 mg to about 150 mg, or about 1 mg to about 100 mg, or about 1 mg to about 90 mg, or about 1 mg to about 80 mg, or about 1 mg to about 70 mg, or about 1 mg to about 60 mg, or about 1 mg to about 50 mg, or about 1 mg to about 45 mg, or about 1 mg to about 40 mg, or about 1 mg to about 40 mg, or about 1 mg to about 35 mg, or about 1 mg to about 30 mg, or about 1 mg to about 25 mg, or about 1 mg to about 20 mg, or about 1 mg to about 10 mg, or about 1 mg to about 5 mg, or about 5 mg to about 400 mg, or about 5 mg to about 300 mg, or about 5 mg to about 200 mg, or about 5 mg to about 150 mg, or about 5 mg to about 100 mg, or about 10 mg to about 150 mg, or about 10 mg to about 100 mg, or about 5 mg to about 80 mg, or about 5 mg to about 60 mg, or about 5 mg to about 50 mg, or about 5 mg to about 45 mg, or about 5 mg to about 40 mg, or about 5 mg to about 40 mg, or about 5 mg to about 35 mg, or about 5 mg to about 30 mg, or about 5 mg to about 25 mg, or about 5 mg to about 20 mg, or about 5 mg to about 10 mg, or about 10 mg to about 90 mg, or about 10 mg to about 80 mg, or about 10 mg to about 60 mg, or about 10 mg to about 50 mg, or about 10 mg to about 45 mg, or about 10 mg to about 40 mg, or about 10 mg to about 40 mg, or about 10 mg to about 35 mg, or about 10 mg to about 30 mg, or about 10 mg to about 25 mg, or about 10 mg to about 20 mg, or about 20 mg to about 100 mg, or about 20 mg to about 90 mg, or about 20 mg to about 80 mg, or about 20 mg to about 60 mg, or about 20 mg to about 50 mg, or about 20 mg to about 45 mg, or about 20 mg to about 40 mg, or about 20 mg to about 35 mg, or about 20 mg to about 30 mg, or about 15 mg to about 50 mg, or about 15 mg to about 40 mg, or about 15 mg to about 35 mg, or a quantity sufficient to be produce

an aversive effect vasodilation when abused but not under conditions of medically appropriate use.

[743] Various irritants can be employed including, for example and without limitation transient receptor potential vanilloid 1 (TRPV1 or VR1) agonists (including resiniferanoids, capsaicinoids, phorboid vanilloids, and terpenoid 1,4-unsaturated dialdehydes, capsaicin, capsaicin analogs and derivatives, resiniferatoxin, olvanil, piperine, zingerone, anandamide, 12- and 15-(S)-hydroperoxy-eicosatetraenoic acids, 5 and 15-(S)-hydroxyeicosatetraenoic acids, phorbol 12-phenylacetate 13-acetate 20-homovanillate, 2 phorbol 12,13-didecanoate 20-homovanillate, leukotriene B(4), tinyatoxin, heptanoylisobutylamide, N-(3-acyloxy-2-benzylpropyl)-N'-dihydroxytetrahydrobenzazepine, tetrahydroisoquinoline thiourea analogs, heptanoyl guaiacylamide, other isobutylamides or guaiacylamides, dihydrocapsaicin, homovanillyl octylester and nonanoyl vanillylamide), acids such as acids with one or more carboxyl moieties (e.g., formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, caprillic acid, capric acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, maleic acid, fumaric acid, and citric acid), sodium lauryl sulfate, poloxamer, sorbitan monoesters, glyceryl monooleates, niacin, mustard, allyl isothiocyanate and p-hydroxybenzyl isothiocyanate, acetylsalicylic acid.

[744] Various cutaneous vasodilators can be employed including, for example and without limitation, niacin acid, nicotinuric acid, beta-hydroxybutyrate and nicotinic receptor (e.g., HM74A or GPR109A) agonists.

[745] In some embodiments, the aversive agent in the dosage form may be niacin, in a quantity of about 1 mg to about 400 mg, or about 1 mg to about 300 mg, or about 1 mg to about 200 mg, or about 1 mg to about 150 mg, or about 1 mg to about 100 mg, or about 1 mg to about 90 mg, or about 1 mg to about 80 mg, or about 1 mg to about 70 mg, or about 1 mg to about 60 mg, or about 1 mg to about 50 mg, or about 1 mg to about 45 mg, or about 1 mg to about 40 mg, or about 1 mg to about 40 mg, or about 1 mg to about 35 mg, or about 1 mg to about 30 mg, or about 1 mg to about 25 mg, or about 1 mg to about 20 mg, or about 1 mg to about 10 mg, or about 1 mg to about 5 mg, or about 5 mg to about 400 mg, or about 5 mg to about 300 mg, or about 5 mg to about 200 mg, or about 5 mg to about 150 mg, or about 5 mg to about 100 mg, or about 10 mg to about 150 mg, or about 10 mg to about 100 mg, or about 5 mg to about 80 mg, or about 5 mg to about 60 mg, or about 5 mg to about 50 mg, or about 5 mg to about 45 mg, or about 5 mg to about 40 mg, or about 5 mg to about 40 mg, or about 5 mg to about 35 mg, or about 5 mg to about 30 mg, or about 5 mg to about 25 mg, or about 5 mg to about 20 mg, or about 5 mg to about 10 mg, or about 10 mg to about 90 mg, or about 10 mg to about 80 mg, or about 10 mg to about 60 mg, or about 10 mg to about 50 mg, or about 10 mg to about 45 mg, or about 10 mg to about 40 mg, or about 10 mg to about 40 mg, or about 10 mg to about 35 mg, or about 10 mg to about 30 mg, or about 10 mg to about 25 mg, or about 10 mg to about 20 mg, or about 20 mg to about 100 mg, or about 20 mg to about 90 mg, or about 20 mg to about 80 mg, or about 20 mg to about 60 mg, or about 20 mg to about 50 mg, or

about 20 mg to about 45 mg, or about 20 mg to about 40 mg, or about 20 mg to about 35 mg, or about 20 mg to about 30 mg, or about 15 mg to about 50 mg, or about 15 mg to about 40 mg, or about 15 mg to about 35 mg, or a quantity sufficient to be produce an aversive effect when abused but not under conditions of medically appropriate use.

[746] Preferably, the bittering agent is selected from the group comprising quinine, denatonium, denatonium saccharide and denatonium benzoate. Preferably, the naso-mucosal, oro-mucosal, respiratory or tissue irritants selected from the group comprising capsaicin, capsaicin analogs, resiniferatoxin, citric acid, sodium lauryl sulfate, niacin and mustard. Preferably, the emetogenic or nausea producing agents selected from the group comprising zinc and pharmaceutically acceptable salts thereof, folate, folic acid, niacin and nicotinamide. Preferably, the cutaneous vasodilator selected from the group comprising niacin and nicotinuric acid.

[747] In some embodiments, one or more aversive agents may be added to the formulation in an amount of less than about 80% by weight, preferably less than about 60% by weight, more preferably less than about 40% by weight of the dosage form, even more preferably less than about 20% by weight of the dosage form, and most preferably less than about 10 by weight of the dosage form (e.g., 0.0000000000000001% to 1%, or 0.000000001% to 3%, or 0.0001% to 10%, or 0.001% to 5%, or 1% to 10%, or 0.001% to 2%, or 1% or 10%, or 2% to 7%) depending on the particular aversive agent used.

[748] In some embodiments, the aversive agent in the dosage form may be about 0.00000000001 mg to about 2000 mg, or about 0.0000001 mg to about 1500 mg, or about 0.000001 mg to about 1000 mg, or about 0.0001 mg to about 1000 mg, or about 0.001 mg to about 1000 mg, or about 0.01 mg to about 1000 mg, or about 0.1 mg to about 1500 mg, or 1 mg to about 800 mg, or about 1 mg to about 500 mg, or about 1 mg to about 300 mg, or about 1 mg to about 150 mg, or about 5 mg to about 400 mg, or about 5 mg to about 200 mg, or about 0.00000000001 mg to about 200 mg, or about 0.00000000001 mg to about 100 mg, or about 0.00000000001 mg to about 50 mg, or about 0.0000001 mg to about 200 mg, or about 0.0000001 mg to about 100 mg, or about 0.00001 mg to about 400 mg, or about 0.0001 mg to about 300 mg.

[749] Various laxatives can be employed as aversive agents including, for example and without limitation, Bis(p-hydroxyphenyl)pyridyl-2-methane, Bisacodyl, bisoxatin, anthraquinone, anthraquinone analogs and derivatives (e.g., buckthorn, casanthranol, cascara, hydroxyanthracene, glucofrangulin), dantron, danthron, docusate (e.g., docusate sodium, docusate calcium, docusate potassium), gastrointestinal chloride channel activators (e.g., chloride channel subtype 2 activators), lubiprostone, magenesium salts (e.g., magnesium citrate, magnesium hydroxide, magnesium oxide), mannitol, oxyphenisatine, polyethylene glycol, poly(ethylene oxide) [PEO-1500], sodium phosphate, phenolphthalein, senna, senna constituents and derivatives (e.g., sennoside A, sennoside B) and sodium picosulfate.

- [750] In some embodiments, the aversive agent in the dosage form may be a laxative in the amount of about 0.001 mg to about 300 mg, or about 0.001 mg to about 200 mg, or about 0.001 mg to about 100 mg, or about 0.001 mg to about 75 mg, or about 0.001 mg to about 50 mg, or about 0.001 mg to about 25 mg, or about 0.001 mg to about 20 mg, or about 0.001 mg to about 10 mg, or about 0.001 mg to about 5 mg, or about 0.001 mg to about 2.5 mg, or about 0.001 mg to about 1 mg, or about 1 mg to about 300 mg, or about 1 mg to about 200 mg, or about 1 mg to about 100 mg, or about 1 mg to about 75 mg, or about 1 mg to about 50 mg, or about 1 mg to about 25 mg, or about 1 mg to about 20 mg, or about 1 mg to about 10 mg, or about 1 mg to about 5 mg, or about 1 mg to about 2.5 mg.
- [751] In some embodiments, the amount of aversive agent in the dosage form of the present invention can be a fixed ratio in relation to the amount of levorphanol in the dosage form. By appropriately selecting the quantity of the aversive agent in the dosage form, aversive effects can be avoided under conditions of proper medical use (e.g., manufacturers prescribing directions). However, under some conditions of abuse, for example excessive intake of the dosage form of the invention, the quantity of aversive agent consumed will exceed the “no effect” or “minimum effect” threshold, thereby producing one or more aversive effects, for example, e.g., nausea, emesis, diarrhea, laxation, cutaneous vasodilation, headache, bitter taste, naso-mucosal irritation, oro-mucosal irritation, precipitation of abstinence from the levorphanol dosage form, precipitation of abstinence from a co-abused drug which is not part of the dosage form, reduction of the pleasurable, mood altering, rewarding, reinforcing, stimulant, depressant or other psychic and physiologic effects of the abusable drug or a co-abused drug, etc.).
- [752] In some embodiments, the “no effect” or “minimum effect” threshold amount of aversive agent can be exceeded when the dosage form of the invention is taken in excess of the manufacturer’s recommendation by a factor of about 1.5, or about 2, or about 2.5, or about 3, or about 4, or about 5, or about 6, or about 7, or about 8, or about 10, or more than 10. In some embodiments, the production of an aversive effect can reduce or stop further abuse of the dosage form, thereby reducing the harm or toxicity of the drug in the subject who is tampering, misusing or abusing the dosage form, e.g., addicts, drug abusers and recreational drug users.
- [753] In some embodiments, the aversive agent in the dosage form may be an opioid antagonist. Opioid antagonists are well known in the art and include naltrexone, methylnaltrexone, naloxone, nalmefene, cyclazocine, cyclorphan, oxilorphan nalorphine and levallorphan or pharmaceutically acceptable salt thereof or mixture thereof. In a preferred embodiment, said antagonist is naltrexone or naloxone. In a most preferred embodiment, said antagonist is naloxone. In some embodiments, the aversive agent in the dosage form may be an opioid antagonist in the amount of about 0.00001 mg to about 800 mg, or about 0.001 mg to about 400 mg, or about 0.01 mg to about 200 mg, or about 0.2 mg to about 100 mg, or about 0.2 mg to about 50 mg, or 0.2 to 8 mg.

- [754] In some embodiments, the ratio of levorphanol base to naloxone base is more than about: 3:1; 4:1, 5:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 12:1, 14:1, 16:1, 18:1, 20:1, 22:1, 24:1, 26:1, 28:1, 30:1, 35:1, 40:1, 45:1 50:1 ; 55:1, 60:1, 65:1, 70:1, 75:1, 80:1, 85:1 or 90:1.
- [755] In some embodiments, the ratio of naloxone may be replaced with naltrexone, and the levorphanol base to naltrexone base ratio is more than about: 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 12:1, 14:1, 16:1, 18:1, 20:1, 22:1, 24:1, 26:1, 28:1, 30:1; 35:1; 40:1; 45:1 50:1 ; 55:1, 60:1, 65:1, 70:1, 75:1, 80:1, 85:1 or 90:1.
- [756] In some embodiments, the present invention is directed to oral pharmaceutical compositions of levorphanol comprising naloxone, where the systemic exposure to naloxone as measured by the area under the plasma naloxone concentration-time curve from time 0 to 48 hours or 0 to infinity (AUC_{0-48} or AUC_{0-inf}) after single dose oral administration of the untampered or intact dosage form is less than about : 20 ng.hr/mL, 18 ng.hr/mL, 15 ng.hr/mL, 12 ng.hr/mL, 10 ng.hr/mL, 8 ng.hr/mL, 7 ng.hr/mL, or 6 ng.hr/mL, or 5 ng.hr/mL, 4 ng.hr/mL, or 3 ng.hr/mL, or 2 ng.hr/mL, or 1.5 ng.hr/mL, or 1 ng.hr/mL, or 0.8 ng.hr/mL, or 0.7 ng.hr/mL, or 0.6 ng.hr/mL, or 0.55 ng.hr/mL, or 0.5 ng.hr/mL, or 0.45 ng.hr/mL, or 0.4 ng.hr/mL, 0.35 ng.hr/mL, or 0.3 ng.hr/mL, or 0.25 ng.hr/mL, or 0.2 ng.hr/mL. In some embodiments, said AUC is after single dose oral administration of the tampered or crushed dosage form.
- [757] In some embodiments, the present invention is directed to oral pharmaceutical compositions of levorphanol comprising naltrexone, where the systemic exposure to naltrexone as measured by the area under the plasma naltrexone concentration-time curve from time 0 to 48 hours or 0 to infinity (AUC_{0-48} or AUC_{0-inf}) after single dose oral administration of the untampered or intact dosage form is less than about : 20 ng.hr/mL, 18 ng.hr/mL, 15 ng.hr/mL, 12 ng.hr/mL, 10 ng.hr/mL, 8 ng.hr/mL, 7 ng.hr/mL, or 6 ng.hr/mL, or 5 ng.hr/mL, 4 ng.hr/mL, or 3 ng.hr/mL, or 2 ng.hr/mL, or 1.5 ng.hr/mL, or 1 ng.hr/mL, or 0.8 ng.hr/mL, or 0.7 ng.hr/mL, or 0.6 ng.hr/mL, or 0.55 ng.hr/mL, or 0.5 ng.hr/mL, or 0.45 ng.hr/mL, or 0.4 ng.hr/mL, 0.35 ng.hr/mL, or 0.3 ng.hr/mL, or 0.25 ng.hr/mL, or 0.2 ng.hr/mL. In some embodiments, said AUC is after single dose oral administration of the tampered or crushed dosage form.
- [758] In some embodiments, the present invention is directed to oral pharmaceutical compositions of levorphanol comprising naloxone, where the peak plasma naloxone concentration (C_{max}) after single dose oral administration of the untampered or intact dosage form is less than about: 4 ng/mL, 3 ng/mL, 2 ng/mL, 1.5 ng/mL, 1.25 ng/mL, or 1 ng/mL, or 0.8 ng/mL, or 0.7 ng/mL, or 0.6 ng/mL, or 0.5 ng/mL, or 0.4 ng/mL, or 0.3 ng/mL, or 0.2 ng/mL, or 0.1 ng/mL. In some embodiments, said C_{max} is after single dose oral administration of the tampered or crushed dosage form.
- [759] In some embodiments, the present invention is directed to oral pharmaceutical compositions of levorphanol comprising naltrexone, where the peak plasma naltrexone concentration (C_{max}) after single dose oral administration of the untampered or intact dosage form is less than about: 4 ng/mL,

3 ng/mL, 2 ng/mL, 1.5 ng/mL, 1.25 ng/mL, or 1 ng/mL, or 0.8 ng/mL, or 0.7 ng/mL, or 0.6 ng/mL, or 0.5 ng/mL, or 0.4 ng/mL, or 0.3 ng/mL, or 0.2 ng/mL, or 0.1 ng/mL. In some embodiments, said C_{max} is after single dose oral administration of the tampered or crushed dosage form.

[760] In some embodiments, the oral levorphanol dosage forms of the invention comprising naloxone or naltrexone in the amounts, ratios or exposure level in the specifications are abuse deterrent in some, most, substantially all or all recreational opioid users and opioid abusers when the dosage form is tampered with and the contents (levorphanol plus naloxone or levorphanol plus naltrexone) are injected.

[761] In some embodiments, the oral levorphanol dosage forms of the invention comprising naloxone or naltrexone in the amounts, ratios or exposure level in the specifications are abuse deterrent in some, most, substantially all or all recreational opioid users and opioid abusers when the dosage form is tampered with and the contents (levorphanol plus naloxone or levorphanol plus naltrexone) are taken orally.

[762] In some embodiments, the dosage form comprises levorphanol, optionally material to render said dosage form controlled release and one or more opioid antagonists, preferably selected from the group comprising naloxone, naltrexone and nalmefene; said opioid antagonist having an in vitro release rate provided herein. In some embodiments, the levorphanol and the opioid antagonist share the same in vitro release rate (dissolution rate) specifications. In other embodiments, the levorphanol and the opioid antagonist have different in vitro release rate (dissolution rate) specifications referred to herein. In yet other embodiments, the in vitro release rate (dissolution rate) specifications referred to herein are applicable only to the levorphanol.

[763] In some embodiments, the dosage form comprises levorphanol, optionally material to render said dosage form controlled release and one or more aversive agents; said aversive agent having an in vitro release rate provided herein. In some embodiments, levorphanol and the aversive agent share the same in vitro release rate (dissolution rate) specifications. In other embodiments, levorphanol and the aversive agent have different in vitro release rate (dissolution rate) specifications referred to herein. In yet other embodiments, the in vitro release rate (dissolution rate) specifications referred to herein are applicable only to the levorphanol.

[764] Aversive agents may include compounds found on the FDA EAFUS database; FDA Food Additives Status List; FDA GRAS list and database; FDA Color Additive Status List; FDA Inactive Ingredients Database; Rowe, Sheskey and Owen, Handbook of Pharmaceutical Excipients, APhA Publications; 5th edition (2006); Goodman & Gilman's The Pharmacological Basis of Therapeutics (Brunton, Lazo and Parker, eds, 11th ed., McGraw Hill (2005); Remington: The Science and Practice of Pharmacy, 21st ed, Lippincott Williams & Wilkins (2005); Martindale: The Complete Drug Reference, 35th Edition, Pharmaceutical Press (2007); United States Pharmacopeia–National Formulary (USP-NF), (USP 30 – NF 25, 2007), the International Programme on Chemical Safety

and Health Canada's List of Acceptable Non-medicinal Ingredients. It should be noted that the above mentioned aversive agents may, in some embodiments be used in the dosage form of the invention for purposes other than as aversive agents, or for both aversive and non-aversive purposes. Such non-aversive uses can include, without limitation, pharmaceutical purposes and pharmacologic purposes. For example, in some embodiments, the laxative agent may be used to counteract the constipating effects of the levorphanol dosage form of the invention. In some embodiments, zinc and pharmaceutically acceptable salts of zinc and niacin may be used for pharmaceutical purposes (e.g., pharmaceutical optimization, drug release and drug stability).

[765] In some embodiments, an aversive agent incorporated into the oral dosage form shares one, or more, or all the dissolution rate specifications as the oral levorphanol in the dosage form.

[766] In some embodiments, an aversive agent incorporated into the oral dosage form shares one, or more of the pharmacokinetic parameter specifications as the oral levorphanol in the dosage form.

[767] In some embodiments, an aversive agent incorporated into the oral dosage form has different dissolution rate specifications, GI delivery and release specifications and pharmacokinetic parameter specifications from the oral levorphanol in the dosage form.

[768] In certain preferred embodiments, the levorphanol in the dosage form is combined with one or more other drugs for the treatment of the same medical condition as the levorphanol or for the treatment of a different medical condition. All modes of co-administration are contemplated, including via an oral, subcutaneous, direct intravenous, slow intravenous infusion, continuous intravenous infusion, intravenous or epidural patient controlled analgesia (PCA and PCEA), intramuscular, intrathecal, epidural, intracisternal, intramuscular, intraperitoneal, transdermal, topical, transmucosal, buccal, sublingual, inhalation, intranasal, epidural, intra-atrial, intranasal, rectal or ocular routes.

[769] **Definitions**

[770] As used herein the terms: (i) "AUC_{0-t}", and "AUC_{0-τ}" (or "AUC_{0-Tau}") mean the area under the plasma drug concentration-time curve from time zero to the intended dosing frequency of the dosage form after first administration (e.g., 8 hours, 12 hours or 24 hours) and to the end of the dosing interval after repeated dosing or at steady-state, respectively; (ii) "AUC_{0-inf}" (means area under the plasma drug concentration-time curve from time zero to infinity first administration; (iii) "AUC₀₋₁", "AUC₀₋₂", "AUC₀₋₃", "AUC₀₋₄", "AUC₀₋₆", "AUC₀₋₈", "AUC₀₋₁₂" "AUC₀₋₂₄" means area under the plasma drug concentration-time curve from time zero to the specified time in hours, for example, AUC₀₋₁₂ is the area under the plasma drug concentration-time curve from time zero to 12 hours after dosing; (iv) "C_{max}" means the maximum observed plasma drug concentration; (v) "C_{min}" means the minimum plasma concentration of the drug after the occurrence of the C_{max} over a dosing interval at steady state or minimum plasma concentration of the drug at a specified time or time interval following dosing and after the occurrence of the C_{max} or means the minimum plasma

concentration of the drug at the end of the intended dosing interval; (vi) “ t_{\max} ” or “ T_{\max} ” means the time of the observed maximum drug concentration (also known as time to achieve C_{\max}); (vii) “half value duration” or “HVD” means the duration after dosing during which plasma concentration of drug are greater than or equal to one-half of C_{\max} , obtained by calculating the time interval beginning when the actual or interpolated plasma concentration first equals or exceeds one-half of C_{\max} and ending at the first time point for which the actual or interpolated plasma concentration falls below one-half of C_{\max} ; (viii) “ W_{50} ” for purposes of the present invention means the width of the plasma concentration time curve at 50% of the height of the C_{\max} over the dosing interval; (ix) “steady state” is a state of equilibrium wherein the amount of the drug reaching the system is approximately the same as the amount of the drug leaving the system or put another way, the patient's body eliminates the drug at approximately the same rate that the drug becomes available to the patient's system through absorption into the blood stream, said “time to steady state” measured by calculating (a) the C_{\min} after each sequential dosing of drug administered at the intended dosing frequency until two consecutive C_{\min} 's are not statistically different at a 10% significance level ($p = 0.10$), or (b) calculated using pharmacokinetic data generated from well conducted single studies, said data from the mean population plasma concentration time data or the individual plasma concentration time data from which a mean value is derived; (x) “percent fluctuation”, “% fluctuation” and “% FL” means the variation in plasma concentrations of the drug computed as: (a) $(C_{\max} - C_{\min}) / C_{\min} \times 100$ (for an individual patient) and $(\text{mean } C_{\max} - \text{mean } C_{\min}) / \text{mean } C_{\min} \times 100$ (for a population), or (b) $(C_{\max} - C_{\min}) / C_{\text{av}} \times 100$ (for an individual patient) and $(\text{mean } C_{\max} - \text{mean } C_{\min}) / \text{mean } C_{\text{av}} \times 100$ (for a population), where C_{\min} is the plasma concentration at the end of the dosing interval; (xi) “accumulation index” or “AI” means (a) the ratio of the minimum plasma concentration of the drug at the end of the intended dosing interval (i.e., 12 hours for a Q12H dosage form and 24 hours for a Q24H dosage form) after steady-state (C_{ssmin}) administration, to the plasma concentration of the drug at the end of the intended dosing interval determined at first administration, or (b) the ratio of the mean plasma concentration of the drug over the dosing interval (i.e., over 12 hours for a Q12H dosage form, and over 24 hours for a Q24H dosage form) after steady-state (C_{ssave}) administration, to the mean plasma concentration of the drug over the first dosing interval, or (c) $1 / (1 - \exp(-\lambda Z \cdot \tau))$, each of (a), (b) and (c) calculated using observed data or using pharmacokinetic data generated from well conducted single studies and each using the mean plasma concentration time data or using individual plasma concentration time data from which a mean value is derived; (xii) “ AUC_{0-n} ” means the area under the plasma drug concentration-time curve from time zero to the specified time point (“n”), where n is the time in hours (unless specified otherwise); (xiii) “ C_{av} ” or “ C_{mean} ” is the average plasma concentration of the drug over the dosing interval; (xiv) “ $\text{AUC}_{0-\text{inf}}$ ” (means area under the plasma drug concentration-time curve from time zero to infinity; (xiv) “AUMCINF” is the area under the moment curve extrapolated to

infinity; (xv) "AUMClast" is the area under the moment curve computed to the last observation; (xvi) "MRT" or "Mean Residence Time" is the average amount of time a particle remains in a compartment or system, calculated by dividing the AUMC by the AUC; (xvii) "MRT_{last}" or "mean unextrapolated mean residence time" is mean residence time when the plasma concentration profile is not extrapolated to infinity, but rather is based on values up to and including the last measured concentration, calculated by dividing the AUMClast by the AUClast, where AUClast the AUC computed to the last observation; (xviii) "MRTINFO", "MRTINF_obs" and "MRT Infinity Observed" is the observed mean residence time extrapolated to infinity, calculated by dividing the AUMCINF by the AUCinf; (xix) "absorption rate constant" the rate at which the drug is absorbed into the central compartment from outside the system, often denoted as K₀₁ and determined by curve fitting plasma concentration-time data for individual subjects to appropriate one or two compartment pharmacokinetic models in WinNonlin™ (Pharsight Corporation), with a first-order extravascular input function, a lag-time and micro-constants; (xx) "T_{lag}" is an empirical pharmacokinetic parameter which estimates the time delay prior to commencement of first order absorption, calculated by in WinNonlin™ (Pharsight Corporation). T_{lag} may also be calculated using other suitable methods, such as those described as suitable by Csizmadia and Endrenyi (Journal of Pharmaceutical Sciences, 1998; 87:608-12); (xxi) "mean absorption time" or "MAT" is the sum of the inverse of the absorption rate constant and T_{lag}; (xxii) "cumulative" area under the plasma concentration time curve", or "cumulative AUC" means the sum of the AUC from the time of drug administration (time zero) to a specified time point, for example, the mean cumulative AUC at 48 hours means the entire AUC from time of drug administration (time zero) to 48 hours; (xxiii) "AUC" means the mean the area under the plasma drug concentration-time curve, wherein the plasma is harvested from blood collected through a peripheral vein.

[771] In some preferred embodiments, the oral dosage form comprises a matrix. In some preferred embodiments, said matrix is a plurality of multiparticulate matrices. In some preferred embodiments, the multiparticulates are compressed into a tablet. In some preferred embodiments, the multiparticulates are disposed in a pharmaceutically acceptable capsule.

[772] In some preferred embodiments, the pharmacokinetic and pharmacodynamic parameters are determined from first administration or single dose administration. In other preferred embodiments, the pharmacokinetic and pharmacodynamic parameters are determined from steady state administration. In yet other preferred embodiments, the pharmacokinetic and pharmacodynamic parameters are determined from at a time between first administration and steady state administration.

[773] In some preferred embodiments, the pharmacokinetic and pharmacodynamic parameters are determined under fed conditions. In other preferred embodiments, the pharmacokinetic and pharmacodynamic parameters are determined under fasted conditions.

- [774] In some preferred embodiments, the pharmacokinetic and pharmacodynamic parameters are determined from an individual subject. In other preferred embodiments, the pharmacokinetic and pharmacodynamic parameters are determined from a population of subjects, said population comprising two or more subjects.
- [775] In some preferred embodiments, the in vivo specifications and claims of the invention are determined after administration of a few or some doses of the invention. In other preferred embodiments, the in vivo specifications and claims of the invention are determined after administration of most, substantially all or all doses of the invention.
- [776] In some preferred embodiments, the pharmacokinetic and pharmacodynamic parameters of the specifications and claims are determined in subjects having a Body Mass Index (BMI) between 18 and 26 kg/m², inclusive (BMI = [weight in kg/ height in m²] x 10,000). In some other preferred embodiments, the pharmacokinetic parameters of the specifications and claims are determined in subjects having a Body Mass Index (BMI) \geq 38 kg/m².
- [777] The term "semipermeable wall" for purposes of the present invention means that the wall is permeable to the passage of an exterior fluid, such as aqueous or biological fluid, in the environment of use, including the gastrointestinal tract, but impermeable to drug.
- [778] The term "first administration", "single administration" or "single dose administration" means administration of a dose of the present invention at the initiation of therapy to an individual patient or a patient population. First administration also includes administration of an initial dose of the present invention to subjects who are not in need of treatment but who are volunteers participating in experimentation and testing.
- [779] The term "steady state" means that the amount of the drug reaching the system is approximately the same as the amount of the drug leaving the system. Thus, at "steady-state", the patient's body eliminates the drug at approximately the same rate that the drug becomes available to the patient's system through absorption into the blood stream.
- [780] As used herein, "dose proportionality", "dose-proportional" and "dose proportional bioavailability" means that change does by a particular percentage changes the drug exposure by a similar percentage, as assessed by the area under the plasma concentration time curve and maximum plasma concentration (C_{max}). For example, if a dosage form provides dose proportional bioavailability, doubling the dose doubles the AUC and C_{max}. Some drugs or dosage forms may be dose proportional bioavailability over a narrow range of doses (e.g., 2 fold, or 3 fold), but may not be dose proportional over a wider range of doses (e.g., 4, 5, 6, or 7 fold). Dose proportionality may be assessed by methods well known in the art. A particularly preferred method is described by Smith BP et al (Confidence interval criteria for assessment of dose proportionality. Pharm Res 17:1278-1283), which is hereby incorporated in its entirety by reference.
- [781] As used herein, "population of patients" or "patient population" means at least two patients

or subjects.

- [782] For purposes of the invention, the term a "patient" or a "subject" in reference to pharmacokinetic and pharmacodynamic parameters means that the specification or claim is directed to the pharmacokinetic or parameters of an individual patient or subject, or to population of patients.
- [783] In certain embodiments, the above in-vivo specifications are achieved after a first administration of the dosage form to a human subject or a population of human subjects.
- [784] In certain alternative embodiments, the above in-vivo specifications are achieved after steady state administration of the dosage form to a human subject or a population of human subjects.
- [785] In certain embodiments, the above in-vivo specifications are achieved after in a fed state after administration of the dosage form to a human subject or a population of human subjects.
- [786] In certain embodiments, the above in-vivo specifications are achieved after in a fasted state after administration of the dosage form to a human subject or a population of human subjects.
- [787] The term "USP Paddle Method", "USP Basket Method" and "USP Paddle or Basket Method" are the respective Paddle and Basket Methods described, e.g., as specified in the United States Pharmacopeia, USP-28 NF-23 (2005), published by the United States Pharmacopeial Convention, Inc, herein incorporated by reference.
- [788] In some embodiments of the invention, pH adjustments of the dissolution media may be achieved by adjustment as required with hydrochloric acid or other acids, sodium hydroxide or other bases, other pharmaceutical excipients and buffers known in the art.
- [789] In some embodiments, the dissolution specifications may be assessed at 50 rpm or 75 rpm instead of 100 rpm. In some embodiments, the dissolution specifications may be assessed in 100 ml, 250 ml, 500 mL or 600 mL of dissolution media instead of 900 mL. In some embodiments, the dissolution specifications may be assessed with the aid of a sinker (e.g., a nonreactive stainless steel wire helix, other inert material, cork borers, cylinders, see, for example, USP 32–NF 27. In some embodiments, the dissolution specifications may be assessed using Simulated Intestinal Fluid (SIF) USP, with or without the inclusion of enzyme, or Simulated Gastric Fluid (SGF) USP instead of distilled water.
- [790] The term "pH-independent" for purposes of the present invention is defined as having characteristics (e.g., dissolution) which are substantially unaffected by pH.
- [791] The term "pH-dependent" for purposes of the present invention is defined as having characteristics (e.g., dissolution) which are substantially affected by pH.
- [792] The term "bioavailability" is defined for purposes of the present invention as the extent to which the drug (e.g., levorphanol) is absorbed from the unit dosage forms.
- [793] All manner of oral extended release pharmaceutical dosage forms of levorphanol may be

used to practice the invention, including, without limitation, liquids, tablets, capsules, powders, gastroretentive dosage forms, tablets and capsules.

[794] In certain situations involving pharmacokinetic evaluations, it may not be possible to provide the same amount of drug for the purposes of a pharmacokinetic comparison, for example, due to a lack of commercially available dosage strengths, or for safety reasons or because such administration would require testing outside the approved method of administration. Under such circumstances, the term “after the same amount of an oral immediate release formulation of levorphanol”, and the like may be waived and different amounts of drug may be evaluated, provided the data are dose normalized using pharmacokinetic approaches well known in the art.

[795] The term “agonist” means a ligand that binds to a receptor and alters the receptor state resulting in a biological response. Conventional agonists increase receptor activity, whereas inverse agonists reduce it (See Neubig et al, IUPHAR Committee on Receptor Nomenclature and Classification, Pharmacol Rev, 2003; Howlett et al., Mol Pharmacol, 1988).

[796] The term “opioid agonist” means a molecule that causes a specific physiologic, pathophysiologic or pharmacologic effect after binding to an opioid receptor. Except when specifically modified, the term “opioid” has the same meaning as “opioid agonist”. For example, the phrases “a wide variety of opioids are used to treat pain” and “opioids can cause side effects” have the same meaning as “a wide variety of opioid agonists are used to treat pain” and “opioid agonists can cause side effects”, respectively. Similarly, the phrases “opioid antagonists may be given in sequestered form” and “a suitable opioid antagonist is may be given” do not refer to “opioid agonists”. For the purposes of the present invention, any drug having exhibiting agonism at the opioid receptor [e.g., agonism at the mu (μ), delta (δ) and kappa (κ) opioid receptors] is an “opioid agonist”, even if it possesses other pharmacologic activity (e.g., NMDA antagonism, opioid antagonism, monoaminergic reuptake inhibition). For example, a drug that exhibits mixed agonist-antagonist effects at one or more opioid receptor is an opioid agonist. Similarly, a drug that exhibits partial agonism at one or more opioid receptor is an opioid agonist.

[797] Opioid agonists include alfentanil, allylprodine, alphaprodine, anileridine, apomorphine, apocodeine, benzylmorphine, bezitramide, buprenorphine, butorphanol, carfentanil, clonitazene, codeine, cyclazocine, cyclorphen, cyprenorphine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydroxymethylmorphinan, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacymorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, methylmorphine, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nociceptin/orphanin FQ (N/OFQ), normorphine,

norpipanone, ohmefentanyl, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, pholcodine, piminodine, piritramide, propheptazine, promedol, profadol, properidine, propiram, propoxyphene, racemorphan, remifentanyl, sufentanyl, tapentadol, tramadol, tilidine, methylnaltrexone, naloxone methiodide, naloxonazine, nalmexone, nalbuphine, nalorphine dinicotinate, naltrindole (NTI), naltrindole isothiocyanate, (NTII), naltriben (NTB), nor-binaltorphimine (nor-BNI), beta-funaltrexamine (b-FNA), BNTX, cyprodime, ICI-174,864, LY117413, MR2266, etorphine, DAMGO, CTOP, diprenorphine, naloxone benzoylhydrazone,bremazocine, ethylketocyclazocine, U50,488, U69,593, spiradoline, DPDPE, [D-Ala²,Glu⁴] deltorphin, DSLET, Met-enkephalin, Leu-enkephalin, (3-endorphin, dynorphin A, dynorphin B, a-neoendorphin, or an opioid having the same pentacyclic nucleus as nalmefene, naltrexone, buprenorphine, levorphanol, meptazinol, pentazocine, dezocine, or their pharmaceutically acceptable salts, prodrugs, esters, analogs, derivatives, solvates, complexes, polymorphs, hydrates and metabolites, as racemates or an individual

[798] An “antagonist” is a drug or ligand that reduces the action of another drug or ligand, generally an agonist. Many antagonists act at the same receptor macromolecule as the agonist. (See Neubig et al, IUPHAR Committee on Receptor Nomenclature and Classification, Pharmacol Rev, 2003; Howlett et al., Mol Pharmacol, 1988).

[799] The term “receptor” means a molecule within a cell, on a cell surface, on a membrane, in tissue, in fluid or otherwise found in humans that serve as a recognition or binding site to cause specific physiologic, pathophysiologic or pharmacologic effects. The term “receptor” also means a cellular macromolecule, or an assembly of macromolecules, that is concerned directly and specifically in chemical signaling between and within cells. Combination of a hormone, neurotransmitter, drug, ligand, or intracellular messenger with its receptor(s) initiates a change in cell function (Neubig et al, IUPHAR Committee on Receptor Nomenclature and Classification, Pharmacol Rev, 2003).

[800] The term “opioid receptor” includes mu (μ), delta (δ) and kappa (κ) opioid receptors, their subtypes and splice variants such as mu₁, mu₂, delta₁, delta₂, kappa₁, kappa₂ and kappa₃, etc.

[801] Opioid antagonists are known or readily determined by individuals who practice the art. Preferably, the opioid antagonists useful for the present invention may be selected from the group consisting of naltrexone, methylnaltrexone, nalbuphine, naloxone, nalmefene, cyclazocine, cyclophorphan, oxilorphan nalorphine, nalorphine dinicotinate, nalmefene, nadide and levallorphan.

[802] In certain preferred embodiments of the present invention, the invention allows for the use of lower doses of levorphanol by virtue of the inclusion or co-administration of an additional drug for the prevention or treatment of pain. By using lower amounts of either or both drugs, the side effects associated with treatment in humans are reduced.

[803] The term "levorphanol" or “1 3-hydroxy-N-methylmorphinan” is defined for purposes of the

invention as comprising: (i) unsalified levorphanol (also known as levorphanol base), its pharmaceutically acceptable salts and mixtures thereof; (ii) the racemate of levorphanol (racemorphan or *d,l* 3-hydroxy-N-methylmorphinan), its pharmaceutically acceptable salts and mixtures thereof; (iii) non-stoichiometric ratios of *l* 3-hydroxy-N-methylmorphinan and *d* 3-hydroxy-N-methylmorphinan, their pharmaceutically acceptable salts and mixtures thereof; (iv) morphinan-3-ol, 17-methyl-, [*R*-(*R**,*R**)]-2,3-dihydroxybutane-dioate (1:1) (salt) dihydrate; or (v) 17-Methylmorphinan-3-ol, tartrate (1:1) (salt) dihydrate; or (vi) esters, solvates, complexes, polymorphs, hydrates or prodrugs of (i) to (v); or (vii) mixtures of one or more of (i) to (vi). Unless specifically modified, (for example, by reference to “levorphanol base”, or “unsalified levorphanol” or “levorphanol hydrobromide” or “levorphanol tartrate”), as used herein, “levorphanol” means one or more of the items in the foregoing (i) to (iv). Preferably, the levorphanol in the composition is unsalified *l* 3-hydroxy-N-methylmorphinan, a pharmaceutically acceptable salt thereof, or a mixture thereof.

[804] Levorphanol tartrate dihydrate has a Chemical Abstract Services No. of 5985-38-6 dihydrate.

[805] As used herein, the mass of levorphanol in any dosage form of the invention or of a test, reference, control or comparator dosage form comprising levorphanol refers to the amount (mass) of unsalified levorphanol, or a pharmaceutically salt of levorphanol, or a mixture thereof. When any dosage form of the invention or of a test, reference, control or comparator dosage form comprises the racemate of levorphanol (i.e., racemorphan or *d,l* 3-hydroxy-N-methylmorphinan), the mass of levorphanol in the specifications and claims refer to mass of the levo isomer of racemorphan (i.e., levorphanol or *l* 3-hydroxy-N-methylmorphinan).

[806] Levorphanol tartrate is commercially sold as levorphanol tartrate dihydrate having a molecular formula of $C_{17}H_{23}NO \cdot C_4H_6O_6 \cdot 2H_2O$, a molecular weight of about 443.5.

[807] In some preferred embodiments, the levorphanol dose of the specifications and claims is the dose of unsalified levorphanol (levorphanol base). In other preferred embodiments, the levorphanol dose of the specifications and claims is the dose of salified levorphanol (a levorphanol salt, e.g., levorphanol tartrate).

[808] As used herein with respect to the levorphanol dosage form of the invention, the term “oral”, “oral dosage form”, “oral pharmaceutical dosage form”, “oral administration”, “oral compositions” “oral pharmaceutical compositions”, “oral tablets”, “oral capsules”, “orally ingested”, “orally”, “oral route” and the like all refer to any method of administration through the mouth. The oral dosage form of the invention is usually ingested intact, although it may be ingested tampered (e.g., crushed) and usually with the aid of water or a beverage to hasten passage through the mouth.

[809] As used herein, “controlled release material”, “controlled release means”, “rate controlling means”, “rate controlling excipient”, “rate controlling ingredient”, “rate controlling material”,

“release rate controlling means”, “release rate controlling excipient”, “release rate controlling ingredient”, “release rate controlling material”, and “material to provide controlled release” means an in vitro or in vivo release rate controlling excipient or material incorporated in the dosage form whose function or primary function is to modify release (e.g, onset of release, rate of release, duration of release) of an active drug (e.g., levorphanol) from a dosage form or a portion (i.e., cause the dosage form to release in other than an immediate release fashion). In more preferred embodiments of the invention, the controlled release material functions to provide one or more of the following, compared to immediate release levorphanol: (1) change in the onset of release; (2) change in the rate of release; (3) change in the duration of release; (4) change in the time of peak plasma concentration; (5) change in the peak plasma concentration; (6) change in the extent of absorption; (7) change in the onset of therapeutic effect; (8) change in the duration of therapeutic effect; and (9) change in the GI anatomic location of release.

[810] As used herein, the term "extended release" dosage forms mean pharmaceutical preparations which release an active ingredient from a dosage form or a portion thereof in other than an immediate release fashion. Extended release pharmaceutical compositions are made by incorporating a controlled release material in the dosage form. Extended release dosage forms are sometimes designed to accomplish pharmaceutical, pharmacokinetic, pharmacodynamic, therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form.

[811] As used herein, the term "extended release" is interchangeably with “controlled release”, “prolonged release”, “slow release”, “sustained release”, “retarded release”, “long acting” and the like. Extended release dosage forms release the active ingredient from a dosage form or a portion thereof over an extended period of time (over a period of time greater than 4 or 6 hours, preferably over for period greater than about 8 hours, and most preferably over for period greater than about 10 hours, 12, 14, 16, 18, 20, 22 or 24 hours. Extended release dosage forms may be either delayed onset formulations, i.e., “delayed onset, extended release” (e.g., a delay in release of 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5 or 8 hours after ingestion, preferably at least 2 hours after ingestion) or “extended release” (i.e., without a significant initial delay in release). In some embodiments, particularly preferred extended release dosage forms are suitable for or intended to be used twice-a-day (e.g., Q12H or Q12H PRN) or once-a-day (e.g., QD, Q24H or Q24H PRN), with once-a-day preferred over twice-a-day.

[812] As used herein, unless specifically modified, the term “extended release levorphanol”, “extended release dosage forms of levorphanol”, “extended release compositions of levorphanol”, “extended release pharmaceutical compositions of levorphanol”, “extended release dosage forms of levorphanol”, “Levorphanol ER”, “pharmaceutical compositions of the invention”, “compositions of the invention”, “dosage forms of the invention”, “pharmaceutical dosage forms of the invention”,

or use of the term “extended release” in association with levorphanol means “extended release levorphanol”, or “delayed onset, extended release” oral levorphanol dosage forms of the invention.

[813] As used herein, “delayed onset” and “delayed release” dosage forms mean pharmaceutical preparations which release begin the first release of an active ingredient from a dosage form or a portion thereof (i) at time other than immediately following oral administration; and/or (ii) after a lag period lasting from minutes to hours (e.g., 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5 or 8 hours); and/or (iii) upon reaching the desired GI anatomic location distal to the stomach (e.g., distal to the duodenum, jejunum, ileum, ileo-cecal junction or colon) or and/or (iii) upon reaching the desired GI environment distal to the stomach (e.g., pH at the point of release, osmotic pressure at the point of release, hydration, microbial flora). Delayed onset, extended release dosage forms are dosage forms that provide duodenal delivery, jejunal delivery, ileal delivery, ileo-colonic delivery or colonic delivery of at least the levorphanol in the dosage form.

[814] As used herein, “delayed onset, extended release” means dosage forms which after a desired lag period post-ingestion (e.g., 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5 or 8 hours), slowly release the active drug from the dosage form over an extended period of time (e.g., over about 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, or 30 hours).

[815] As used herein, “controlled release material”, “controlled release means”, and “material to provide controlled release” means an in vitro or in vivo release rate controlling excipient or material incorporated in the dosage form whose function or primary function is to modify release (e.g, onset of release, rate of release, duration of release) of an active drug (e.g., levorphanol) from a dosage form or a portion (i.e., cause the dosage form to release in other than an immediate release fashion), in other words to cause the dosage form to be extended release dosage form. In particularly preferred embodiments of the invention, the controlled release material functions to provide one or more of the following: (1) delay in the onset of release; (2) delay in the rate of release; (3) prolonged or extended duration of release; (4) delay in the onset of therapeutic effect; (5) delay in onset of side effects; (6) delay in the onset of psychic or mood altering effects; (7) reduced abuse liability; (8) prolonged or extended duration of therapeutic effect; or (9) more robust therapeutic effect; (10) a pharmacokinetic profile consistent with dosage forms which are extended release or delayed onset, extended release; (11) a pharmacodynamic profile consistent with dosage forms which are extended release or delayed onset, extended release; and (12) reduced potential for misuse, abuse, addiction and drug diversion.

[816] In some preferred embodiments, one or more of the specifications for extended release dosage forms of levorphanol also apply to delayed onset, extended release dosage forms of levorphanol.

[817] As used herein with respect to the levorphanol dosage form of the invention, “duodenal release” and “duodenal delivery” are interchangeable and refer to in vivo release of all, substantially

all or most levorphanol from the dosage form into the portion of gastrointestinal tract distal to the stomach. In some embodiments, duodenal release or duodenal delivery dosage forms of the invention provide in vivo release of all, substantially all or most levorphanol from the dosage form rapidly upon reaching the portion of gastrointestinal tract distal to the stomach. In other embodiments, duodenal release and duodenal delivery dosage forms of the invention provide in vivo release of all, substantially all or most levorphanol from the dosage form slowly upon reaching the portion of gastrointestinal tract distal to the stomach.

[818] As used herein with respect to the levorphanol dosage form of the invention, “jejunal release” and “jejunal delivery” are interchangeable, and refers to in vivo release of all, substantially all or most levorphanol from the dosage form into the portion of gastrointestinal tract distal to the duodenum. In some embodiments, jejunal release” or “jejunal delivery dosage forms of the invention provide in vivo release of all, substantially all or most levorphanol from the dosage form rapidly upon reaching the portion of gastrointestinal tract distal to the duodenum. In other embodiments, duodenal release and duodenal delivery dosage forms of the invention provide in vivo release of all, substantially all or most levorphanol from the dosage form slowly upon reaching the portion of gastrointestinal tract distal to the duodenum.

[819] As used herein with respect to the levorphanol dosage form of the invention, “ileal release” and “ileal delivery” are interchangeable and refers to in vivo release of all, substantially all or most levorphanol from the dosage form into the portion of gastrointestinal tract distal to the jejunum. In some embodiments, ileal release or ileal delivery dosage forms of the invention provide in vivo release of all, substantially all or most levorphanol from the dosage form rapidly upon reaching the portion of gastrointestinal tract distal to the jejunum. In other embodiments, ileal release and ileal delivery dosage forms of the invention provide in vivo release of all, substantially all or most levorphanol from the dosage form slowly upon reaching the portion of gastrointestinal tract distal to the jejunum.

[820] As used herein with respect to the levorphanol dosage form of the invention, “ileo-colonic release” and “ileo-colonic delivery” are interchangeable and are interchangeable and refer to in vivo release of all, substantially all or most levorphanol from the dosage form into the portion of gastrointestinal tract distal to the jejunum and/or distal to the ileum. In some embodiments, ileo-colonic release or ileo-colonic delivery dosage forms of the invention provide in vivo release of all, substantially all or most levorphanol from the dosage form rapidly upon reaching the portion of gastrointestinal tract distal to the jejunum or distal to the ileum. In other embodiments, ileo-colonic release and ileo-colonic delivery dosage forms of the invention provide in vivo release of all, substantially all or most levorphanol from the dosage form slowly upon reaching the portion of gastrointestinal tract distal to the jejunum or distal to the ileum.

[821] As used herein with respect to the levorphanol dosage form of the invention, “colonic

release” and “colonic delivery” are interchangeable and refer to in vivo release of all, substantially all or most levorphanol from the dosage form into the portion of gastrointestinal tract distal to the ileum. In some embodiments, colonic release and colonic delivery dosage forms of the invention provide in vivo release of all, substantially all or most levorphanol from the dosage form rapidly upon reaching the portion of gastrointestinal tract distal to the ileum. In other embodiments, colonic release and colonic delivery dosage forms of the invention provide in vivo release of all, substantially all or most levorphanol from the dosage form slowly upon reaching the portion of gastrointestinal tract distal to the ileum.

[822] Duodenal delivery, jejunal delivery, ileal delivery, ileo-colonic delivery or colonic delivery dosage forms are in the form of delayed onset extended release dosage forms

[823] When applied to the present invention, the term "immediate release", "immediate release dosage forms", "immediate release composition", "immediate release tablet", "immediate release capsule", "immediate release formulation", immediate release forms" and the like is a dosage form which is formulated to release the active drug from the dosage form immediately (i.e., without an attempt to delay or prolong the release of the active drug from the dosage form as is the case, for example, with extended release dosage forms) or a dosage form which allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug). Immediate release dosage forms may be in any form, including tablet, capsule, solution, suspension, powder, micronized, granulated etc. When applied to levorphanol dosage forms of the invention, unless further modified to alter the meaning, "immediate release" refers to oral dosage forms. In the absence of a commercially available oral immediate release levorphanol product, an available parenteral or intranasal formulation of levorphanol or a salt thereof may be used orally, or a solution of levorphanol or a salt thereof may be prepared or an immediate release tablet may be prepared for the purpose of in vivo testing requiring immediate release levorphanol. Alternatively, an immediate release formulation of levorphanol may be prepared by encapsulating liquid or uncompressed solid levorphanol, or by compressing levorphanol into tablet form without excipients or material that impart a delay or retardation to its release. Immediate release dosage forms generally disintegrate in \leq about 0.5 hours, and generally substantially or completely dissolve in \leq about 0.25, or \leq about 0.5, or \leq about 0.75, or \leq about 1 hour, when measured by the recommended or appropriate USP compendial methods (for example some dosage forms may be tested by USP Basket Method or USP Paddle Method at 100 rpm in 900 mL of water at 37 °C).

[824] For purposes of the invention, the oral extended release and oral immediate release formulations are pharmacokinetically dose proportional. In such formulations, the pharmacokinetic parameters (e.g., AUC and C_{max}) generally increase linearly from one dosage strength to another. Therefore the pharmacokinetic parameters of a particular dose can be inferred from the parameters

of a different dose of the same formulation.

- [825] In some preferred embodiments, extended release dosage forms and delayed onset, extended release dosage forms release levorphanol at such a rate that plasma concentrations and/or therapeutic effects are maintained within the therapeutic range (above the minimum effective therapeutic concentration) but below toxic levels for most, substantially all or all of the intended duration (e.g., over a period of about 6 to about 30 hours, preferably over a period of time indicative of a Q12H, Q12H PRN, Q24H or Q24H PRN administration, more preferably over a period of time indicative of Q24H or Q24H PRN administration).
- [826] All terms or phrases not expressly defined herein shall have the meaning in the applicants pending patent applications referenced herein.
- [827] The phrase “comprising a therapeutically effective amount of levorphanol” means “comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or prodrugs, esters, analogs, derivatives, solvates, complexes, polymorphs and hydrates thereof, as racemates or an individual diastereoisomers or enantiomeric isomers thereof or mixtures thereof”.
- [828] Unless modified, when used to describe the dosage form of the invention, “levorphanol” means unsalified levorphanol (levorphanol base) or a pharmaceutically acceptable salt of levorphanol, or prodrugs, esters, analogs, derivatives, solvates, complexes, polymorphs and hydrates thereof, as racemates or an individual diastereoisomers or enantiomeric isomers thereof or mixtures thereof.
- [829] When the dosage form includes a pharmaceutically acceptable salt, any salt may be use. Preferably, the salt is the tartrate salt of levorphanol.
- [830] The singular forms "a", "an" and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "a polymer" includes a single polymer as well as a mixture of two or more different polymers, reference to "a permeation enhancer" includes a single permeation enhancer as well as two or more different permeation enhancer in combination, and the like.
- [831] The mean drowsiness score is the score in mm on a 100 mm VAS scale bounded on the left by “no drowsiness” and on the right by “extreme drowsiness”.
- [832] The mean nausea score is the score in mm on a 100 mm VAS scale bounded on the left by “no nausea” and on the right by “extreme nausea”.
- [833] The mean dizziness score is the score in mm on a 100 mm VAS scale bounded on the left by “no dizziness” and on the right by “extreme dizziness”.
- [834] The mean vomiting score is the number of episodes of vomiting or retching.
- [835] The “NNH” or “number needed to harm” is a measure that indicates how many patients would require a specific treatment to cause harm in one patient. As used herein, the “NNH or

“number needed to harm” is a measure that includes: (i) how many opioid naive healthy subjects would require treatment to cause moderate or severe sedation (or drowsiness) in one subject, where moderate to severe drowsiness is defined as a VAS score of ≥ 50 mm on a 100 mm scale bounded on the left by “no sedation or drowsiness” and on the right by “extreme sedation or drowsiness”; (ii) how many opioid naive healthy subjects would require treatment to cause moderate or severe nausea in one subject, where moderate to severe nausea is defined as a VAS score of ≥ 50 mm on a 100 mm scale bounded on the left by “no nausea” and on the right by “extreme nausea”; (iii) how many opioid naive healthy subjects would require treatment to cause dizziness in one subject, where dizziness is defined as unsteadiness, imbalance, lightheadedness, spinning sensation or sensation that one is falling.

- [836] The “drug effects” questionnaire assesses the extent to which subjects currently felt a drug effect, on a scale of 1 to 5 (1 = “I feel no effect from it at all”; 2 = “I think I feel a mild effect, but I’m not sure”; 3 = “I feel an effect, but it is not real strong”; 4 = “I feel a strong effect”; 5 = “I feel a very strong effect”). This questionnaire can be used to examine the overall drug effects, preferably in drug abusers and recreational drug users.
- [837] The “drug liking” questionnaire assesses the extent to which subjects currently like the effects of the drug on a 100-mm VAS, bounded on the left by “0 = dislike a lot”, bounded on the right by “100 = like a lot”. This questionnaire can be used to examine the overall drug liking of, preferably in drug abusers and recreational drug users.
- [838] The “take again” questionnaire assesses whether subjects would take the drug again if given the opportunity. The patient is asked “If given an opportunity, would you take this drug again? (circle one: YES or NO). This questionnaire can be used to examine the overall desirability of the drug experience, preferably in drug abusers and recreational drug users.
- [839] On the “coasting” questionnaire the patient is asked to put a mark on a horizontal line that best describes their response to the question: “Do you feel like you are coasting or spaced out? The horizontal line is a visual analog scale (VAS) bounded on the left by “not at all” and on the right by “extremely”. This questionnaire can be used to examine the degree to which subjects feel like they are coasting or spaced out, preferably in drug abusers and recreational drug users.
- [840] Three performance tasks may be employed for measuring skills related to driving.
- [841] The “critical tracking task” measures the patient’s ability to control a displayed error signal in a first-order compensatory tracking task. The error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Compensatory joystick movements correct the error by returning the cursor to the midpoint. The frequency at which the patient loses the control is the critical frequency. The critical tracking task measures the psychomotor control during a closed loop operation. It is a laboratory analog to on-the-road tracking performance.
- [842] The “stop signal task” measures motor impulsivity, which is defined as the inability to

inhibit an activated or pre-cued response leading to errors of commission. The task requires patients to make quick key responses to visual go signals, i.e. the letters ABCD presented one at a time in the middle of the screen, and to inhibit any response when a visual stop signal, i.e. "*" in one of the four corners of the screen, is presented at predefined delays. The main dependent variable is the stop reaction time on stop signal trials that represents the estimated mean time required to inhibit a response.

[843] The "Tower of London" (TOL) is a decision-making task that measures executive function and planning. The task consists of computer generated images of begin- and end-arrangements of three colored balls on three sticks. The subject's task is to determine as quickly as possible, whether the end-arrangement can be accomplished by "moving" the balls in two to five steps from the beginning arrangement by pushing the corresponding number coded button. The total number of correct decisions is the main performance measure.

[844] As used herein, "plasma" is the virtually cell-free supernatant of venous blood containing anticoagulant (such as citrated, EDTA or heparinized blood) obtained after centrifugation. For example, venous whole blood may be centrifuged at about 3000 rpm for 15 minutes at 4 °C and the resulting supernatant (plasma) is harvested and stored in a freezer, at about -20 °C or lower (e.g., -70 °C) until assayed.

[845] As used herein, "serum" is the undiluted, extracellular portion of venous blood after adequate coagulation is complete. For example, venous whole blood is collected and allowed to coagulate. When coagulation is complete, the sample is centrifuged for at least about 10 minutes at about 3000 rpm.

[846] Although plasma is usually preferred over serum for a variety of reasons (e.g, time savings, higher yield, prevention of coagulation-induced interferences and prevention of coagulation-induced changes), there are a few conditions under which serum may be preferred over plasma (e.g., avoiding analyte assay interference from anticoagulants, avoiding contamination with cations). For the purposes of this invention, the some or all of the specifications and claims relating to plasma are also applicable to serum.

[847] As used herein, "plasma T_{lag} " refers to a time period from first administration (or first dosing) of levorphanol to the occurrence of first of two consecutive mean plasma levorphanol concentrations from the higher of the following: (i) a concentration at least equal to four times the lower limit of quantification (LLOQ) for the levorphanol; or (ii) a concentration at least equal to 5% of the mean C_{max} of the levorphanol; provided however, that the second consecutive levorphanol plasma concentration is obtained not less than about 15 minutes and not more than about 30 minutes after the first plasma levorphanol concentration is also at least equal to the higher of (i) or (ii); and provided however, that the plasma concentrations of levorphanol are determined by sequential venous blood sampling not less than about every 15 minutes and not more than about

every 30 minutes after first administration and the mean concentration is determined from not less than 18 healthy subjects receiving the levorphanol in a fasted or fed state.

[848] As used herein, the “lower limit of quantification” “LLOQ”, “lower limit of quantitation” and “LLQ” are interchangeable and mean the lowest concentration of the standard curve that can be measured with acceptable accuracy and precision as defined in Bioanalytical Method Validation, Guidance for Industry, Food and Drug Administration, May 2001, which is hereby incorporated in its entirety by reference, where (i) accuracy and precision are determined by replicate analysis using a minimum of five determinations per concentration level (excluding blank samples); and (ii) accuracy is within $\pm 20\%$ of the theoretical value; and (iii) precision around the mean value is not in excess of 20% of the coefficient of variation (CV); and (iv) the analyte response at the LLOQ is at least 5 times the response compared to blank response; and (v) the analyte peak (response) should be identifiable and discrete.

[849] As used herein, " $T_{lagD(x)}$ " refers to the time from the start of dissolution testing to the first attainment of an in-vitro release of about 5% by weight of the active drug from the dosage form when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water at 37 °C, where " x " is the pH of the dissolution media.

[850] In some embodiments, the dosage form of the invention, one or more or all of the specifications and claims applicable to the prevention and treatment of pain or addiction disorders is also applicable to the prevention or treatment of any other disease or disorder that responds to opioid agonists or to levorphanol.

[851] The treatment of all diseases and disorders is contemplated by the use of this invention. The treatment of all diseases and disorders is contemplated by the use of this invention

[852] In some preferred embodiments, the oral pharmaceutical dosage forms of levorphanol are used to treat pain, sickle cell disease pain, cough, dyspnea, opioid addiction disorders, acute herpes zoster, visceral pain, and opioid dependence.

[853] As used herein, “cough” includes acute cough, chronic cough, iatrogenic cough, post-infectious cough, and cough secondary to asthma, COPD, lung cancer, gastroesophageal reflux disease, respiratory bacterial and viral infections, and upper airway cough syndrome.

[854] As used herein, the term “pain” includes: (i) peripheral neuropathic pain, e.g., acute and chronic inflammatory demyelinating polyradiculopathy, alcoholic polyneuropathy, chemotherapy-induced polyneuropathy, complex regional pain syndrome (CRPS) Type I and Type II, entrapment neuropathies (e.g., carpal tunnel syndrome), HIV sensory neuropathy, iatrogenic neuralgias (e.g., postthoracotomy pain, postmastectomy pain), idiopathic sensory neuropathy, painful diabetic neuropathy, phantom limb pain, postherpetic neuralgia, trigeminal neuralgia, radiculopathy (e.g., cervical thoracic, lumbosacral), sciatica, acute herpes zoster pain, temporomandibular joint disorder pain and postradiation plexopathy; and (ii) central neuropathic pain, e.g., compressive myelopathy

from spinal stenosis, HIV myelopathy, multiple sclerosis pain, Parkinson's disease pain, postischemic myelopathy, post postradiation myelopathy, poststroke pain, posttraumatic spinal cord injury and syringomyelia; and (iii) cancer associated neuropathic pain, e.g., chemotherapy induced polyneuropathy, neuropathy secondary to tumor infiltration or nerve compression, phantom breast pain, postmastectomy pain, postradiation plexopathy and myelopathy; (iv) chronic pain, e.g., back pain, rheumatoid arthritis, osteoarthritis, inflammatory pain, non-inflammatory pain, myofascial pain, cancer pain, visceral pain, somatic pain, pelvic pain, musculoskeletal pain, post-traumatic pain, bone pain and idiopathic pain; (v) acute pain, e.g., acute postsurgical pain (including laparoscopic, laparotomy, gynecologic, urologic, cardiothoracic, arthroscopic, gastrointestinal, neurologic, orthopedic, oncologic, maxillofacial, ophthalmic, otolaryngologic, soft tissue, plastic, cosmetic, vascular and podiatric surgery, including abdominal surgery, abdominoplasty, adenoidectomy, amputation, angioplasty, appendectomy, arthrodesis, arthroplasty, arthroscopy, bilateral cingulotomy, biopsy, brain surgery, breast biopsy, cauterization, cesarean section, cholecystectomy, circumcision, commissurotomy, cordotomy, corneal transplantation, cricothoracotomy, discectomy, diverticulectomy, episiotomy, endarterectomy, endoscopic thoracic sympathectomy, foreskin restoration, fistulotomy, frenectomy, frontalis lift, fundectomy, gastrectomy, grafting, heart transplantation, hemicorporectomy, hemorrhoidectomy, hepatectomy, hernia repair, hypnosurgery, hysterectomy, kidney transplantation, laminectomy, laparoscopy, laparotomy, laryngectomy, lithotripsy, lobotomy, lumpectomy, lung transplantation, mastectomy, mammoplasty, mastectomy, mastoidectomy, mentoplasty, myotomy, myringotomy, nephrectomy, nissen fundoplication, oophorectomy, orchidectomy, parathyroidectomy, penectomy, phalloplasty, pneumotomy, pneumonectomy, prostatectomy, psychosurgery, radiosurgery, ritidoplasty, rotationplasty, sigmoidostomy, sphincterotomy, splenectomy, stapedectomy, thoracotomy, thrombectomy, thymectomy, thyroidectomy, tonsillectomy, tracheotomy, tracheostomy, tubal ligation, ulnar collateral ligament reconstruction, ureterosigmoidostomy, vaginectomy, vasectomy, vulvectomy; renal colic; incisional pain; inflammatory incisional pain; nociceptive incisional pain; acute neuropathic incisional pain following surgery), renal colic, trauma, acute back pain, burn pain, burn dressing change pain, migraine pain, tension headache pain, acute musculoskeletal pain, acute exacerbation or flare of chronic back pain, acute exacerbation or flare of osteoarthritis, acute exacerbation or flare of chronic pain, breakthrough chronic non-cancer pain, breakthrough cancer pain, acute exacerbation or flare of rheumatoid arthritis, acute exacerbation or flare of myofascial pain, acute exacerbation or flare of chronic idiopathic pain, acute exacerbation or flare of neuropathic pain, procedure related pain (e.g., arthroscopy, laparoscopy, endoscopy, intubation, bone marrow biopsy, soft tissue biopsy, catheterization), and other self-limiting pain states.

[855] As used herein, the term "acute pain" refers to self-limiting pain that subsides over time and usually lasting less than about 30 days and more preferably lasting less than about 21 days. Acute

pain does not include chronic conditions such as chronic neuropathy, chronic neuropathic pain and chronic cancer and non-cancer pain.

- [856] As used herein, "neuropathic pain" is pain initiated or caused by a primary lesion or dysfunction of the nervous system and includes (i) peripheral neuropathic pain and (ii) central neuropathic pain.
- [857] As used herein, the term "chronic pain" includes all non-neuropathic pain usually lasting more than 30 days, including inflammatory pain, non-inflammatory pain, muscle pain, joint pain, fascia pain, visceral pain, bone pain and idiopathic pain.
- [858] The term "therapeutic effectiveness" is defined for purposes of the present invention as a satisfactory prevention, reduction in or elimination of signs and symptoms of the medical disorder, disease or syndrome (e.g., pain), along with a tolerable level of side effects, as determined by the human patient.
- [859] The term "analgesic effectiveness" is defined for purposes of the present invention as a satisfactory prevention, reduction in or elimination of pain, along with a tolerable level of side effects, as determined by the human patient.
- [860] The analgesic effects of the dosage form of the present invention may be evaluated as described below. The choice of doses, patient population, type of pain and study design will vary depending on the needs of the study. Evaluation in acute and chronic pain is contemplated. The increased therapeutic benefits associated with the administration of the dosage form may in some embodiments be evaluated after third molar surgery and bunionectomy surgery.
- [861] In the case of the third molar extraction model, male and female patients with acute postsurgical pain following the removal of one or more bony impacted third molars are participants. In the case of the bunionectomy surgery model, male or female patients requiring primary unilateral first metatarsal bunionectomy surgery alone or with ipsilateral hammertoe repair (without additional collateral procedures) under regional anesthesia (e.g., Mayo block) are participants. Within 4 to 6 hours after completion of either surgery, patients who are experiencing moderate or severe pain, as measured by a visual analog pain intensity scale (VAS \geq 50 mm) and by a categorical pain intensity scale (moderate or severe pain descriptor), and who meet all other inclusion/exclusion criteria are admitted to the study. Patients are randomly assigned to receive test and reference or control treatments. Pain intensity (VAS and categorical), pain relief (categorical) and whether pain is half-gone is recorded by the patient under the supervision of the investigator or study coordinator at the various time points: Baseline (0 hour – pain intensity only), 15, 30 and 45 minutes, and at 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after administration of study medication, and immediately prior to the first rescue dose. Time to onset of perceptible and meaningful pain relief is evaluated using the two stopwatch method. Patients record their global evaluation of study medication at the completion of the 8-hour assessment or at the time of first rescue medication use. Efficacy endpoints include Total

Pain Relief (TOTPAR), Sum of Pain Intensity Difference (SPID) and Sum of Pain Relief Intensity Difference (SPRID) at various time points, Time to First Rescue, Time Specific Pain Intensity Difference (PID), Time Specific Pain Relief (PR), Peak Pain Intensity Difference (PPID), Peak Pain Relief (PPR), Time to Confirmed Perceptible Pain Relief (stopwatch) and Time to Meaningful Pain Relief (stopwatch) and Patient Global Evaluation.

[862] In the case of chronic pain of osteoarthritis, the therapeutic benefits associated with the administration of the dosage form in some embodiments is demonstrated in repeated dose randomized, double-blind, controlled studies are assigned to receive test and reference or control treatments. Typically, patients who meet the American College of Rheumatology criteria for knee and/or hip OA are washed off their analgesics for 2 to 7 days to allow for pain of moderate to severe intensity to return (Babul et al. *Journal of Pain and Symptom Management* 2004;28:59-71). Once a stable baseline pain score is established, patients are randomized to treatment, usually for a period of one to 12 weeks. Pain, joint stiffness and physical function can be measured with a multidimensional instrument, such as the WOMAC, quality of life with the SF-12 or SF-36 and adverse events with a non-directed questionnaire at baseline and at post-baseline return visits. Response to pain, stiffness, physical function, quality of life and adverse events are calculated as change from baseline and compared between treatments. Sample sizes in the studies are sufficient to demonstrate the increased therapeutic benefit of the invention.

[863] In the case of postherpetic neuralgia, the analgesic efficacy of the invention may be demonstrated in repeated dose randomized double-blind, controlled studies. Patients are randomized to receive are assigned to receive test and reference or control treatments. Patients with a history of postherpetic neuralgia ≥ 3 months and pain of at least moderate intensity are enrolled in the study. Patients with hypersensitivity to study medications, a history of drug or alcohol abuse and significant pain of alternate etiology are generally excluded. Patients meeting study eligibility criteria are “washed off” their analgesics in some embodiments, generally for 2 to 7 days to allow for pain of moderate to severe intensity to return. Once a stable baseline pain score is established, patients are randomized to treatment, usually for a period of 4 to 12 weeks. Pain intensity is assessed one to several times a day and in some cases only once weekly using VAS, categorical or numerical rating scales. Various dimensions of neuropathic pain may be assessed, including steady pain (ongoing pain), brief pain (paroxysmal pain) and skin pain (allodynia). Pain may also be assessed at scheduled clinic study visits. Pain may also be assessed using standardized pain scales such as the Neuropathic Pain Symptom Inventory (Bouhassira et al., *Pain* 2004;108:248-57), or interference measures of the Brief Pain Inventory (Cleeland, CRC Press, 1991:293-305 & *Ann Acad Med Singapore* 1994;23:129-38). Patient Global Impression of Change (Farrar et al., *Pain* 2001;94:149-580) and quality of life may be assessed. Examples of randomized, placebo or active studies conducted in postherpetic neuralgia are known in the art (e.g., Watson and Babul,

Neurology 1998;50:1837-41). Adverse events may be assessed using a non-directed questionnaire or a symptom checklist. Response to pain, function, quality of life and adverse events are calculated as change from baseline and compared between treatments.

[864] As used herein, the "Orange Book" as it is commonly known is the database of Approved Drug Products with Therapeutic Equivalence Evaluations maintained by or on behalf of the US Food and Drug Administration, (<http://www.fda.gov/cder/ob/default.htm>, accessed February 15, 2008), the content of which is hereby incorporated by reference.

[865] "Drug", "drug substance", "substance", "therapeutic", "therapeutic agent", "pharmacological agent", "pharmaceutical agent", "active agent", "active ingredient", "agent" "active pharmaceutical ingredient" or "API" are used interchangeably and are intended to have their broadest interpretation as to any therapeutically active substance which is delivered to a living organism to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body. In general, this includes therapeutic agents in all of the major therapeutic areas.

[866] As used herein, "dosage forms" is interchangeable with "formulations", "compositions", "pharmaceutical compositions", "pharmaceutical preparations", "preparations" or "doses". The foregoing compositions, when referring to levorphanol, means extended release dosage forms comprising unsalified levorphanol (*l* 3-hydroxy-N-methylmorphinan base), a pharmaceutically acceptable salt of levorphanol, the racemate of levorphanol (*d,l* 3-hydroxy-N-methylmorphinan), non-stoichiometric ratios of *l* 3-hydroxy-N-methylmorphinan and *d* 3-hydroxy-N-methylmorphinan, pharmaceutically acceptable salts thereof, or esters, solvates, complexes, polymorphs and hydrates thereof, or mixture thereof.

[867] The term "subject" for purposes of treatment is used interchangeably with "patient", "male", "female" and "human", and includes any human subject.

[868] "Pharmaceutically or therapeutically acceptable excipient or carrier" or "excipient" refers to a substance which does not interfere with the effectiveness or the biological activity of the active ingredients and which is not toxic to the subject. In some embodiments of the present invention, pharmaceutically or therapeutically acceptable excipients or carriers may play a role in imparting or optimizing the rate and extent of absorption or levorphanol or additional drugs in the pharmaceutical composition. In some embodiments of the present invention, pharmaceutically or therapeutically acceptable excipients or carriers may play a role in stabilizing the levorphanol or additional drugs in the pharmaceutical composition. Excipients are widely known in the art (see, for example, FDA EAFUS database; FDA Food Additives Status List; FDA GRAS list and database; FDA Color Additive Status List; FDA Inactive Ingredients Database; Rowe, Sheskey and Owen, Handbook of Pharmaceutical Excipients, APhA Publications; 5th edition (2006); Goodman & Gilman's The Pharmacological Basis of Therapeutics (Brunton, Lazo and Parker, eds, 11th ed.,

McGraw Hill (2005); Remington: The Science and Practice of Pharmacy, 21st ed, Lippincott Williams & Wilkins (2005); Martindale: The Complete Drug Reference, 35th Edition, Pharmaceutical Press (2007); United States Pharmacopeia–National Formulary (USP-NF), (USP 30 – NF 25, 2007), the International Programme on Chemical Safety and Health Canada’s List of Acceptable Non-medicinal Ingredients).

[869] Any pharmaceutically acceptable excipient may be included in the dosage form, in any molecular weight, particle size, viscosity or amount. In some embodiments, the total amount of pharmaceutically acceptable excipient is about 0.0001% to about 99 percent, preferably about 0.5% to 95 percent and more preferably about 5% to about 85% on a dry weight basis of the composition.

[870] As used herein, the term “aversive”, “aversive agents”, “aversion producing agents” and “aversive compounds” means to compounds contained within the dosage form that produce an aversive, undesirable, repugnant, distasteful, unpleasant, unacceptable physiologic effect, unacceptable psychic effect, or that pharmacologically block or reduce physiologic effects sought by recreational drug users, addicts and drug abusers, including one or more of the following effects: mood alterations; euphoria, pleasure; a feeling of high; a feeling of drug liking; anxiolysis; sedation; calmness; a state of relaxation; psychotomimesis; hallucinations; alterations in perception, cognition and mental focus; drowsiness; and psychological reinforcement.

[871] The term “tampering” or “tamper” means any manipulation by mechanical, thermal, chemical and/or pharmacologic means which changes the physical or chemical properties of the dosage form, e.g., to liberate the levorphanol for immediate release if it is in extended release form, or to make the levorphanol available for inappropriate use such as administration by an alternate route, e.g., parenterally. The tampering can be, e.g., by means of crushing, shearing, grinding, mechanical extraction, solvent extraction, solvent immersion, combustion, heating or any combination thereof.

[872] The term “abuse”, “drug abuse”, “opioid abuse”, “recreational drug use” and “drug misuse” in the context of the present invention means, use: (i) in quantities or by methods and routes of administration that do not conform to standard medical practice; (ii) outside the scope of specific instructions for use provided by a qualified medical professional; (iii) outside the supervision of a qualified medical professional; (iv) outside the approved instructions on proper use provided by the drug’s legal manufacturer; (v) which is not in specifically approved dosage forms for medical use as pharmaceutical agents; (vi) where there is an intense desire for and efforts to procure same; (vii) compulsive use; (viii) through acquisition by manipulation of the medical system, including falsification of medical history, symptom intensity, disease severity, patient identity, doctor shopping, prescription forgeries; (ix) where there is impaired control over use; (x) despite harm; (xi) by procurement from non-medical sources; (xii) by others through sale or diversion by the individual into the non-medical supply chain; (xiii) for medically unapproved or mood altering

purposes.

- [873] The term "mood altering" is defined for purposes of the present invention to mean that the "high", "liking", pleasurable, euphoric, alerting, calming, anxiolytic, auditory and visual perception altering, relaxing, psychotomimetic, rewarding and reinforcing following use of levorphanol.
- [874] The term "abuse resistant", "abuse deterrent", "tamper resistant", "deter abuse" and "resist abuse" (as well of the words "resist" or "deter" when applied levorphanol) are used interchangeably in the context of the present invention and include pharmaceutical compositions, methods and processes that resist, deter, discourage, diminish, delay and/or frustrate: (i) the physical, chemical, thermal or pharmacologic manipulation or tampering of the dosage form (e.g., crushing, shearing, grinding, chewing, dissolving, melting, needle aspiration, inhalation, insufflation, extraction by mechanical, thermal and chemical means, and/or filtration); (ii) use or misuse of the dosage form outside the scope of specific instructions for use provided by a qualified medical professional; (iii) use outside the supervision of a qualified medical professional; (iv) use outside the approved instructions on proper use provided by the drug's legal manufacturer (e.g., intravenous use, intranasal use, inhalational use and oral ingestion to provide high peak concentrations, use in excess quantities, etc.); (v) the conversion of an extended release dosage form of the invention into a more immediate release form; (vi) the intentional and iatrogenic increase in physical and psychic effects sought by recreational drug users, addicts, and patients with pain who have an addiction disorder; (vii) attempts to procure the dosage form by manipulation of the medical system and from non-medical sources; (viii) the sale or diversion of the dosage form into the non-medical supply chain and for medically unapproved or unintended mood altering purposes; (ix) the intentional, unintentional or accidental attempts at otherwise changing the physical, pharmaceutical, pharmacological and/or medical properties of the dosage form from what was intended by the manufacturer; (x) the psychic, pleasurable, reinforcing or rewarding effects of the dosage form when used as directed or when used outside the approved instructions on proper use provided by the drug's legal manufacturer.
- [875] "Therapeutically effective amount" or "therapeutically-effective" refers to the amount of an active agent sufficient to induce a desired biological result. That result may be alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system.
- [876] "Therapeutically effective amount of levorphanol" refers to the amount of oral levorphanol sufficient to prevent, to cure, or at least partially arrest a medical disorder, disease, sign or symptom for which the levorphanol has been prescribed to a subject.
- [877] The term "effective amount" means the quantity of a compound according to the invention necessary to prevent, to cure, or at least partially arrest a medical disorder, disease, sign or symptom for which the levorphanol has been prescribed to a subject.
- [878] The term "pharmaceutically acceptable salt" as used herein refers to a salt which is

toxicologically safe for human and animal administration. Nonlimiting examples of salts include hydrochlorides, hydrobromides, hydroiodides, sulfates, bisulfates, nitrates, citrates, tartrates, bitartrates, phosphates, malates, maleates, napsylates, fumarates, succinates, acetates, terephthalates, pamoates and pectinates. In some embodiments, the pharmaceutical composition is a salt or complex of inorganic cation salts, organic salts such primary, secondary, tertiary and quaternary amines include substituted amines

[879] It is contemplated that the present invention may be used alone or in combination with other drugs to provide additive, complementary, or synergistic therapeutic effects or for the treatment of entirely different medical conditions.

[880] Other pharmaceutically active ingredients from various therapeutic classes may also be used in combination with the present invention. In some embodiment, co-administered may be used to provide additive, complementary, superadditive or synergistic therapeutic effects. In some embodiment, co-administered may be used to provide a different therapeutic effects from the present invention or to treat the side effects of the present invention. They include, but are not limited to drugs to treat disorders, diseases and maladies, and signs and symptoms thereof referred to in Harrison's Principles of Internal Medicine, 16th Edition, 2004, Kasper DL, Braunwald W, Fauci A, Hauser S, Longo D, and Jameson JL (eds)], which is hereby incorporated in its entirety by reference The drug being used in combination therapy with the present invention can be administered by any route, including parenterally, orally, topically, transdermally, sublingually, and the like.

[881] As used herein, "levorphanol responsive conditions", levorphanol responsive medical conditions", "opioid responsive conditions", "opioid responsive medical conditions", "levorphanol or opioid responsive medical conditions", "in need to levorphanol", and the like refer to any medical condition in which levorphanol can be employed for a therapeutically beneficial outcome.

[882] The terms "medical condition", "malady", "disease", "disorder" and "pathological states" are used interchangeably and are intended to have their broadest interpretation to refer to any physiologic, pathologic or pathophysiologic state in a human or other mammal that can be prevented, treated, managed or altered to produce a desired, usually beneficial effect.

[883] In some preferred embodiments, the dosage form provides an oral pharmaceutical composition for the treatment of a levorphanol responsive medical condition comprising a therapeutically effective amount of levorphanol, and a controlled release material, said levorphanol given alone or in combination with another drug in the same dosage form or in a different dosage form to treat the same or a different condition or to treat side effects of levorphanol or to deter abuse of the levorphanol.

[884] In some embodiments, the oral levorphanol is intended to prevent or treat pain. A co-administered drug (in the same or different dosage form, by any route of administration) may be

used to provide additive, complementary, superadditive or synergistic therapeutic analgesic effects, including other NSAIDs, NO-NSAIDs, COX-2 selective inhibitors, acetaminophen, tramadol, local anesthetics, antidepressants, beta adrenergic agonists, alpha-2 agonists, selective prostanoid receptor antagonists, cannabinoid agonists, other opioid receptor agonists, NMDA receptor antagonists, gabapentin, pregabalin, gabapentinoids, neuronal nicotinic receptor agonists, calcium channel antagonists, sodium channel blockers, superoxide dismutase mimetics, p38 MAP kinase inhibitors, TRPV1 agonists, dextromethorphan, dextrorphan, ketamine, glycine receptor antagonists, antiepileptics, and any other drugs that can be shown by a person proficient in the art to prevent or treat pain.

- [885] In some embodiments, a preferred combination includes levorphanol with acetaminophen.
- [886] In other embodiments, particularly preferred combinations include levorphanol with an NSAID. Nonsteroidal anti-inflammatory drugs typically have analgesic, anti-inflammatory, and antipyretic properties. Their mode of action appears to involve inhibition of cyclooxygenases (COX-1 and COX-2), leukotriene biosynthesis, and antibradykinin activity. NSAIDs may be non-selective (inhibit COX-1 and COX-2 isozymes) or COX-2 selective (preferentially inhibit the COX-2 isozymes).
- [887] In other embodiments, more preferred combinations include levorphanol with other opioids.
- [888] In certain preferred embodiments of the present invention, an effective amount of another drug to treat the levorphanol responsive condition, a levorphanol related side effect (e.g., laxative, CNS stimulant or anti-emetic) or a co-existing medical condition may be incorporated into the dosage form. Such a coadministered drug may be in any form, including immediate release, controlled release and delayed release. The co-administered drug may be incorporated at a therapeutic dose or a subtherapeutic dose. In certain preferred embodiments of the present invention where the dosage form is a delayed onset, extended release, an effective amount of another drug to treat the levorphanol responsive condition in immediate release form may be particularly advantageous. In certain preferred embodiments, an NSAID, acetaminophen or a COX-2 inhibitor in immediate release form may be advantageously incorporated into the dosage form. In some embodiments, another drug to treat the same condition as the oral levorphanol or to treat a different condition may be incorporated into the oral dosage form, where the other drug shares one, or more of the dissolution rate specifications, GI delivery and release specifications and pharmacokinetic parameter specifications as the oral levorphanol in the dosage form.
- [889] The above embodiments of the invention can be provided by modifying a wide variety of controlled release formulations known to those skilled in the art.
- [890] The invention is also directed to a process for the manufacture of pharmaceutical compositions and dosage forms disclosed herein

METHODS OF CARRYING OUT THE INVENTION**DOSAGE FORMS**

- [891] Pharmaceutical composition and methods of the present invention comprise levorphanol base or pharmaceutically acceptable salts in racemic or enantiomeric form, or mixtures thereof, or prodrugs thereof intended oral administration as extended release dosage forms.
- [892] Preferred extended release dosage forms of the invention are "extended release" or "delayed onset, extended release formulations".
- [893] All oral extended release pharmaceutical dosage forms of the invention are contemplated, including, without limitation oral suspensions, tablets, chewable tablets, capsules, lozenges, effervescent tablets, effervescent powders, non-effervescent powders, gastroretentive tablets and capsules, orally disintegrating tablets.
- [894] The formulation may optionally comprise excipients, including release controlling excipients and non-release controlling excipient. Non-limiting examples of these auxiliary materials (or pharmaceutically acceptable excipients) are (i) Binders such as acacia, alginic acid and salts thereof, cellulose derivatives, methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, magnesium aluminum silicate, polyethylene glycol, gums, polysaccharide acids, bentonites, hydroxypropyl methylcellulose, gelatin, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, crospovidone, povidone, polymethacrylates, hydroxypropylmethylcellulose, hydroxypropylcellulose, starch, pregelatinized starch, ethylcellulose, tragacanth, dextrin, microcrystalline cellulose, sucrose, or glucose, and the like; (ii) Disintegrants such as starches, pregelatinized corn starch, pregelatinized starch, celluloses, cross-linked carboxymethylcellulose, crospovidone, cross-linked polyvinylpyrrolidone, a calcium or a sodium alginate complex, clays, alginates, gums, or sodium starch glycolate, and any disintegration agents used in tablet preparations; (iii) Filling agents such as lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrates, dextran, starches, pregelatinized starch, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like; (iv) Stabilizers such as any antioxidation agents, buffers, or acids, and the like; (v) Lubricants such as magnesium stearate, calcium hydroxide, talc, colloidal silicon dioxide, sodium stearyl fumarate, hydrogenated vegetable oil, stearic acid, glyceryl behenate, magnesium, calcium and sodium stearates, stearic acid, talc, waxes, Stearowet, boric acid, sodium benzoate, sodium acetate, sodium chloride, DL-leucine, polyethylene glycols, sodium oleate, or sodium lauryl sulfate, and the like; (vi) Wetting agents such as oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, sodium oleate, or sodium lauryl sulfate, and the like; (vii) Diluents such lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, dibasic calcium phosphate, sucrose-based diluents, confectioner's sugar,

monobasic calcium sulfate monohydrate, calcium sulfate dihydrate, calcium lactate trihydrate, dextrates, inositol, hydrolyzed cereal solids, amylose, powdered cellulose, calcium carbonate, glycine, or bentonite, and the like; (viii) Anti-adherents or glidants such as talc, corn starch, DL-leucine, sodium lauryl sulfate, and magnesium, calcium, or sodium stearates, and the like; (ix) Pharmaceutically compatible carriers such as acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerin, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearyl lactylate, carrageenan, monoglyceride, diglyceride, or pregelatinized starch, and the like; and (x) excipients referred to herein.

[895] Nanoparticles and Micronization

[896] The particle size of levorphanol may be reduced using a variety of available techniques. The API is micronized to obtain the requisite particle size of the invention. Micronization may be carried out using dry milling technique. A variety of conventional mills are available for dry milling, including ball mill, attritor mill, vibratory mill, air jet mill and media mills (such as a sand mill and a bead mill). The milling may be carried out using the levorphanol alone or with other pharmaceutically acceptable excipients. Particle size reduction may also be achieved using high pressure homogenization. Also, supercritical fluid technique may be utilized for particle size reduction. The desired particle size may also be obtained by modifying the reaction conditions during the manufacturing of levorphanol API.

[897] The dosage form of the invention may include at least one surface stabilizer in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of levorphanol and at least one surface stabilizer, not including other excipients.

[898] The surface stabilizer may be selected from the group comprising an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, and an ionic surface stabilizer. The surface stabilizer may also be selected from the group comprising cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxy methylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxy methylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and

formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol); lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone. In some dosage forms of the invention, the surface stabilizer is cationic surface selected from the group comprising a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid. In some dosage forms of the invention, the surface stabilizer is cationic surface selected from the group comprising cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulfate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride, dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, Polyquat 10™ (polyquaternium 10), tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearylalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, Mirapol™ and Alkaquat™ (quaternized ammonium salt polymers), alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar. In some dosage forms of the invention, the surface stabilizer is selected from the group comprising hydroxypropyl cellulose, sodium lauryl sulfate, copolymers of vinyl

pyrrolidone and vinyl acetate, polyvinylpyrrolidone, or a mixture thereof.

[899] Nanoparticulate drugs are particles consisting of the drug, having associated with the surface thereof a non-crosslinked surface stabilizer. Methods of making nanoparticulate active agent compositions are described, for example: (i) in U.S. Patent No. 5,518,187; 5,862,999; 5,718,388; 5,510,118; 5,298,262; 5,302,401; 5,318,767; 5,326,552; 5,328,404; 5,336,507; 5,340,564; 5,346,702; 5,349,957; 5,352,459; 5,399,363; 5,494,683; 5,401,492; 5,429,824; 5,447,710; 5,451,393; 5,466,440; 5,470,583; 5,543,133; 5,552,160; 5,560,931; 5,565,188; 5,569,448; 5,571,536; 5,573,749; 5,580,579; 5,585,108; 5,587,143; 5,591,456; 5,593,657; 5,622,938; 628,981; 5,834,025; 6,165,506; 6,221,400; 6,264,922; 6,267,989; 6,270,806; 6,375,986; 6,428,814; 6,431,478; 6,432,381; 6,592,903; 4,826,689; 4,997,454; 5,741,522; 5,776,496; and (ii) by de Villiers MM, et al, Nanotechnology in Drug Delivery (Biotechnology: Pharmaceutical Aspects), Springer; 1 edition (October 27, 2008); Gupta RB and Kompella UB. Nanoparticle Technology for Drug Delivery (Drugs and the Pharmaceutical Sciences), Informa Healthcare; 1 edition (January 13, 2006); Thassu D et al, Nanoparticulate Drug Delivery Systems (Drugs and the Pharmaceutical Sciences), Informa Healthcare; 1 edition (March 30, 2007). Some dosage forms of the invention contain amorphous small particle compositions, described, for example, in U.S. Patent No. 4,783,484; 4,826,689; 4,997,454; and 5,776,496. In some embodiments, the levorphanol in the above examples may require milling to assure that they meet the particle size requirements of the invention. The choice of particle size will vary depending on the objectives of the dosage form. In some embodiments, the dosage form in the examples comprises levorphanol (i) with particles smaller than 50,000 nm, 40,000 nm, 20,000 nm, 10,000 nm, 5,000 nm; or (ii) with a substantial percentage of particles smaller than 50,000 nm, 40,000 nm, 20,000 nm, 10,000 nm, 5,000 nm; or (iii) with a significant percentage of particles smaller than 50,000 nm, 40,000 nm, 20,000 nm, 10,000 nm, 5,000 nm.

[900] **Liquid Filled Thermosoftening Extended Release Dosage**

[901] A liquid filled thermosoftening extended release dispersion systems provides an alternative dosage form of extended release levorphanol suitable for dosing up to once-a-day (e.g., Q12H or Q24H) to a human patient. This dosage form is advantageously utilized to prepare a dosage form which minimizes the use of typical excipients found on oral solid dosage form capsules and tablets, such as excipients such as glidants, lubricants, diluents, fillers, binders, disintegrants and is relatively easy to scale-up. The manufacturing process may optionally be performed entirely in situ in a single heated mixing vessel prior to transfer to a filling machine for encapsulation.

[902] In some embodiments, liquid filled thermosoftening extended release dispersion systems are a preferred dosage form of the invention. In contrast to hot melt extrusion, which is typically used to make compressed tablets of molten material and some pellet forms for encapsulation, the liquid filled dosage forms of the invention have important advantages. It is a relatively simple, cost

effective method for manufacture of the dosage form of the invention without a large number of processing steps and equipment. Hot melt extrusion has several disadvantages: (i) the dosage forms manufactured using hot melt extrusion represent complex mixtures of the active drug, functional excipients and various processing aids. Functional excipients can include the carrier matrix, plasticizers, controlled release material, release rate modifiers, thermal lubricants, diluents, antioxidants, and other pharmaceutical excipients.; (ii) carefully controlled processing conditions during the extrusion and downstream; (iii) high equipment cost due to the sophisticated metallurgy required as the mix is subjected to considerable mechanical shear stress (e.g., from the rotating screw), and thermal stress (e.g., from the high pressure and processing temperatures); (iv) unlike the liquid fill method described above, the preparation of the molten mass is only a small part of in the manufacture of a hot melt extrusion product - the extrudate needs to be cooled (e.g., air, nitrogen) on conveyors and pellets cut to the desired size and shape.

[903] The dosage form comprises the following material filled into capsules: (1) A and B; or (2) A and C; or (3) A and D; or (4) A and E; or (5) A, B and F; or (6) A, B and G; or (7) A, C and F; or (8) A, C and G; or (9) A, B, F and G; or (10) A, C, F and G, or (11) A,D and F, (12) A, D and G, or (13) A, E and F, or (14) A, E and G, or (15) A, D, F and G, or (16) A, E, F and G; wherein said material optionally includes (H); wherein, (A) = levorphanol; (B) = one or more compounds selected from each of the groups [i.e., at least one compound from one (i) and at least one compound from one (ii)] consisting of (i) glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (C) = one or more compounds selected from each of the groups consisting of (i) polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macrogolglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; and (ii) coconut oil, a coconut oil derivative, hydrogenated coconut oil, and fractionated coconut oil, or the respective esters, derivatives or mixture thereof; (D) = one or more compounds selected from the groups consisting of coconut oil, glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, and beeswax, or the respective esters, derivatives or mixture thereof; (E) = one or more compounds selected from the groups consisting of coconut oil, hydrogenated vegetable oils, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macrogolglycerides and pharmaceutically acceptable waxes, or esters thereof, or derivatives thereof or mixtures thereof; (F) = a thixotrope; (G) a release rate modifier; and (H) = one or more pharmaceutically acceptable excipients..

- [904] Any release rate modifier may be incorporated into the dosage form. Preferred release rate modifiers are selected from the group comprising hydroxypropyl methylcellulose, cellulose acetate, powdered cellulose, cellulose acetate phthalate, hydroxyethyl cellulose, silicified microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, low-substituted hydroxypropyl cellulose, carboxymethylcellulose, carboxymethylcellulose calcium, hypromellose acetate succinate, hypromellose phthalate, and ethylcellulose, and mixture thereof. A particularly preferred release modifier is HPMC.
- [905] Any thixotrope may be release rate modifier may be incorporated. Preferred thixotropes are selected from the group comprising silicon dioxide, silca, fumed silicon dioxides, or a mixture of silicon dioxide and aluminum oxide (e.g., Aerosil™, Aerosil™ COK84, Aerosil™ 200), microcrystalline methylcellulose, bentonite clay, hectorite clay, magnesium aluminum silicate, montmorillonite, lithium magnesium silicate and stearylaluminum hectorite. Particularly preferred thixotropes are silicon dioxide, silca, fumed silicon dioxides, a mixture of silicon dioxide and aluminum oxide, bentonite and microcrystalline methylcellulose, with silicon dioxide, silca, fumed silicon dioxides, mixtures of silicon dioxide and aluminum oxide being especially preferred.
- [906] The dosage form may be prepared using the following general method: (i) dispense the desired amount of compound selected from the group comprising: glyceryl behenate, glycerol monostearate, hydrogenated vegetable oil, hydrogenated cottonseed oil, hydrogenated palm kernel oil, hydrogenated soybean oil, beeswax, coconut oil, hydrogenated coconut oil, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, glyceryl behenate, glyceryl palmitostearate, lauroyl macrogolglycerides, pharmaceutically acceptable waxes, or their respective esters, derivatives or mixture thereof into a mixer; (ii) heat at least up to the melting point of the highest melting point compound and until fully melted; (iii) if the dosage form calls for hydroxypropyl methyl cellulose (HPMC), dispense the desired amount of HPMC into the mixer; (iv) mix until dispersed into a homogeneous mixture; (v) if the dosage form calls for a thixotrope, dispense the desired amount of thixotrope into the same vessel; (vi) mix until dispersed into a homogeneous mixture; (vii) if the if the dosage form calls for a pharmaceutically acceptable excipient, dispense the desired amount of excipient and mix until dispersed into a homogeneous mixture; (viii) dispense the desired amount of levorphanol (i.e., base, pharmaceutically acceptable salt or mixture thereof) into the same vessel; (ix) stir thoroughly with a high shear mixer until dispersed into a homogeneous mixture; (x) transfer the mix into a liquid filling capsule machine; (xi) fill into capsules (e.g., hard gelatin or HPMC capsule); (xii) optionally, transfer the capsules to a banding machine and band the capsules.
- [907] If desired, additional excipients, active agents to treat the same condition or a different condition and aversive agents in releasable or nonreleasable form, each in any desired amount may be added to the above described mixing process. The order of mixing of the capsule material may

be modified. In certain cases, the order of mixing will depend, among other things on the amount of material, its physicochemical properties, stability and interaction with the active drug and other material.

- [908] The capsules may optionally be cured at any temperature, preferably at controlled temperature; preferably at controlled humidity, preferably at less than 75% or less than 60%; preferably for a specified time period; preferably for a minimum time period before testing the product performance (e.g., dissolution testing); preferably at a temperature which is less than the lowest melting point material in the dosage form; preferably at about 20 to 25°C and or at about 15 to 30°C; preferably for about 0.5 to 7 days or at least about 24 or 48 hours. Curing can serve different purposes, depending on the dosage form and its constituents. In the case of liquid filled thermosoftening extended release dispersion systems of levorphanol, curing is intended to solidify the dosage form and to stabilize the physicochemical interactions between its various constituents.
- [909] The extended release levorphanol capsules may optionally be banded to provide tamper evidence, deter counterfeiting, improve mechanical strength, provide color brand differentiation, improve product stability and reduce oxygen diffusion. Reducing oxygen diffusion is important to enhance the stability of the dosage form and to reduce the oxidation of certain material prone to oxidation, e.g., polyoxyethylene oxides or lipids.
- [910] All types of capsules, including hard shell capsules and soft gelatine capsules, and capsule sizes, including size 000 to size 5 may be used, although hard shell capsules, particularly gelatin and HPMC are preferred. Capsule sizes for human use typically vary from size 000 to size 5 (size 000, 00, 0, 1, 2, 3, 4, and 5), with 0, 1 and 2 being the most commonly employed capsules. Manufacturers of gelatin capsule manufacturers can provide custom gelatin capsules specifically manufactured for filling liquids. An alternative to gelatin capsules is HPMC capsules. Since manufacturers of HPMC capsules utilize a variety of excipients and methods of manufacture, the performance of HPMC capsules may vary. Although HPMC capsules are gaining increased attention, their widespread use of pharmaceutical dosage forms does have some constraints, including high permeability to oxygen and poor solubility in acidic media.
- [911] The thermosoftening compound can include, without limitation, hard fats, synthetic thermosoftening agents or macroglycerides. Hard fats are typically hydrogenated glycerides obtained from natural sources and include Sterotex™ HM and Gelucire™ 30/01 and 43/01 which are respectively sourced from derived from soybean oil and palm oil. Type II hydrogenated vegetable oils, which tend to have a lower melting point are less preferred than Type II hydrogenated vegetable oils, which generally have a higher melting point (approximately 55°C to 75°C). Hard fats can provide hydrophobic properties and increased viscosity to the dosage form.
- [912] Synthetic thermosoftening agents include are high MW poly(ethylene glycol) (PEG), also known as poly(ethylene oxide) (PEO) and polyoxyethylene (POE). PEG, PEO or POE refers to a

polymer of ethylene oxide. The three names are synonymous, but by tradition, PEG has generally referred to polymers with a MW below 20,000 g/mol, PEO to polymers with a MW above 20,000 g/mol, and POE to a polymer of any MW. Depending on their MW, PEG and PEO are liquids or low-melting point solids. High MW PEG's of over at least 1500 are preferred, with PEG over a MW of 4,000 to 10,000 most preferred. Another synthetic thermosoftening agent that may be utilized is a solid grade poloxamer, which are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly(ethylene oxide)). Since the length of the polymer blocks can be modified, different poloxamers may have different properties. Poloxamers are commonly named with the letter P followed by 3 digits, the first 2 digits x 100 providing the approximate MW of the polyoxypropylene core, and the final digit x 10 providing the percentage polyoxyethylene content. A preferred grade is P188, which is a solid with a average MW range of 7,680 to 9,510 and a polyethylene content of 80%. Other grades of poloxamer, e.g., P338 and P407, may also be utilized.

[913] A variation of the above dosage form involves blending the material as described above into a homogeneous mixture but instead of liquid filling the capsule, extruding the mixture, e.g., using a twin-screw extruder, to form strands and preferably cooling the extrudate and cut the strands into multiparticulates of any diameter, preferably, less than 5 mm or less than 4 mm. The multiparticulates may then be filled into a capsule or compressed into a tablet.

[914] The capsule dosage form of the invention may optionally be allowed to cool down and then filled with immediate release levorphanol or another active drug in the form of a powder, a liquid that doesn't solidify, a liquid that solidifies at room temperature, another capsule (capsule within a capsule), multiparticulates of any size or a tablet, prior to capsule closure.

[915] The capsule dosage form of the invention may optionally be allowed to cool down and then filled with immediate release levorphanol or another active drug in the form of a powder. Alternatively, immediate release levorphanol or another active drug may be filled into a capsule first, followed by filling with the material comprising the extended release levorphanol and thermosoftening agent.

[916] The capsule dosage or tablet dosage form of the invention may optionally be overcoated with immediate release levorphanol or another active drug or with material to provide a delayed onset, extended release dosage form or targeted delivery into the duodenum, jejunum, ileum and/or colon. A variety of material and methods may be employed, including use of pH sensitive polymers, as described herein.

CONTROLLED-RELEASE DOSAGE FORMS

[917] In some preferred embodiments, the dosage form comprises a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt of levorphanol, or a mixture thereof and controlled release material to render said dosage form suitable for extended release in a human

patient; said material substantially providing said release through diffusion-control from a matrix or a reservoir. A matrix diffusion-control system consists of a release rate controlling material such as a polymer with drug uniformly dissolved or dispersed in it. A reservoir diffusion-control system separates the drug compartment from a polymer membrane that presents a barrier to diffusion to yield a drug flux which may be either zero order or first order. Osmotic delivery extended release systems are a subset of diffusion-controlled dosage forms

[918] Extended release levorphanol may be formulated as a hydrophobic matrix dosage forms. Such compositions do not necessarily require a polymer as controlled release material to provide an extended release profile. In such dosage forms, the rate controlling means are the water insoluble material described herein. Release rate modifiers are usually incorporated to modulate the rate of release of drug.

[919] Extended release levorphanol may be formulated as a hydrophilic matrix, where swellable polymers serve as the controlled release material. The polymers are usually swellable polymers which expand upon contacting aqueous media for prolonged periods to form a gel layer which then modulates drug release. Such dosage forms control release rate of active through erosion and diffusion processes. Among the most widely used polymers are hypromellose, sodium alginate, polyethylene oxide and xanthan gum.

[920] Extended release levorphanol may be formulated as a reservoir dosage forms, which usually comprise a reservoir (which is the core tablet) often devoid of controlled release material and a coating layer which provides the controlled release means to the dosage form. The general method of release of active from such dosage forms is by diffusion. Reservoir dosage forms may comprise multiparticulates or may be a tablet core which is coated. The controlled release material is commonly acrylic copolymers or a cellulose, with pore formation provided by compounds such as hypromellose, as described herein

[921] Extended release levorphanol may be coated with controlled release polymer over a core, with the core itself in immediate release form or incorporating additional controlled release means of the active drug.

[922] All oral extended release pharmaceutical dosage forms of the invention are contemplated. The preparation of oral extended release pharmaceutical dosage forms has been described in the art - see for example, (i) Remington: the science of Pharmacy Practice, 21st Edition, 2006, Lippincott, Williams & Wilkins, Baltimore, MD; and (ii) Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form. Gibson, M (ed). CRC Press, 2001; and (iii) Niazi, S. Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products (Volume 1 of 6), CRC Press, 2004 (iiib) Niazi, S. Handbook of Pharmaceutical Manufacturing Formulations: Uncompressed Solid Products (Volume 2 of 6), CRC Press, 2004;; and (iv) Mollet, H, Grubenmann A, Payne H. Formulation Technology: Emulsions,

Suspensions, Solid Forms, Wiley-VCH, 2001; (v) Donald Wise, Handbook of Pharmaceutical Controlled Release Technology, CRC; 1st edition (August 15, 2000); (vi) Chheng-ju Kim, Controlled Release Dosage Form Design, Informa Healthcare (October 25, 1999); (vii) Xiaoling Li, Design of Controlled Release Drug Delivery Systems, McGraw-Hill Professional; 1 edition (November 3, 2005); (viii) Jean-Maurice Vergnaud, Controlled Drug Release Of Oral Dosage Forms, CRC (July 31, 1993); (ix) L.T. Fan and S.K. Singh. Controlled Release: A Quantitative Treatment, Springer-Verlag (July 1989); (x) Tapash K. Ghosh and Bhaskara R. Jasti (eds). Theory and Practice of Contemporary Pharmaceutics, CRC; 2Rev Ed edition (November 23, 2004); (xi) Xiaoling Li and Bhaskara R. Jasti (eds). Design of Controlled release Drug Delivery Systems; (xii) Anya M. Hillery, Andrew W. Lloyd and James Swarbrick (eds). Drug Delivery and Targeting: For Pharmacists and Pharmaceutical Scientists, CRC (September 27, 2001); (xiii) Ram I. Mahato. Pharmaceutical Dosage Forms and Drug Delivery, CRC; 1 edition (June 7, 2007); (xiv) Vasant V. Ranade and Manfred A. Hollinger. Drug Delivery Systems, Second Edition, CRC; 2 edition (August 26, 2003); (xv) Ashok Katdare and Mahesh Chaubal (eds). Excipient Development for Pharmaceutical, Biotechnology, and Drug Delivery Systems, Informa Healthcare; 1 edition (July 28, 2006); (xvi) Binghe Wang, Teruna J. Siahaan and Richard A. Soltero. Drug Delivery: Principles and Applications, Wiley-Interscience (March 28, 2005); (xvii) Liu et al, Diffusion-Controlled Drug Delivery Systems, Chapter 4, pages 107-137, and Wang et al, Dissolution Controlled Drug Delivery Systems, Chapter 5, pages 139-172, and Shojaei et al, Gastric Retentive Dosage Forms, Chapter 6, pages 173-201, and Srikonda et al, Osmotic Controlled Drug Delivery Systems, Chapter 7, pages 203-229, each in: Xiaoling Li, Design of Controlled Release Drug Delivery Systems (page 1-430), McGraw-Hill Professional, (November 3, 2005); (xix) Allen LV et al, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Lippincott Williams & Wilkins; 8 edition, August 1, 2004; and (xx) Mathiowitz E, Encyclopedia of Controlled Drug Delivery, Volume One and Two, John Wiley & Sons; illustrated edition, June 1999, all of which are hereby incorporated in their entirety by reference for all purposes.

[923] A wide variety of methods for the preparation of controlled release dosage form are known in the art. These methods may be employed for the preparation of controlled release dosage forms of the invention, including but not limited to: (i) Diffusion-controlled Products: in some embodiments such products employ a water-insoluble polymer to control the flow of water and the subsequent egress of dissolved drug from the dosage form. Both diffusion and dissolution processes are involved. In "reservoir" systems, a core of drug is coated with the polymer and, in "matrix" systems, the drug is dispensed throughout the matrix. Cellulose derivatives are commonly used in the reservoir systems, while the matrix systems may use methylacrylate-methyl methacrylate, polyvinyl chloride, hydrophilic polymers such as cellulose derivatives or fatty compounds including carnauba wax; (ii) Dissolution-Controlled Products: in some embodiments such products control the

rate of dissolution of the drug (and therefore absorption) by slowly soluble polymers or by microencapsulation. Once the coating is dissolved, the active drug becomes available for dissolution. By varying the thicknesses or amount of coating and its composition, the rate of active drug release can be controlled. Some dosage forms contain a portion of the total dose as in immediate release form to provide an early "pulse dose". Spheroid (pellet) dosage forms of diffusion or dissolution-controlled products can be encapsulated or prepared as a tablet. One potential advantage of encapsulated spheroid products is that the onset of absorption is less sensitive to gastric emptying, since the entry of the spheroids into the duodenum tends to be more uniform than with non-disintegrating extended-release tablet formulations; (iii) Erosion Products: in some embodiments, such products control the release of active drug by the erosion rate of a carrier matrix. The release rate is determined by the rate of erosion; (iv) Osmotic Pump Systems: in some embodiments such products control the rate of release of active drug by the constant inflow of water across a semipermeable membrane into a reservoir which contains an osmotic agent. The drug is either mixed with the agent or is located in a reservoir. The dosage form contains one or more small passageways, or through pores within a membrane through which drug in suspension or solution is pumped at a rate determined by the rate of entry of water due through osmotic pressure. The rate of release is can be kept relatively constant; (v) Ion Exchange Resins: in some embodiments, such products control the release of active drug bound to an ion exchange resin by release of drug in the ionic environment within the GI tract.

[924] The preparation of oral extended release pharmaceutical dosage forms has also been described in the art. Nonlimiting examples are provided in U.S. Patent No. 7427414; 7422758; 7413750; 7413749; 7387793; 7316821; 7229642; 7198803; 7189414; 7125567; 7074430; 7070806; 7052706; 6979463; 6936275; 6932981; 6905709; 6902742; 6793936; 6733783; 6730325; 6726931; 6716449; 6709677; 6699508; 6699506; 6692769; 6692766; 6682759; 6667060; 6645527; 6599529; 6579536; 6517868; 6440458; 6387404; 6344215; 6342250; 6326027; 6319520; 6306438; 6274599; 6254887; 6245356; 6245351; 6228398; 6221399; 6210714; 6162463; 6159501; 6156342; 6153623; 6143353; 6143322; 6132772; 6103261; 6074674; 6048548; 6039980; 6034085; 6030642; 6024982; 5952005; 5885616; 5869100; 5858408; 5795882; 5773025; 5681585; 5674533; 5656295; 5656291; 5639476; 5614218; 5591452; 5589190; 5582837; 5580578; 5549912; 5520931; 5512293; 5508042; 5500227; 5484607; 5472712; 5451409; 5399358; 5378474; 5334392; 5330766; 5314697; 5281415; 5262164; 5242910; 5229135; 5202128; 5198220; 5196202; 5186930; 5173299; 5128144; 5114718; 5084267; 5077051; 5047248; and 5043165, all of which are hereby incorporated in their entirety by reference for all purposes.

[925] **Matrix-Based Dosage Forms**

[926] A matrix system comprises homogeneously mixed active drug and pharmaceutically acceptable excipients. Matrix based extended release dosage forms can have a number of

advantages, including, manufacture with conventional equipment, reduced development costs, the ability to accommodate active drugs with a variety of physicochemical attributes and varying drug loads.

[927] In some embodiments, the extended release formulations of the present invention are provided as matrix-based dosage forms. Matrix formulations according to the invention may include hydrophilic, e.g., water-soluble, and/or hydrophobic, e.g., water-insoluble, polymers. The matrix formulations of the present invention may optionally be prepared with functional coatings, which may be enteric, e.g., exhibiting a pH-dependent solubility, or non-enteric, e.g., exhibiting a pH-independent solubility.

[928] Matrix formulations of the present invention may be prepared by using, for example, direct compression or wet granulation. A functional coating, as noted above, may then be applied in accordance with the invention. Additionally, a barrier or sealant coat may be applied over a matrix tablet core prior to application of a functional coating. The barrier or sealant coat may serve the purpose of separating an active ingredient from a functional coating, which may interact with the active ingredient, or it may prevent moisture from contacting the active ingredient.

[929] In a matrix-based dosage form in accordance with the present invention, the levorphanol and optional pharmaceutically acceptable excipient(s) are dispersed within a polymeric matrix, which typically comprises one or more water-soluble polymers and/or one or more water-insoluble polymers. The drug may be released from the dosage form by diffusion and/or erosion.

[930] In one embodiment, a matrix-based dosage form comprises levorphanol, a filler such as starch, lactose, or microcrystalline cellulose; a controlled-release polymer, such as hydroxypropyl methylcellulose or polyvinyl pyrrolidone; a disintegrant, such crospovidone, or starch; a lubricant, such as magnesium stearate or stearic acid; a surfactant, such as sodium lauryl sulfate or polysorbates; and a glidant, such as colloidal silicon dioxide or talc. The amounts and types of polymers, and the ratio of water-soluble polymers to water-insoluble polymers in the inventive formulations are generally selected to achieve a desired release profile of levorphanol. For example, by increasing the amount of water insoluble-polymer relative to the amount of water soluble-polymer, the release of the drug may, in some embodiments, be delayed or slowed. This is due, in part, to an increased impermeability of the polymeric matrix, and, in some cases, to a decreased rate of erosion during transit through the GI tract.

[931] The controlled-release dosage form may optionally include a controlled release material which is incorporated into a matrix along with the levorphanol, or which is applied as a controlled release material coating over a substrate comprising the drug (the term "substrate" encompassing beads, pellets, spheroids, tablets, tablet cores, etc). The controlled release material may be hydrophobic or hydrophilic as desired. The oral dosage form according to the invention may be provided as, for example, granules, spheroids, pellets or other multiparticulate formulations. An

amount of the multiparticulates which is effective to provide the desired dose of levorphanol over time may be placed in a capsule or may be incorporated in any other suitable oral solid form, e.g., compressed into a tablet. On the other hand, the oral dosage form according to the present invention may be prepared as a tablet core coated with a controlled-release coating, or as a tablet comprising a matrix of drug and controlled release material, and optionally other pharmaceutically desirable ingredients (e.g., diluents, binders, colorants, lubricants, etc.). The controlled release dosage form of the present invention may also be prepared as a bead formulation or an osmotic dosage formulation.

[932] In certain preferred embodiments of the present invention, the controlled-release formulation is achieved via a matrix (e.g. a matrix tablet) which includes a controlled-release material as set forth below. A dosage form including a controlled-release matrix provides in-vitro dissolution rates of levorphanol within the preferred ranges and that releases the levorphanol in a pH-dependent or pH-independent manner. The materials suitable for inclusion in a controlled-release matrix will depend on the method used to form the matrix. The oral dosage form may contain between 1% and 99% (by weight) of at least one hydrophilic or hydrophobic controlled release material.

[933] Any pharmaceutically acceptable hydrophobic or hydrophilic controlled-release material which is capable of imparting controlled-release of the levorphanol may be used in accordance with the present invention. Preferred controlled-release polymers include alkylcelluloses such as ethylcellulose, acrylic and methacrylic acid polymers and copolymers, and cellulose ethers, especially hydroxyalkylcelluloses (e.g., hydroxypropylmethylcellulose) and carboxyalkylcelluloses. Preferred acrylic and methacrylic acid polymers and copolymers include methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), glycidyl methacrylate copolymers, ethylcellulose, cellulose acetate cellulose propionate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly (methyl methacrylate), poly (ethyl methacrylate), poly (butyl methacrylate), poly (isobutyl methacrylate), and poly (hexyl methacrylate), poly (isodecyl methacrylate), poly (lauryl methacrylate), poly (phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl acrylate), poly (octadecyl acrylate), poly (ethylene), poly (ethylene) low density, poly (ethylene) high density, poly (ethylene oxide), poly (ethylene terephthalate), poly (vinyl isobutyl ether), poly (vinyl acetate), poly (vinyl chloride) or polyurethane, and/or mixtures thereof. Certain preferred embodiments utilize mixtures of any of the foregoing controlled-release materials in the matrices of the invention.

[934] The matrix also may include a binder. In such embodiments, the binder preferably contributes to the controlled-release of the levorphanol from the controlled-release matrix. Preferred

hydrophobic binder materials are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends. Preferred hydrophobic binder materials which may be used in accordance with the present invention include digestible, long chain (C₈-C₅₀, especially C₁₂-C₄₀), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils, natural and synthetic waxes and polyalkylene glycols. Preferably, the hydrophobic binder materials useful in the invention have a melting point from about 30 to about 200 °C, preferably from about 45 to about 90 °C. When the hydrophobic material is a hydrocarbon, the hydrocarbon preferably has a melting point of between 25 and 90 °C. Of the long chain (C₈-C₅₀) hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to 98% (by weight) of at least one digestible, long chain hydrocarbon.

[935] The oral dosage form contains up to 98% (by weight) of at least one polyalkylene glycol. The hydrophobic binder material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic acid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about 30 to about 100 °C.

[936] In certain preferred embodiments, a combination of two or more hydrophobic binder materials are included in the matrix formulations. If an additional hydrophobic binder material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive.

[937] One particular suitable controlled-release matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one C₁₂-C₃₆, preferably C₁₄-C₂₂, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The hydroxyalkyl cellulose is preferably a hydroxy (C₁ to C₆) alkyl cellulose, such as hydroxypropyl cellulose, hydroxypropyl methylcellulose and, especially, hydroxyethyl cellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of the levorphanol release required. The aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In more preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of the levorphanol release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably

contains between 20% and 50% (by wt) of the aliphatic alcohol. When a polyalkylene glycol is present in the oral dosage form, then the combined weight of the aliphatic alcohol and the polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

[938] In one preferred embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the levorphanol from the formulation. A ratio of the hydroxyalkyl cellulose to the aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being more preferred.

[939] The polyalkylene glycol maybe, for example, polypropylene glycol or, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1,000 and 15,000 especially between 1,500 and 12,000.

[940] Another suitable controlled-release matrix comprises an alkylcellulose (especially ethylcellulose), a C₁₂ to C₃₆ aliphatic alcohol and, optionally, a polyalkylene glycol.

[941] In one embodiment of the present invention, one or more release rate modifiers may be incorporated into the formulation, including, without limitation, hydroxypropyl methylcellulose, cellulose acetate, powdered cellulose, cellulose acetate phthalate, hydroxyethyl cellulose, silicified microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, low-substituted hydroxypropyl cellulose, carboxymethylcellulose, carboxymethylcellulose calcium, hypromellose acetate succinate, hypromellose phthalate, and ethylcellulose, and mixture thereof. Release rate modifiers can also have additional useful properties that optimize the formulation. In addition to the above ingredients, a controlled-release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

[942] In order to facilitate the preparation of a solid, controlled-release oral dosage form according to the invention there is provided, in a further aspect of the present invention, a process for the preparation of a solid, controlled-release oral dosage form according to the present invention comprising incorporating the levorphanol or a salt thereof in a controlled-release matrix. Incorporation in the matrix may be effected, for example, by (a) forming granules comprising at least one hydrophobic and/or hydrophilic material as set forth above (e.g., a water soluble hydroxyalkyl cellulose) together with the levorphanol; (b) mixing the at least one hydrophobic and/or hydrophilic material-containing granules with at least one C₁₂-C₃₆ aliphatic alcohol, and (c) optionally, compressing and shaping the granules. The granules may be formed by any of the procedures well-known to those skilled in the art of pharmaceutical formulation. For example, in one preferred method, the granules may be formed by wet granulating hydroxyalkyl cellulose/levorphanol with water. In a particular preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially

between 1.75 and 3.5 times, the dry weight of the levorphanol.

- [943] In certain embodiments, the dosage form comprises a plurality of matrices described above.
- [944] The matrices of the present invention may also be prepared via a melt pelletization technique. In such circumstance, the levorphanol in finely divided form is combined with a binder (also in particulate form) and other optional inert ingredients, and thereafter the mixture is pelletized, e.g., by mechanically working the mixture in a high shear mixer to form the pellets (granules, spheres). Thereafter, the pellets (granules, spheres) may be sieved in order to obtain pellets of the requisite size. The binder material is preferably in particulate form and has a melting point above about 40 °C. Suitable binder substances include, for example, hydrogenated castor oil, hydrogenated vegetable oil, other hydrogenated fats, fatty alcohols, fatty acid esters, fatty acid glycerides, and the like.
- [945] Controlled-release matrices can also be prepared by, e.g., melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic binder material, e.g. a wax, and incorporating a powdered drug therein. To obtain a controlled release dosage form, it may be necessary to incorporate a hydrophobic controlled release material, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic binder material.
- [946] The hydrophobic binder material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve controlled release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like binder substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).
- [947] In addition to the above ingredients, a controlled release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the particulate if desired. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.
- [948] The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the levorphanol, together with a controlled release material and preferably a binder material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded, e.g., using a twin-screw extruder, to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The strands are cooled and cut into multiparticulates. The multiparticulates

are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and provides controlled release of the therapeutically active agent for a time period of from about 6 to at least about 24 hours.

[949] An optional process for preparing the melt extruded formulations of the present invention includes directly metering into an extruder a hydrophobic controlled release material, a therapeutically active agent, and an optional binder material; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

[950] Plasticizers, such as those described herein, may be included in melt-extruded matrices. The plasticizer is preferably included as from about 0.1 to about 30% by weight of the matrix. Other pharmaceutical excipients, e.g., talc, mono or poly saccharides, colorants, flavorants, lubricants and the like may be included in the controlled release matrices of the present invention as desired. The amounts included will depend upon the desired characteristic to be achieved.

[951] The diameter of the extruder aperture or exit port can be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

[952] A melt extruded multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For purposes of the present invention, the terms "melt-extruded multiparticulate(s)" and "melt-extruded multiparticulate system(s)" and "melt-extruded particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic controlled release material as described herein. Preferably the melt-extruded multiparticulates will be of a range of from about 0.1 to about 12 mm in length and have a diameter of from about 0.1 to about 5 mm. In addition, it is to be understood that the melt-extruded multiparticulates can be any geometrical shape within this size range. Alternatively, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

[953] In one preferred embodiment, oral dosage forms are prepared that include an effective amount of melt-extruded multiparticulates within a capsule. For example, a plurality of the melt-extruded multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by gastric fluid.

[954] In another preferred embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tableting equipment using standard techniques.

Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, 21st ed., 2005 incorporated by reference herein.

[955] In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Pat. No. 4,957,681, hereby incorporated by reference.

[956] Optionally, the controlled-release matrix multiparticulate systems or tablets can be coated, or the gelatin capsule can be further coated, with a controlled release coating such as the controlled release coatings described above. Such coatings preferably include a sufficient amount of hydrophobic and/or hydrophilic controlled-release material to obtain a weight gain level from about 2 to about 25 percent, although the overcoat may be greater depending upon, e.g., the physical properties of the drug and the desired release rate, among other things.

[957] The dosage forms of the present invention may further include combinations of melt-extruded multiparticulates containing one or more drugs. Furthermore, the dosage forms can also include an amount of an immediate release therapeutically active agent for prompt therapeutic effect. The immediate release therapeutically active agent may be incorporated, e.g., as separate pellets within a gelatin capsule, or may be coated on the surface of, e.g., melt extruded multiparticulates. The unit dosage forms of the present invention may also contain a combination of, e.g., controlled release beads and matrix multiparticulates to achieve a desired effect.

[958] The controlled-release formulations of the present invention preferably slowly release the therapeutically active agent, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The controlled-release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of controlled-release material, by varying the amount of plasticizer relative to other matrix constituents, hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

[959] In other embodiments of the invention, melt-extruded formulations are prepared without the inclusion of the therapeutically active agent, which is added thereafter to the extrudate. Such formulations typically will have the therapeutically active agent blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation. Such formulations may be advantageous, for example, when the therapeutically active agent included in the formulation is sensitive to temperatures needed for softening the hydrophobic material and/or the retardant material.

[960] Typical melt-extrusion production systems suitable for use in accordance with the present invention include a suitable extruder drive motor having variable speed and constant torque control, start-stop controls, and ammeter. In addition, the production system will include a temperature control console which includes temperature sensors, cooling means and temperature indicators throughout the length of the extruder. In addition, the production system will include an extruder

such as twin-screw extruder which consists of two counter-rotating intermeshing screws enclosed within a cylinder or barrel having an aperture or die at the exit thereof. The feed materials enter through a feed hopper and are moved through the barrel by the screws and are forced through the die into strands which are thereafter conveyed such as by a continuous movable belt to allow for cooling and being directed to a pelletizer or other suitable device to render the extruded ropes into the multiparticulate system. The pelletizer can consist of rollers, fixed knife, rotating cutter and the like. Suitable instruments and systems will be apparent to those of ordinary skill in the art.

[961] A further aspect of the invention is related to the preparation of melt-extruded multiparticulates as set forth above in a manner which controls the amount of air included in the extruded product. By controlling the amount of air included in the extrudate, the release rate of the therapeutically active agent from the, e.g., multiparticulate extrudate, can be altered significantly. In certain embodiments, the pH dependency of the extruded product can be altered as well.

[962] Thus, in a further aspect of the invention, the melt-extruded product is prepared in a manner which substantially excludes air during the extrusion phase of the process. This may be accomplished, for example, by using a Leistritz extruder having a vacuum attachment. In certain preferred embodiments the extruded multiparticulates prepared according to the invention using the Leistritz extruder under vacuum provides a melt-extruded product having different physical characteristics. In particular, the extrudate is substantially non-porous when magnified, e.g., using a scanning electron microscope which provides an SEM (scanning electron micrograph). Such substantially non-porous formulations provide a faster release of the therapeutically active agent, relative to the same formulation prepared without vacuum. SEMs of the multiparticulates prepared using an extruder under vacuum appear very smooth, and the multiparticulates tend to be more robust than those multiparticulates prepared without vacuum.

[963] The oral dosage form contains up to 98% (by weight) of at least one polyalkylene glycol.

[964] In certain formulations, the use of extrusion under vacuum provides an extruded multiparticulate product which is more pH-dependent than its counterpart formulation prepared without vacuum. Alternatively, the melt-extruded product is prepared using a Werner-Pfleiderer twin screw extruder.

[965] In certain embodiments, a spheronizing agent is added to a granulate or multiparticulates of the present invention and then spheronized to produce controlled release spheroids. The spheroids are then optionally overcoated with a controlled release coating by methods such as those described herein.

[966] Spheronizing agents which may be used to prepare the multiparticulate formulations of the present invention include any art-known spheronizing agent. Cellulose derivatives are preferred, and microcrystalline cellulose is especially preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel™ PH 101. The spheronizing agent is preferably included as

about 1 to about 99% of the multiparticulate by weight.

- [967] In addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkylcellulose, such as hydroxypropylcellulose, are preferred.
- [968] In addition to the levorphanol and spheronizing agent, the multiparticulate formulations of the present invention may include a controlled release material such as those described hereinabove. Preferred controlled-release materials for inclusion in the multiparticulate formulations include acrylic and methacrylic acid polymers or copolymers, and ethylcellulose. When present in the formulation, the controlled-release material will be included in amounts of from about 1 to about 80% of the multiparticulate, by weight. The controlled-release material is preferably included in the multiparticulate formulation in an amount effective to provide controlled release of the levorphanol from the multiparticulate.
- [969] Pharmaceutical processing aids such as binders, diluents, and the like may be included in the multiparticulate formulations. Amounts of these agents included in the formulations will vary with the desired effect to be exhibited by the formulation.
- [970] Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in the Handbook of Pharmaceutical Excipients, APhA Publications; 5 edition (January 5, 2006) incorporated by reference herein.
- [971] The multiparticulates may be overcoated with a controlled-release coating including a controlled-release material such as those described hereinabove. The controlled-release coating is applied to a weight gain of from about 5 to about 30%. The amount of the controlled-release coating to be applied will vary according to a variety of factors, e.g., the composition of the multiparticulate and the chemical and/or physical properties of the drug.
- [972] Matrix multiparticulates may also be prepared by granulating the spheronizing agent together with the levorphanol, e.g. by wet granulation. The granulate is then spheronized to produce the matrix multiparticulates. The matrix multiparticulates are then optionally overcoated with the controlled release coating by methods such as those described hereinabove. Another method for preparing matrix multiparticulates, for example, by (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and the levorphanol or the levorphanol salt; (b) mixing the hydroxyalkyl cellulose containing granules with at least one C₁₂-C₃₆ aliphatic alcohol; and (c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxyalkyl cellulose/levorphanol with water. In a more preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the levorphanol.

- [973] In yet other alternative embodiments, a spheronizing agent, together with the active ingredient can be spheronized to form spheroids. Microcrystalline cellulose is preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel™ PH 101. In such embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxy propyl cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate co-polymer, or ethyl cellulose. In such embodiments, the controlled release material coating will generally include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.
- [974] Spheroids of the present invention comprise a matrix formulation as described above or bead formulation as described hereinafter having a diameter of between 0.1 mm and 2.5 mm, especially between 0.5 mm and 2 mm.
- [975] The spheroids are preferably film coated with a controlled release material that permits release of the levorphanol (or salt) at a controlled rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other stated properties, the in-vitro release rate outlined above. The controlled-release coating formulations of the present invention preferably produce a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.
- [976] **Preparation of Coated Bead Formulations**
- [977] In certain preferred embodiments of the present invention the oral solid controlled release dosage form of the present invention comprises a plurality of coated substrates, e.g., inert pharmaceutical beads such as nu pariel 18/20 beads. An aqueous dispersion of hydrophobic material is used to coat the beads to provide for the controlled release of the levorphanol. In certain preferred embodiments a plurality of the resultant stabilized solid controlled-release beads may be placed in a gelatin capsule in an amount sufficient to provide an effective controlled-release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media.
- [978] The stabilized controlled-release bead formulations of the present invention slowly release the levorphanol, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The controlled-release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the aqueous dispersion of hydrophobic controlled release material, altering the manner in which the plasticizer is added to the aqueous dispersion of hydrophobic controlled release material, by varying the amount of plasticizer relative to hydrophobic controlled release material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be

modified, for example, by increasing or decreasing the thickness of the controlled release coating.

[979] Substrates coated with a therapeutically active agent are prepared, e.g. by dissolving the therapeutically active agent in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wurster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the levorphanol to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropyl methylcellulose, etc. with or without colorant (e.g., Opadry™) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the substrate. The resultant coated substrate may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from the hydrophobic controlled-release coating.

[980] An example of a suitable barrier agent is one which comprises hydroxypropyl methylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

[981] The substrates may then be overcoated with an aqueous dispersion of the hydrophobic controlled release material as described herein. The aqueous dispersion of hydrophobic controlled release material preferably further includes an effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat™ or Surelease™, may be used. If Surelease™ is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit™ can be used.

[982] The coating solutions of the present invention preferably contain, in addition to the film-former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, color can be added to Aquacoat™ via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to water soluble polymer solution and then using low shear to the plasticized Aquacoat™. Alternatively, any suitable method of providing color to titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

[983] The plasticized aqueous dispersion of hydrophobic controlled release material may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the aqueous dispersion of hydrophobic material to obtain a predetermined controlled-release of said therapeutically active agent when said coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the therapeutically active agent, the

manner of incorporation of the plasticizer, etc. After coating with the hydrophobic controlled release material, a further overcoat of a film-former, such as Opadry™, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

[984] Another method of producing controlled release bead formulations suitable for about 24-hour administration is via powder layering. The powder-layered beads are prepared by spraying an aqueous binder solution onto inert beads to provide a tacky surface, and subsequently spraying a powder that is a homogenous mixture of the levorphanol and hydrous lactose impalpable onto the tacky beads. The beads are then dried and coated with a hydrophobic material such as those described hereinabove to obtain the desired release of drug when the final formulation is exposed to environmental fluids. An appropriate amount of the controlled release beads are then, e.g. encapsulated to provide a final dosage form which provides effective plasma concentrations for the intended duration of effect or dosing frequency.

[985] **Controlled Release Osmotic Dosage**

[986] In another embodiment, the extended release formulations of the present invention are provided as osmotic pump dosage forms. In an osmotic pump dosage form, a core containing the levorphanol and optionally one or more osmotic excipients is typically encased by a selectively permeable membrane having at least one orifice. The selectively permeable membrane is generally permeable to water, but impermeable to the drug. When the system is exposed to GI fluids, water penetrates through the selectively permeable membrane into the core containing the drug and optional osmotic excipients. The osmotic pressure increases within the dosage form. Consequently, the drug is released through the orifice in an attempt to equalize the osmotic pressure across the selectively permeable membrane. In more complex pumps, the dosage form may contain two internal compartments in the core. The first compartment contains the drug and the second compartment may contain a polymer, which swells on contact with aqueous fluid. After ingestion, this polymer swells into the drug-containing compartment, diminishing the volume occupied by the drug, thereby delivering the drug from the device at a controlled rate over an extended period of time. Such dosage forms are often used when a zero order release profile is desired.

[987] Osmotic pumps are well known in the art. The osmotic pumps useful in accordance with the present invention may be formed by compressing a tablet of an osmotically active drug, or an osmotically inactive drug in combination with an osmotically active agent, and then coating the tablet with a selectively permeable membrane which is permeable to an exterior aqueous-based fluid but impermeable to the drug and/or osmotic agent.

[988] One or more delivery orifices may be drilled through the selectively permeable membrane wall. Alternatively, one or more orifices in the wall may be formed by incorporating leachable pore-forming materials in the wall. In operation, the exterior aqueous-based fluid is imbibed through the

selectively permeable membrane wall and contacts the drug to form a solution or suspension of the drug. The drug solution or suspension is then pumped out through the orifice as fresh fluid is imbibed through the selectively permeable membrane.

[989] As used herein, "wall" is an exterior wall and it surrounds and defines an internal area or compartment of the dosage form.

[990] The semipermeable membrane requires certain properties, such as impermeability to the passage of active drug, and maintenance of dimensional integrity to provide a steady driving force during drug release. Typical materials for the selectively permeable membrane include selectively permeable polymers known in the art to be useful in osmosis and reverse osmosis membranes, such as cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, agar acetate, amylose triacetate, beta glucan acetate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, polyamides, polyurethanes, sulfonated polystyrenes, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethyl aminoacetate, cellulose acetate ethyl carbamate, cellulose acetate chloracetate, cellulose dipalmitate, cellulose dioctanoate, cellulose dicaprylate, cellulose dipentanlate, cellulose acetate valerate, cellulose acetate succinate, cellulose propionate succinate, methyl cellulose, cellulose acetate p-toluene sulfonate, cellulose acetate butyrate, lightly cross-linked polystyrene derivatives, cross-linked poly(sodium styrene sulfonate), poly(vinylbenzyltrimethyl ammonium chloride), cellulose acetate, cellulose diacetate, cellulose triacetate, and/or mixtures thereof.

[991] The osmotic agents that can be used in the pump are typically soluble in the fluid that enters the device following administration, resulting in an osmotic pressure gradient across the selectively permeable wall against the exterior fluid. Suitable osmotic agents include, but are not limited to, magnesium sulfate, calcium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, sodium sulfate, d-mannitol, urea, sorbitol, inositol, raffinose, sucrose, glucose, hydrophilic polymers such as cellulose polymers, or inorganic salts of carbohydrates, mixtures thereof.

[992] The osmotic pump dosage form may contain a second compartment containing a swellable polymer. Suitable swellable polymers typically interact with water and/or aqueous biological fluids, which causes them to swell or expand to an equilibrium state. Acceptable polymers exhibit the ability to swell in water and/or aqueous biological fluids, retaining a significant portion of such imbibed fluids within their polymeric structure, so as to increase the hydrostatic pressure within the dosage form. The polymers may swell or expand to a very high degree, usually exhibiting a 2- to 40-fold volume increase. The polymers can be non-cross-linked or cross-linked. In one embodiment, the swellable polymers are hydrophilic polymers. Suitable polymers include, but are not limited to, poly(hydroxy alkyl methacrylate) having a molecular weight of from 30,000 to 5,000,000; kappa-carrageenan; polyvinylpyrrolidone having a molecular weight of from 10,000 to

360,000; anionic and cationic hydrogels; polyelectrolyte complexes; poly(vinyl alcohol) having low amounts of acetate, cross-linked with glyoxal, formaldehyde, or glutaraldehyde, and having a degree of polymerization from 200 to 30,000; a mixture including methyl cellulose, cross-linked agar and carboxymethyl cellulose; a water-insoluble, water-swellaable copolymer produced by forming a dispersion of finely divided maleic anhydride with styrene, ethylene, propylene, butylene or isobutylene; water-swellaable polymers of N-vinyl lactams; and/or mixtures of any of the foregoing.

[993] The term "orifice" as used herein comprises means and methods suitable for releasing the drug from the dosage form and includes aperture, passageway, bore, pore, porous element through which the drug can be pumped, diffuse or migrate through a fiber, capillary tube, porous overlay, porous insert, microporous member, and porous composition. Orifice includes one or more apertures orifices that have been bored through the selectively permeable membrane by mechanical procedures. Alternatively, an orifice may be formed by incorporating an erodible element, such as a gelatin plug, in the selectively permeable membrane. In such cases, the pores of the selectively permeable membrane forms a "passageway" for the passage of the drug. The passageway includes also a compound that erodes or is leached from wall in the fluid environment of use to produce at least one passageway. Representative compounds for forming a passageway include erodible poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable compounds such as fluid-removable pore-forming polysaccharides, acids, salts or oxides. A passageway can be formed by leaching a compound from wall such as sorbitol, sucrose, lactose, maltose, or fructose, to form a controlled-release dimensional pore-passageway. The passageway can have any shape, such as round, triangular, square and elliptical, for assisting in the release of levorphanol and, optionally, other included releasable active agents from the dosage form. The dosage form can be manufactured with one or more passageways on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are disclosed in U.S. Patent No. 3,845,770, 3,916,899 4,063,064, 4,088,864, 4,200,098 and 4,285,987. Other passageway formulations are method of making same are described in the art. The orifice or passage way may be of any size and surface area. Osmotic delivery systems of the invention include at least one orifice or passageway in the dosage form. When the orifice is one or more apertures orifices that have been bored through the selectively permeable membrane by mechanical procedures, preferably, the orifice size is preferably about 0.2 mm to about 1.5 mm, more preferably, about 0.4 mm to about 1.2 mm, and most preferably, about 0.5 mm to about 0.8 mm. The osmotic pumps useful in accordance with this invention may be manufactured by techniques known in the art. For example, the drug and other ingredients may be milled together and pressed into a solid having the desired dimensions (e.g., corresponding to the first compartment). The swellaable polymer is then formed, placed in contact with the drug, and both are surrounded with the

selectively permeable agent. If desired, the drug component and polymer component may be pressed together before applying the selectively permeable membrane. The selectively permeable membrane may be applied by any suitable method, for example, by molding, spraying, or dipping.

[994] A variety of parameters may be modified to achieve the desired release profile (for example, rate of release, a zero order release, first order release, delayed onset,) by controlling key variables in the manufacture of the osmotic dosage form of the invention, including, without limitation, the orifice size, active drug and excipient particle size, solubility of active drug, osmotic pressure, nature and thickness of the semipermeable membrane.

[995] The osmotic pressure impacts on the rate of release from the osmotic dosage form. In order to achieve zero order release, it is important to maintain a saturated solution of the active drug. Frequently, the osmotic pressure generated by the saturated drug solution may not be sufficient to achieve the required driving force, requiring the addition of osmogens such as a bicarbonate salt to provide the required osmotic gradient and to prevent blockage of the orifice by the drug.

[996] The release rate of the active drug depends in part on its solubility inside the drug delivery system. Therefore, the active drug should have sufficient solubility to be delivered using this dosage form. In the case levorphanol salts of low-solubility compounds, alternative methods may be utilized, including use of swellable polymers or drug solubility modifiers, such as cyclodextrin which may be co-compressed with the active drug. Alternatively, other salt forms of the active drug may be used to modify solubility.

[997] The osmotic dosage forms preferably include a bilayer core comprising a drug layer and a delivery or push layer, wherein the bilayer core is surrounded by a semipermeable wall and optionally having at least one passageway disposed therein. In certain embodiments, the bilayer core comprises a drug layer with the levorphanol or a salt thereof and a displacement or push layer. In certain preferred embodiments the drug layer may also comprise at least one hydrophilic polymers. Hydrophilic polymers include osmopolymers, hydrogels and osmogels. They are maintain a concentration gradient across the membrane, create a driving force for the imbibement of water and assist in maintaining the uniformity of the active drug in the hydrated dosage form. In some embodiments, the hydrophilic polymers is a polymer hydrogel. The polymer hydrogel may have an average molecular weight of between about 500 and about 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula $(C_6H_{12}O_5)_n \cdot H_2O$, wherein n is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) represented by, e.g., a poly(ethylene oxide) and a poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000 or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium or potassium, the alkyl is methyl, ethyl, propyl,

or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 500,000 number-average molecular weight.

[998] In certain preferred embodiments of the present invention, the delivery or push layer comprises an osmopolymer. Examples of an osmopolymer include but are not limited to a member selected from the group consisting of a polyalkylene oxide and a carboxyalkylcellulose. The polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. The polyalkylene oxide may be a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 average molecular weight, polyethylene oxide comprising a 5,000,000 average molecular weight, polyethylene oxide comprising a 7,000,000 average molecular weight, cross-linked polymethylene oxide possessing a 1,000,000 average molecular weight, and polypropylene oxide of 1,200,000 average molecular weight. Typical osmopolymer carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkylcellulose, sodium carboxymethyl cellulose, potassium carboxymethyl cellulose, sodium carboxyethylcellulose, lithium carboxymethyl cellulose, sodium carboxyethylcellulose, carboxyalkyl hydroxyalkylcellulose, carboxymethyl hydroxyethyl cellulose, carboxyethyl hydroxyethylcellulose and carboxymethyl hydroxypropylcellulose. The osmopolymers used for the displacement layer exhibit an osmotic pressure gradient across the semipermeable wall. The osmopolymers imbibe fluid into dosage form, thereby swelling and expanding as an osmotic hydrogel (also known as osmogel), whereby they push the levorphanol or pharmaceutically acceptable salt thereof from the osmotic dosage form.

[999] The push layer may also include one or more osmotically effective compounds also known as osmagents and as osmotically effective solutes. They imbibe an environmental fluid, for example, from the gastrointestinal tract, into dosage form and contribute to the delivery kinetics of the displacement layer. Examples of osmotically active compounds comprise a member selected from the group consisting of osmotic salts and osmotic carbohydrates. Examples of specific osmagents include but are not limited to sodium chloride, potassium chloride, magnesium sulfate, lithium phosphate, lithium chloride, sodium phosphate, potassium sulfate, sodium sulfate, potassium phosphate, glucose, fructose and maltose.

[1000] The push layer may optionally include a hydroxypropylalkylcellulose represented by a member selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropyl ethylcellulose, hydroxypropyl isopropylcellulose, hydroxypropyl butylcellulose, and hydroxypropyl pentylcellulose.

[1001] The push layer optionally may comprise a nontoxic colorant or dye. Examples of colorants or dyes include but are not limited to Food and Drug Administration Colorant (FD&C), such as FD&C No. 1 blue dye, FD&C No. 4 red dye, red ferric oxide, yellow ferric oxide, titanium dioxide,

carbon black, and indigo.

- [1002] The push layer which is devoid of levorphanol may also optionally comprise an antioxidant to inhibit the oxidation of the excipients of the push layer. Some nonlimiting examples of antioxidants include but are not limited to a member selected from the group consisting of ascorbic acid, ascorbyl palmitate, edetate disodium (EDTA), citric acid, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaretic acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphatocopherol, propylgallate, other chelating agents, other hindered phenols and aromatic amines.
- [1003] In certain alternative embodiments, the dosage form comprises a homogenous core comprising the levorphanol or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable polymer (e.g., polyethylene oxide), optionally a disintegrant (e.g., polyvinylpyrrolidone), optionally an absorption enhancer (e.g., a fatty acid, a surfactant, a chelating agent, a bile salt, etc.). The homogenous core is surrounded by a semipermeable wall having a passageway (as defined above) for the release of the levorphanol or pharmaceutically acceptable salt thereof.
- [1004] In certain embodiments, the semipermeable wall comprises a member selected from the group consisting of a cellulose ester polymer, a cellulose ether polymer and a cellulose ester-ether polymer. Representative wall polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkenylates, and mono-, di- and tricellulose alkynylates. The poly(cellulose) used for the present invention comprises a number-average molecular weight of 20,000 to 7,500,000.
- [1005] Additional semipermeable polymers for the purpose of this invention comprise acetaldehyde dimethylcellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose diacetate, propylcarbamate, cellulose acetate diethylaminoacetate; semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable cross-linked polymer formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Patent No. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,876; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable crosslinked polystyrenes; semipermeable cross-linked poly(sodium styrene sulfonate); semipermeable crosslinked poly(vinylbenzyltrimethyl ammonium chloride); and semipermeable polymers possessing a fluid permeability of 2.5×10^{-8} to 2.5×10^{-2} (cm²/hr.atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. Other polymers useful in the present invention are known in the art in U.S. Patent No. 3,845,770; 3,916,899 and 4,160,020; and in Handbook of Common Polymers, Scott, J. R. and W. J. Roff, 1971, CRC Press, Cleveland, Ohio.

- [1006] In certain embodiments, preferably the semipermeable wall is nontoxic, inert, and it maintains its physical and chemical integrity during the dispensing life of the drug. In certain embodiments, the dosage form comprises a binder as described above.
- [1007] In certain embodiments, the dosage form comprises a lubricant, which may be used during the manufacture of the dosage form to prevent sticking to die wall or punch faces. Examples of lubricants include but are not limited to magnesium stearate, sodium stearate, stearic acid, calcium stearate, magnesium oleate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, and magnesium palmitate.
- [1008] **Coatings**
- [1009] The dosage forms of the present invention may optionally be coated with one or more coatings suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal fluid. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. Other preferred embodiments include a pH-dependent coating that releases the levorphanol in desired areas of the gastrointestinal (GI) tract, e.g., the stomach or small intestine, such that an absorption profile is provided which is capable of providing at least about twelve hour and preferably up to twenty-four hour analgesia to a patient. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.
- [1010] Formulations according to the invention that utilize pH-dependent coatings may also impart a repeat-action effect whereby unprotected drug is coated over an enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include a controlled release material such as, e.g., shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.
- [1011] In another preferred embodiment, the present invention is related to a stabilized solid controlled dosage form comprising the levorphanol coated with a hydrophobic controlled release material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion.
- [1012] In certain preferred embodiments, the controlled release coating is derived from an aqueous dispersion of the hydrophobic controlled release material. The coated substrate containing the levorphanol (e.g., a tablet core or inert pharmaceutical beads or spheroids) is then cured until an endpoint is reached at which the substrate provides a stable dissolution. The curing endpoint may be

determined by comparing the dissolution profile (curve) of the dosage form immediately after curing to the dissolution profile (curve) of the dosage form after exposure to accelerated storage conditions of, e.g., at least one month at a temperature of 40 °C and a relative humidity of 75%.

[1013] In preferred embodiments, the controlled release coatings include a plasticizer such as those described herein.

[1014] In certain embodiments, it is necessary to overcoat the substrate comprising the levorphanol with a sufficient amount of the aqueous dispersion of e.g., alkylcellulose or acrylic polymer, to obtain a weight gain level from about 2 to about 50%, e.g., about 2 to about 25% in order to obtain a controlled-release formulation. The overcoat may be lesser or greater depending upon the physical properties of the therapeutically active agent and the desired release rate, the inclusion of plasticizer in the aqueous dispersion and the manner of incorporation of the same, for example.

[1015] **Alkylcellulose Polymers**

[1016] Cellulosic materials and polymers, including alkylcelluloses are controlled release materials well suited for coating the substrates, e.g., beads, tablets, etc. according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or on any combination, as all or part of a hydrophobic coating according to the invention.

[1017] One commercially-available aqueous dispersion of ethylcellulose is Aquacoat™. Aquacoat™ is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat™ with a suitable plasticizer prior to use.

[1018] Another aqueous dispersion of ethylcellulose is commercially available as Surelease™. This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

[1019] **Acrylic Polymers**

[1020] In other preferred embodiments of the present invention, the controlled release material comprising the controlled-release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate

copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

[1021] In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

[1022] In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

[1023] Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit™. There are several different types of Eudragit™. For example, Eudragit™ E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit™ L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit™ S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit™ RL and Eudragit™ RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit™ RL and RS are pH-independent.

[1024] In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available as Eudragit™ RL30D and Eudragit™ RS30D, respectively. Eudragit™ RL30D and Eudragit™ RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit™ RL30D and 1:40 in Eudragit™ RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit™ RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

[1025] The Eudragit™ RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a controlled-release formulation having a desirable dissolution profile. Desirable controlled-release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit™ RL, 50% Eudragit™ RL and 50% Eudragit™ RS, and 10% Eudragit™ RL:Eudragit™ 90% RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit™ L.

[1026] **Plasticizers**

[1027] In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic controlled release material, the inclusion of an effective amount of a plasticizer in

the aqueous dispersion of hydrophobic material will further improve the physical properties of the controlled-release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing controlled-release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

- [1028] Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.
- [1029] Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit™ RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.
- [1030] In certain embodiments, the addition of a small amount of talc to the controlled release coating reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.
- [1031] The release of the therapeutically active agent from the controlled-release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic controlled release material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.
- [1032] The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.
- [1033] The controlled-release coatings of the present invention can also include erosion-promoting agents such as starch and gums.
- [1034] The controlled-release coatings of the present invention can also include materials useful for

making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

[1035] The release-modifying agent may also comprise a semi-permeable polymer. In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

[1036] These and other embodiments of the present invention will readily occur to those of ordinary skill in the art in view of the disclosure herein.

[1037] **Targeted Gastrointestinal Delivery**

[1038] Targeted delivery of the levorphanol dosage form of the present invention for release and subsequent absorption are achieved to provide delayed onset, extended release dosage forms and other extended release dosage forms. In addition, conventional extended release products which release the active drug rapidly on ingestion may be coated or embedded with further controlled release material designed to provide a lag time before release of drug upon ingestion.

[1039] A wide variety of methods for the preparation of delayed onset dosage form are known in the art. These methods may be employed for the preparation of delayed onset dosage forms of the invention, including but not limited to: (i) Prodrug approach: in some embodiments such products control the rate of release of active drug by azo-bond conjugates, glycoside conjugates, glucuronide conjugates, cyclodextrin conjugates, dextran conjugates, polypeptide conjugates; (ii) Polymeric coating: in some embodiments, such products control the release of active drug by coating with pH sensitive polymers and coating with biodegradable polymers; (iii) Embedding in matrices: in some embodiments, such products control the release of active drug by embedding in pH sensitive matrices, embedding in biodegradable hydrogels and matrices (e.g., amylose, chondroitin sulfate, chitosan, inulin, dextran, guar gum, pectin). Other approaches include the use of time dependent systems, Pulsincap[™], CODDES[™] and intestinal pressure controlled delivery systems.

[1040] In some embodiments, the need for a rapid initial dose may require that a portion of the dose (e.g., up to about 1%, or 3%, or 5%, or 7%, or 10%, or 12%, or 15%, or 17%, or 20%, or 22%, or 25%, or 30%) is provided without delay as an immediate release dosage form (e.g., without limitation, a capsule within a capsule, a tablet within a capsule, an immediate release overcoat on a tablet or a capsule, an immediate release solution, suspension, powder or matrix within an extended release capsule) in order to achieve, for example, immediate symptom relief

[1041] An extended release tablet or capsule formulation may be overcoated with one or more polymers to provide levorphanol release in the appropriate gastrointestinal environment (defined, in some embodiments by location in the GI tract, pH at the point of release, osmotic pressure at the point of release, hydration, microbial flora, and/or the time after ingestion at the point of release).

[1042] In some embodiments, the dosage form of the invention is in the form of a compressed tablet, or a capsule, said tablet or capsule coated with a polymer to retard or delay its release to

achieve the objectives of the invention, said polymers including polymethacrylates (copolymerisate of methacrylic acid and either methylmethacrylate or ethyl acrylate (Eudragit™), cellulose based polymers e.g. cellulose acetate phthalate (Aquateric™) or polyvinyl derivatives e.g. polyvinyl acetate phthalate (Coateric™).

[1043] In some embodiments, the dosage form of the invention is in the form of a compressed tablet or a capsule, said tablet or capsule coated with one or more anionic polymers with methacrylic acid as a functional group (Eudragit™ polymer, Evonik Degussa, Darmstadt, Germany) to retard or delay its release to achieve the objectives of the invention, said polymers including Eudragit™ L 30 D-55 or Eudragit™ L 100-55 which dissolve in the duodenum or at about pH > 5.5, or Eudragit™ L 100 which dissolves in the jejunum or at a pH of about 6, or Eudragit™ S100, which dissolves in the ileum or at a pH > 7.0, or Eudragit™ FS 30D, which dissolves in the colon or at a pH of about 6, which dissolve at a pH > 7.0.

[1044] In some embodiments, the dosage form of the invention can provide delayed and subsequently ileo-colonic or colonic release over an extended period of time (an extended release) by use of multiple polymers. In one embodiment, at the center of the dosage form is a core containing the levorphanol. The levorphanol is then coated with one or more layers of polymers that permit the drug to pass through the stomach, duodenum and jejunum (and optionally the ileum) without substantial absorption. As the dosage form reaches the alkaline pH of the ileum and colon (or optionally, upon arrival near or in the colon, for example upon traversing the ileo-cecal junction), the polymer allows permeability to water and thereby allows drug to diffuse from the dosage form and be available for systemic absorption in the terminal ileum and/or in the colon.

[1045] In some embodiments, the dosage form of the invention is in the form of a capsule, said capsule made from materials known in the art, including gelatin, plasticizers, starch, hydroxypropylmethyl cellulose (HPMC), pullulan capsule.

[1046] In some embodiments of the invention, the levorphanol is formulated as an immediate release or controlled release tablet or capsule formulation. If used as prepared, the dosage form would usually release some of the levorphanol from the dosage form in the stomach, duodenum, jejunum and ileum. Some suitable coatings include US Patent No. 4,311,833; 4,377,568; 4,385,078; 4,457,907; 4,462,839; 4,518,433; 4,556,552; 4,606,909; 4,615,885; 4,670,287; 5,536,507; 5,567,423; 5,591,433; 5,597,564; 5,609,871; 5,614,222; 5,626,875; 5,629,001; and 6,608,075, all of which are incorporated herein in their entirety by reference.

[1047] In some embodiments of the invention, preferred coating compositions include alkyl and hydroxyalkyl celluloses and their aliphatic esters, e.g., methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxybutyl cellulose, hydroxyethylethyl cellulose, hydroxypropylmethyl cellulose, hydroxybutylmethyl cellulose, hydroxypropyl cellulose phthalate, hydroxypropylmethyl cellulose phthalate and hydroxypropylmethyl cellulose acetate

succinate; carboxyalkyl celluloses and their salts, e.g., carboxymethylethyl cellulose; cellulose acetate phthalate; cellulose acetate trimellitate, polycarboxymethylene and its salts and derivatives; polyvinyl alcohol and its esters: polyvinyl acetate phthalate; polycarboxymethylene copolymer with sodium formaldehyde carboxylate; acrylic polymers and copolymers, e.g., methacrylic acid-methyl methacrylic acid copolymer and methacrylic acid-methyl acrylate copolymer; edible oils such as peanut oil, palm oil, olive oil and hydrogenated vegetable oils; polyvinylpyrrolidone; polyethylene glycol and its esters: natural products such as shellac, and zein.

[1048] In some embodiments of the invention, other preferred coatings include polyvinylacetate esters, e.g., polyvinyl acetate phthalate; alkylene glycol ether esters of copolymers such as partial ethylene glycol monomethylether ester of ethylacrylate-maleic anhydride copolymer or diethyleneglycol monomethylether ester of methylacrylate-maleic anhydride copolymer, N-butylacrylate-maleic anhydride copolymer, isobutylacrylate-maleic anhydride copolymer or ethylacrylate-maleic anhydride copolymer; and polypeptides resistant to degradation in the gastric environment, e.g., polyarginine and polylysine. Other suitable coatings and methods to make and use delayed onset, extended release, extended release, duodenal release, jejunal release, ileal release, ileo colonic release and colonic release pharmaceutical compositions and dosage forms of oral levorphanol are well known in the [see for example, Colonic Drug Delivery (page 287-294), Wilson CG, In: Modified- Release Drug Delivery Technology, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008; Biopolymers and Colonic Delivery, Wilson CG, Mukherji G, Shah HK (pages 295-309), In: Modified- Release Drug Delivery Technology, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008; Enteric Coating for Colonic Delivery, Shah HK, Mukherji G, Brogmann B, Wilson CG (pages 311-324), In: Modified- Release Drug Delivery Technology, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008; Programmed Drug Delivery Systems and the Colon, Wilson CG, Shah HK, Lee WW, Brogmann B, Mukherji G (pages 325-335), In: Modified- Release Drug Delivery Technology, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008; Targeting the Colon Using COLAL™ : A Novel Bacteria-Sensitive Drug Delivery System, McConnell EL, Basit AW (pages 343-348), In: Modified- Release Drug Delivery Technology, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008; Remington: the science of Pharmacy Practice, 21st Edition, 2006, Lippincott, Williams & Wilkins, Baltimore, MD; Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form. Gibson, M (ed). CRC Press, 2001; Niazi, S. Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products (Volume 1 of 6), CRC Press, 2004; Niazi, S. Mollet, H, Grubenmann A, Payne H. Formulation Technology: Emulsions,

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Singh Characterization and relevance of physicochemical interactions among components of a novel multiparticulate formulation for colonic delivery. *Int J Pharm*, 2007 Aug 16;341(1-2):143-51; Gazzaniga et al. Oral Colon Delivery: Rationale & Time-based Drug Design Strategy. *Discov Med*, 2006 Dec;6(36):223-8; Singh Modified-release solid formulations for colonic delivery. *Recent Pat Drug Deliv Formul*, 2007;1(1):53-63; Akhgari et al. Combination of time-dependent & pH-dependent polymethacrylates as a single coating formulation for colonic delivery of indomethacin pellets. *Int J Pharm*, 2006 Aug 31;320(1-2):137-42; Ibekwe et al. A comparative in vitro assessment of the drug release performance of pH-responsive polymers for ileo-colonic delivery. *Int J Pharm*. 2006 Feb 3;308(1-2):52-60; Al-Saidan et al. In vitro and in vivo evaluation of guar gum-based matrix tablets of rofecoxib for colonic drug delivery. *Curr Drug Deliv*, 2005 Apr;2(2):155-63; Basit. Advances in colonic drug delivery. *Drugs*. 2005;65(14):1991-2007; Bott et al. In vivo evaluation of a novel pH- & time-based multiunit colonic drug delivery system. *Aliment Pharmacol Ther*. 2004 Aug 1;20(3):347-53; Qi et al. A novel pH- and time-dependent system for colonic drug delivery. *Drug Dev Ind Pharm*. 2003 Jul;29(6):661-7; 21; Shareef et al. Colonic drug delivery: an updated review. *AAPS PharmSci*. 2003;5(2):E17. Review. PubMed PMID: 12866944; Tuleu et al. Colonic delivery of sodium butyrate via oral route: acrylic coating design of pellets and in vivo evaluation in rats. *Methods Find Exp Clin Pharmacol*. 2001 Jun;23(5):245-53; Gupta et al. A novel pH- and time-based multi-unit potential colonic drug delivery system. I. Development. *Int J Pharm*. 2001 Feb 1;213(1-2):83-91; Gupta et al. A novel pH- & time-based multi-unit potential colonic drug delivery system. II. Optimization of multiple response variables. *Int J Pharm*. 2001 Feb 1;213(1-2):93-102; Muraoka et al. Evaluation of intestinal pressure-controlled colon delivery capsule containing caffeine as a model drug in human volunteers. *J Control Release*. 1998 Mar 2;52(1-2):119-29; Niwa et al. Preparation & evaluation of a time-controlled release capsule made of ethylcellulose for colon delivery of drugs. *J Drug Target*. 1995;3(2):83-9. Erratum in: *J Drug Target* 96;3(6):478; Ashford et al. Targeting drugs to the colon: delivery systems oral administration. *J Drug Target*. 1994;2(3):241-57], all hereby incorporated by reference in their entirety.

[1049] In some embodiments of the invention, the coating material may be mixed with various excipients including plasticizers such as triethyl citrate, acetyl triethyl citrate, diethyl phthalate, dibutyl phthalate, dibutyl subacate, dibutyl tartrate, dibutyl maleate, dibutyl succinate and diethyl succinate and inert fillers such as chalk or pigments.

[1050] The composition and thickness of the coating may be selected to dissolve immediately upon contact with the digestive juice of the intestine. Alternatively, the composition and thickness of the external coating may be selected to be a time-release coating which dissolves over a selected period of time, as is well known in the art.

[1051] The amount of enteric coating depends on the particular coating composition used and is preferably sufficient to substantially prevent the absorption of in the stomach, duodenum, jejunum

and, in some embodiments, the ileum as well.

- [1052] In some embodiments of the invention, hydroxyalkyl celluloses and their aliphatic esters, carboxyalkyl celluloses and their salts, polycarboxymethylene and its salts and derivatives, polyvinyl alcohol and its esters, polycarboxymethylene copolymer with sodium formaldehyde carboxylates, poly-vinylpyrrolidone, and polyethylene glycol and its esters can be applied as coatings by first dissolving the compound in a minimum amount of water. Alcohol is then added to the point of incipient cloudiness. The mixture can then be applied by conventional techniques.
- [1053] In some embodiments, application of cellulose acetate phthalate may be accomplished by simply dissolving the cellulose acetate phthalate in a minimum amount of alcohol and then applying by conventional techniques. Hydrogenated vegetable oils may be applied by first dissolving the oil in a minimal amount of a non-polymer solvent, such as methylene chloride, chloroform or carbon tetrachloride, then adding alcohol to the point of incipient cloudiness and then applying by conventional techniques.
- [1054] In some embodiments, the dosage form of is a capsule or tablet, said dosage form pre-coated with an excipient, prior to coating with a polymer.
- [1055] In some embodiments, the capsule dosage form is sealed after filling in the overlapping region of capsule body and cap by commonly known sealing techniques like banding or applying a sealing liquid and/or heat to the gap between capsule body and cap. Preferred is a sealing process, in which a sealing liquid which may include a solvent applied individually and uniformly to the external edge of the gap of a capsule to be sealed to form a liquid ring around the circumference of the capsule, removing excess sealing liquid from the exterior of the capsule and drying the capsule by applying thermal energy from outside. Such a sealing before coating can prevent problems e.g. with non-uniformity of the coating at the gap or development of fissures during storage under stressing conditions, which can lead to early leaking of the capsule content into the stomach. In some embodiments, the banding is achieved through the application of a ring of liquid gelatin or hypromellose on the external surface of the capsule. In some embodiments, a double-band sealing technique is used to ensure ensures that if an air bubble or unevenness occurs in the first band, it will be eliminated by the second application. Capsule banding can provide tamper evidence, deter counterfeiting, improve mechanical strength, provide color brand differentiation, improve product stability and reduce oxygen diffusion.
- [1056] For controlled or slow release of the drug from the dosage form in some embodiments, the composition of the pH sensitive coating will dissolve, but other controlled release mechanisms will provide for slow release of the drug in the preferred anatomic location and/or at the preferred time after oral ingestion and/or in the preferred gastrointestinal environment, including preferred pH, preferred osmotic pressure in the lumen, preferred osmotic pressure in the dosage form, preferred hydration level, preferred microbial environment, preferred level of GI peristalsis or agitation.

- [1057] In some embodiments, preferred coating materials are those which dissolve at a pH between 5 and 7.6, for example, > about 5, or > about 5.2, or > about 5.5, or > about 5.7, or > about 6, or > about 6.1, or > about 6.2, or > about 6.3, or > about 6.4, or > about 6.5, or > about 6.6, or > about 6.7, or > about 6.8, or > about 6.9, or > about 7, or > about 7.2, or > about 7.4, or > about 7.6.
- [1058] In some embodiments, preferred coating materials include polymers such as cellulose acetate trimellitate (CAT), hydroxypropylmethyl cellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP) and shellac. In some embodiments, especially preferred materials for aqueous film coating are copolymers of methacrylic acid and ethyl acrylate, Eudragit™ L30D-55 (Evonik Degussa, Darmstadt, Germany).
- [1059] In some embodiments, for release in the terminal ileum or colon any coating can be used which ensures that the dosage form does not disintegrate until it reaches the desired location. In some embodiments, the coating may be one which is pH-sensitive, redox-sensitive or sensitive to particular enzymes or bacteria, such that the coating only dissolves or finishes dissolving in the colon. Thus the capsules will not release the drug until it is in the terminal ileum or colon.
- [1060] In some embodiments, preferred coating materials are those which dissolve at a pH of 7 or above. Generally, such coatings only start to dissolve when they have left the stomach and passed through the duodenum and in cases the jejunum and/or terminal ileum. Generally, by the time the dosage form has reached the terminal ileum or colon the coating will have completely dissolved. Such a coating can be made from a variety of polymers including, without limitation, cellulose acetate trimellitate (CAT) hydroxypropylmethyl cellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), shellac and copolymers of methacrylic acid and ethyl acrylate. In some embodiments, especially preferred materials for aqueous film coating are copolymers of methacrylic acid and ethyl acrylate to which a monomer of methylacrylate has been added during polymerization. (Eudragit™ FS 30 D, Evonik Degussa, Darmstadt, Germany). Due to the free carboxylic acid group the polymer dissolves at pH 7 or above making it particularly suitable for delivery into the colon.
- [1061] It should be noted that when delayed but (subsequently) extended release of levorphanol is desired, upon dissolution or disintegration of the pH sensitive coating or material, a variety of mechanisms can provide extended release of the drug, including diffusion from matrix, membranes or pores, osmotic pressure, hydration, etc)
- [1062] Using preparation Eudragit™ FS 30D a coating thickness of 5 to 15 mg polymer per cm² of capsule surface is preferred in some embodiments.
- [1063] The colonic region is rich in microbial anaerobic organisms providing reducing conditions. Thus the coating may suitably comprise a material which is redox-sensitive. Such coatings may comprise azopolymers which can for example consist of a random copolymer of styrene and hydroxyethyl methacrylate, cross-linked with divinylazobenzene synthesized by free radical

polymerization, the azopolymer being broken down enzymatically and specifically in the colon or may consist of disulphide polymers.

[1064] Other materials providing release in the colon are amylose, for example a coating composition can be prepared by mixing amylose-butan-1-ol complex (glassy amylose) with an aqueous dispersion of Ethocel or a coating formulation comprising an inner coating of glassy amylose and an outer coating of cellulose or acrylic polymer material, calcium pectinate, pectin, a polysaccharide which is totally degraded by colonic bacterial enzymes, chondroitin sulfate and resistant starches, dextran hydrogels, modified guar gum such as borax modified guar gum, cyclodextrins, beta.-cyclodextrin, saccharide containing polymers, which can include a polymeric construct comprising a synthetic oligosaccharides-containing biopolymer including methacrylic polymers covalently couples to oligosaccharides such as cellobiose, lactulose, raffinose, and stachyose, or saccharide-containing natural polymers including modified mucopolysaccharides such as cross-linked chondroitin sulfate and metal pectin salts, for example calcium pectate, methacrylate-galactomannan and pH sensitive hydrogels.

[1065] Pharmaceutical compositions of the present invention can be prepared using methods described in the art. There is a wide body of literature and other prior art on the delivery, release and absorption of drug from oral dosage forms wherein said delivery, release and absorption is "targeted", i.e., where said delivery, release and absorption is: (i) achieved at the desired anatomic location of the GI tract; (ii) substantially avoided at certain anatomic locations of the GI tract; (iii) achieved after a particular amount of time has elapsed post-ingestion; (iv) achieved when the GI environment meets certain conditions (e.g., pH, electrolyte concentration, enzymes, hydration, bacterial flora, and the like).

[1066] Extended release pharmaceutical compositions are disclosed in U.S. Patent No. 7,196,059, 7,189,414, 7,163,696, 7,157,444, 7,119,079, 7,112,578, 7,109,239, 7,094,425, 7,041,651, 7,030,082, 7,022,683, 6,930,093, 6,919,348, 6,916,791, 6,897,205, 6,893,662, 6,867,183, 6,852,693, 6,824,790, 6,777,000, 6,770,625, 6,761,901, 6,747,014, 6,743,445, 6,734,170, 6,727,287, 6,699,848, 6,692,766, 6,677,321, 6,669,951, 6,632,454, 6,632,451, 6,630,453, 6,555,136, 6,552,072, 6,531,152, 6,525,078, 6,432,967, 6,428,968, 6,346,547, 6,340,476, 6,326,364, 6,277,411, 6,238,689, 6,231,888, 6,228,396, 6,217,904, 6,200,605, 6,200,602, 6,197,763, 6,166,044, 6,166,024, 6,106,864, 6,074,689, 6,063,402, 6,039,975, 5,948,407, 5,914,132, 5,905,081, 5,889,028, 5,866,619, 5,849,327, 5,846,983, 5,843,479, 5,840,332, 5,814,336, 5,811,388, 5,744,166, 5,691,343, 5,686,106, 5,686,105, 5,681,584, 5,672,359, 5,670,158, 5,656,294, 5,656,290, 5,651,983, 5,631,022, 5,554,388, 5,525,634, 5,514,663, 5,482,718, 5,183,802, 5,122,376, 4,904,474, 4,705,515 and 4,627,851, and in US Patent Application No. 20070167416, 20070112075, 20070087939, 20070072828, 20070071820, 20070071806, 20070060580, 20070059366, 20070054945, 20070026067, 20070020254,

20070020197, 20070003626, 20060280795, 20060251720, 20060223787, 20060189635, 20060177507, 20060121091, 20060105045, 20060099243, 20060083718, 20060045865, 20060041109, 20060003995, 20050287276, 20050281781, 20050260262, 20050249716, 20050222040, 20050220861, 20050209271, 20050208132, 20050186267, 20050182134, 20050181053, 20050169996, 20050158408, 20050153908, 20050153907, 20050152978, 20050118326, 20050112201, 20050107334, 20050101611, 20050090473, 20050090451, 20050069550, 20050058701, 20050043298, 20050009848, 20050009768, 20050009767, 20050009766, 20050008702, 20050008688, 20040267240, 20040258754, 20040253304, 20040241173, 20040229831, 20040224898, 20040219216, 20040186045, 20040185107, 20040176319, 20040162263, 20040162259, 20040161459, 20040147445, 20040142880, 20040126422, 20040121967, 20040110837, 20040109894, 20040062778, 20040052846, 20040038866, 20040017387, 20040013687, 20030207851, 20030194439, 20030181380, 20030170181, 20030162717, 20030152617, 20030133978, 20030083232, 20030077326, 20030069170, 20030040497, 20030022843, 20030008914, 20020147156, 20020127198, 20020110593, 20020110590, 20020098235, 20020058061, 20020035139, 20020015729, 20010052137, 20010039262, 20010036473, 20010031748 and 20010026807, which are hereby fully incorporated by reference herein in their entirety.

[1067] Pharmaceutical compositions of the present invention can be prepared to provide targeted delivery of levorphanol, wherein the targeted delivery of the immediate or controlled release dosage forms can advantageously provide, among other things, (i) improved efficacy; (ii) improved safety; (iii) reduced appeal to drug addicts, drug abusers and recreational drug users; (iv) reduced nausea; (v) reduced drowsiness; (vi) reduced psychic effects desired by drug addicts, drug abusers and recreational drug users; (vii) reduced desirability for co-abuse with alcohol or other drugs of abuse; and (viii) reduced risk of diversion.

[1068] Pharmaceutical compositions of the present invention can be prepared using methods described in the art achieve delivery, release and absorption of drug from oral dosage forms, wherein said delivery, release and absorption is "targeted", e.g., by way of non-limiting examples, where said delivery, release and absorption is: (i) achieved at the desired anatomic location of the GI tract (e.g., upon arrival in the duodenum, or jejunum, or ileum, or ileo-cecal junction, or cecum, or ascending colon, or transverse colon, or descending colon); (ii) substantially avoided at certain anatomic locations of the GI tract (e.g., stomach, or stomach and duodenum, or stomach, duodenum and jejunum, or stomach, duodenum, jejunum and ileum); (iii) achieved after a particular amount of time has elapsed post-ingestion (e.g., ≥ 1.5 hours or ≥ 2 hours, or ≥ 2.5 hours, or ≥ 3 hours, or ≥ 3.5 hours, or ≥ 4 hours, or ≥ 4.5 hours, or ≥ 5 hours, or ≥ 5.5 hours, or ≥ 6 hours, or ≥ 6.5 hours, or ≥ 7 hours, or ≥ 7.5 hours); (iv) achieved when the dosage form has come in contact or substantial contact or sustained contact with a desired gastrointestinal pH environment (e.g., pH > 3, or pH >

3.5, or pH > 4, or pH >4.5, or pH, > 5, or pH > 5.5, or pH > 6, or pH > 7, or pH > 7.5, or pH > 7.8); (v) achieved when the dosage form has come in contact with desired microbial flora (e.g., colonic microbial flora); (vi) achieved when the GI environment meets certain other conditions (e.g., electrolyte concentration, enzymes, hydration, and the like); (vii) a combination of two or more of the foregoing.

[1069] Pharmaceutical compositions of the present invention can be prepared using methods described, referenced or disclosed in Singh and Kim, *Int J Pharm.* 2007;341:143-51; Jain et al., *Crit Rev Ther Drug Carrier Syst.* 2006;23:349-400; Ugurlu et al., *Eur J Pharm Biopharm.* 2007;67:202-10; Sinha et al., *J Pharm Pharmacol.* 2007;59:359-65; Gazzaniga et al., *Discov Med.* 2006;6:223-8; Rhaman et al., *AAPS PharmSciTech.* 2006;7:E47; Akhgari et al., *Int J Pharm.* 2006;320:137-42; Bourgeois et al., *J Drug Target.* 2005;13:277-84; Curini et al., *Bioorg Med Chem Lett.* 2005;15:5049-52; Lamprecht et al., *J Control Release.* 2005;104:337-46; Verbeke et al., *Aliment Pharmacol Ther.* 2005;21:187-94; Bruce et al., *Eur J Pharm Biopharm.* 2005;59:85-97; Lamprecht et al., *Eur J Pharm Biopharm.* 2004;58:37-43; Mura et al., *J Drug Target.* 2003;11:365-71; Lamprecht et al., *J Control Release.* 2003;90:313-22; Wiwattanapatapee et al., *J Control Release.* 2003;88:1-9; Waterman et al., *J Control Release.* 2003;86:293-304; Park et al., *Arch Pharm Res.* 2002;25:964-8; Tuleu et al., *Aliment Pharmacol Ther.* 2002;16:1771-9; Gupta et al., *Drug Dev Ind Pharm.* 2002;28:207-15; Turkoglu et al., *Eur J Pharm Biopharm.* 2002;53:65-73; Tuleu et al., *Methods Find Exp Clin Pharmacol.* 2001;23:245-53; Stubbe et al., *J Control Release.* 2001;75:103-14; Shibata et al., *J Pharm Pharmacol.* 2001;53:441-7; Jeong et al., *J Control Release.* 2001;71:175-82; Hu et al., *J Pharm Pharmacol.* 2000;52:1187-93; Hu et al., *Pharm Res.* 2000;17:160-7; Ahrabi et al., *Eur J Pharm Sci.* 2000;10:43-52; Yoshikawa et al., *J Pharm Pharmacol.* 1999;51:979-89; Ahrabi et al., *Drug Dev Ind Pharm.* 1999;25:453-62; Hu et al., *J Control Release.* 1998;56:293-302; Kakoulides et al., *J Control Release.* 1998;52:291-300; Kakoulides et al., *J Control Release.* 1998;54:95-109; Muraoka et al., *J Control Release.* 1998;52:119-29; Takaya et al., *J Control Release.* 1998;50:111-22; Muraoka et al., *Nippon Rinsho.* 1998;56:788-94; Kenyon et al., *Aliment Pharmacol Ther.* 1997;11:205-13; Takaya et al., *J Drug Target.* 1997;4:271-6; Matsuda et al., *J Drug Target.* 1996;4:59-67; Jones SP, *J Drug Target.* 1996;3:477-8; Fedorak et al., *Gastroenterology.* 1995;108:1688-99; Takaya et al., *J Pharm Pharmacol.* 1995;47:474-8; Niwa et al., *J Drug Target.* 1995;3:83-9; Ashford and Fell, *J Drug Target.* 1994;2:241-57, *Colonic Drug Delivery* (page 287-294), Wilson CG, In: *Modified- Release Drug Delivery Technology*, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008; *Biopolymers and Colonic Delivery*, Wilson CG, Mukherji G, Shah HK (pages 295-309), In: *Modified- Release Drug Delivery Technology*, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008; *Enteric Coating for Colonic Delivery*, Shah HK, Mukherji G, Brogmann B, Wilson CG (pages 311-324), In: *Modified- Release*

Drug Delivery Technology, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008; Programmed Drug Delivery Systems and the Colon, Wilson CG, Shah HK, Lee WW, Brogmann B, Mukherji G (pages 325-335), In: Modified- Release Drug Delivery Technology, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008; Targeting the Colon Using COLAL™ : A Novel Bacteria-Sensitive Drug Delivery System, McConnell EL, Basit AW (pages 343-348), In: Modified- Release Drug Delivery Technology, Second Edition, Vol. 1, Rathbone MJ, Hadgraft J, Roberts MS, Lane ME (eds), Informa Healthcare USA Inc. 2008, Niazi, S. Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products (Volume 1 of 6), CRC Press, 2004, which are hereby fully incorporated by reference herein in their entirety.

[1070] A wide variety of materials can be used for preparing the dosage form according to this invention. This invention therefore contemplates the use of materials other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[1071] The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever. A wide variety of methods known in the art for the preparation of oral extended release dosage forms may be incorporated into the invention. Similarly, a wide variety of methods known in the art for the in vitro and in vivo evaluation of analgesics and oral extended release dosage forms may be incorporated into the invention. Other suitable dosage forms may also be prepared by modification of the examples herein and by use of material other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions. Similarly, other suitable methods for the evaluation of dosage forms may also be used by modification of the examples herein and by use of methods other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

[1072] The dose and dosing frequency of extended release levorphanol will vary depending on of the nature of the patient population, the characteristics of the medical condition under treatment, and other factors described herein. Similarly, the in vitro and in vivo release characteristics of extended release levorphanol, including the dissolution rate and plasma concentration time profile may be modified based on the clinical need of the patient, and other factors described herein.

[1073] The percent loading of the levorphanol onto the dosage form may be varied depending on the physiochemical and pharmaceutical properties controlled release material, excipients, the

selected salt of levorphanol and the desired release profile and duration of action.

[1074] The ingredients used for the preparation of the levorphanol dosage form may be modified depending on the selection, dose and desired duration of effect. In some embodiments, a change in the dose or amount levorphanol will not require a significant change in the amount of other ingredients. In other embodiments, a proportional change in the amount of other ingredients is required to maintain the desired properties. In yet other embodiments, a change in the dose or amount levorphanol necessitates a change in the nature and/or amount of ingredients to provide the required characteristics of the levorphanol (e.g., duration of effect, rate and extent of absorption, therapeutic concentrations and effect, etc.).

[1075] A wide variety of formulations of extended release levorphanol have been prepared and evaluated by the applicant.

EXAMPLES

[1076] Example 1

[1077] Excipients and capsule size selection

[1078] The target capsule size for this project was size 2 gelatin capsule. A fill weight of 325 mg was selected to assist with patient compliance and to allow the possibility of increasing the active dosage quantity by scaling up the fill weight into a larger, but still within an acceptable, capsule size. This meant that levorphanol tartrate dihydrate would be present at about 3.08% w/w in this 325 mg overall, 10 mg levorphanol product. The dosage unit was to be designed with inbuilt abuse resistance.

[1079] A range of thermosoftening materials with melting points up to about 75°C were considered. Several potential release rate modifiers as described herein were considered but hydroxypropyl methylcellulose (HPMC) was chosen as the preferred release rate modifier. An HPMC (Methocel™ K 15M) was incorporated into the formulations to accelerate release and provide a level of abuse deterrence. Formulations containing only levorphanol, a water soluble material, with a water insoluble base excipient made separation of the active by extraction relatively easy in the setting of tampering for abuse. HPMC was chosen as we have found it to enhance abuse resistance, having the property of being water soluble, and thus would 'follow' levorphanol during attempted aqueous extraction, making separation of the levorphanol more difficult. HPMC is supplied in high viscosity grades which was found to impart a viscous nature to aqueous extracts of dosage units i.e. during scenarios when levorphanol was extracted with a small amount of water (e.g. in a small spoon) then, at best, an unpleasant mixture was produced that has a 'gummy' appearance and blocks attempts at filtration. Similarly this type of extract was much more difficult to draw into a syringe and provided a strong visual warning that it is not a pure solution of levorphanol. Additionally, we have found that HPMC behaves in an unusual manner in aqueous

solution. Most water soluble materials increase in solubility as the water temperature rises. HPMC was most soluble in cold water, becoming less soluble with temperature increases until, at about 40°C, it was totally insoluble. Solutions of HPMC that heated to 40°C or above turned into solid gels. This means that although an HPMC may be added to increase release rates from a dosage unit, by providing channels through which the levorphanol can diffuse, it can also actively deter abuse by extraction from the dosage form and by other means of tampering. If an abuser tries to extract levorphanol with warm or hot water then the HPMC will become completely insoluble and actively resist the diffusion of levorphanol through the relatively impermeable base excipient. This resists the generation of injectable solutions, interferes with 'snorting' or 'dose dumping' (due to the viscous solutions produced) and resists extraction at elevated temperature.

[1080] A fumed silicon dioxide was chosen as both a thixotrope and contributor to abuse deterrence. Aerosil™ is the commercial name for fumed silicon dioxide manufactured by Degussa Hüls who produce a range of Aerosils™ with differing properties. These include different particle size, hydrophobic or hydrophilic characteristics or blended with additional materials for specific purposes. Aerosil™ 200 was chosen as the Aerosil™ of choice as it is pharmaceutically acceptable, 100% fumed silicon dioxide and effectively thickens aqueous systems. In this dosage form Aerosil™ 200 increased viscosity in the formulation. If an abuser attempts to add a small quantity of water to produce a solution (e.g. for injection), the Aerosil™ 200 (and other silicon dioxides and silica) contribute to maintain or increase the viscosity of any resulting solution. This complements the action of HPMC. Furthermore, silicon dioxide does not melt below 100°C (or even 1000°C) and is insoluble. The thickening effect of Aerosil™ is unaffected by heat; thus an abuser attempting to melt a dosage unit will find that the structure and shape of the dosage unit tends to remain unchanged when sufficient Aerosil™ is incorporated even though the melting point of all other excipients has been exceeded.

[1081] Miglyol™ 812N, a fractionated coconut oil, was used to impart softness and stickiness to formulations that contained waxes that were naturally hard and could potentially be ground into powders. Additionally, the solubility of oils in organic solvents added to the difficulty of attempted extraction and isolation of levorphanol using materials such as alcohols. This oil was selected as it is, pharmaceutically acceptable, of low viscosity and not susceptible to oxidation and rancidity.

[1082] Example 2

[1083] The material used included:

[1084] Material

Material	Material
Aerosil™ 200	Methocel™ K100M
Beeswax, yellow refined	Miglyol™ 812
Cithrol™ GMS 0400	Potassium dihydrogen orthophosphate
Compritol™ 888 ATO	Precirol™ AT05
Ethanol 96%	Size 2 clear/clear gelatin capsules

Fractionated coconut oil	Size 2 white/white gelatin capsules
Hydrokote™ 112	Sodium hydroxide
Levorphanol tartrate	Sodium metabisulphite (97%)
Methocel™ K15M	Sodium metabisulphite
Water	Sterotex™ NF

[1085] Example 3

[1086] Dissolution Testing

[1087] Dissolution testing was carried out with the USP paddle method using standard round bottomed vessels, a temperature of 37°C, with a paddle speed of 75 rpm on a dissolution apparatus with thermostatically controlled water heater. Except where otherwise specified, the dissolution medium was 600 mL of Simulated Intestinal Fluid (SIF) USP, pH 6.8 without the inclusion of enzyme. Capsules were weighed down with 316 stainless steel sinking wire, wrapped round each capsule. The levorphanol dissolution release profiles were initially determined by UV measurement and later the process was changed to use HPLC.

[1088] Samples of suitable formulations were placed on stability stored at 25°C/60%RH and 40°C/75%RH in glass jars for one or more months (dependent on date of final formulation acceptance). Dissolution testing was carried out on these samples and the data compared with their T₀ data.

[1089] Example 4

[1090] Abuse resistance testing

[1091] Since levorphanol is an opioid analgesic, it is subject to tampering and non-medical use. Consequently, the dosage forms were also evaluated for abuse resistance. The series of tests chosen to evaluate abuse resistance and the source of the test included: Test 1a) Extraction with alcohol on whole dosage unit (Oral Drug Delivery patent application US 2004/0161382 A1 (P 11, [0122])). Method: An intact dosage unit was placed in 18 mL of 0.1N HCl in a 60 mL amber bottle and shaken at 240 rpm on an orbital shaker for 30 minutes. After 30 mins, 12 mL of ethanol (95-96%) was added to each bottle. A 1 mL sample was removed from each bottle (T₀) after swirling by hand for one minute. The solution was placed back in the orbital shaker for further shaking at 240 rpm. Additional 1 mL samples were obtained after 10, 20, 30, 40, 60 and 180 min of further shaking for each bottle. Analyze and graph the results on a linear scale of cumulative release (%) vs. time (mins). Test 1b) Extraction with alcohol on a crushed or cut dosage unit (extension of test in above patent). Method: After crushing with a single crush using a spatula, the tampered tablet or capsule was placed in 18 mL of 0.1N HCl in a 60 mL amber bottle and shake at 240 rpm on an orbital shaker for 30 mins. The test was continued as in the preceding paragraph. Test 2) Extraction into water (Oral Drug Delivery patent application US 2004/0161382 A1 (P12, [0130])). Method: For capsules the outer shell was removed. The tablet or capsule plug was then crushed with a mortar and pestle and ground in 5 mL of water for 5 minutes. The resulting suspension was filtered

through a 0.45 micron filter into a flask and diluted to 10 ml with water. The drug collected in the filtrate was then quantified. Test 3) Crush to small particles with mortar and pestle. Method: The dosage form was frozen in a domestic freezer for 24 hours. The capsule shell was then removed with a scalpel and the removed plug then ground with a mortar and pestle for one minute. The resulting powder was then sieved through a suitable sieve (ca 600 micron) and, by weighing the content of powder passing through the sieve was measured. Test 4 is intentionally omitted. Test 5) Extraction into acid. Method: The dosage form was crushed with a mortar and pestle and heated to boiling in 5 mL of vinegar (8% acetic acid). The resulting suspension was filtered through a 0.45 micron filter into a flask and diluted to 10 ml with water. The active drug content was then quantified. Test 6) Application of heat – melting temperature. Method: The squashed contents of the dosage were heated on a hot plate until melted. The temperature of melting was determined and the syringability of the melt was determined by aspirating and then expelling the aspirate from 1.2 mm needle attached to a syringe.

[1092] Example 5

[1093] Binary mix compatibility trials

[1094] Binary mixes were prepared of levorphanol in potential excipients (in some instances a third material, fractionated coconut oil was used to bring two non-melting materials into intimate contact). The excipients used were chosen according to their ability to influence the dissolution profile of the formulated product. The properties considered were aqueous solubility (from partially soluble to highly insoluble) and their ability to modify viscosity and/or release characteristics e.g. different viscosity grades of HPMC and thixotropic modifiers such as different grades of fumed silicon dioxide.

[1095] For the placebo samples, approximately 2g of excipient was weighed into two clear glass scintillation vials. One sample was placed in stability storage at 40C 75%RH and one at 5C for the initial analysis. For the active samples approximately 9.5g of excipient was weighed into a clear glass scintillation vials. Approximately 0.5g of levorphanol was weighed into the same vial. The mixture was stirred by spatula to thoroughly mix the components. The components were additionally mixed by high shear for 1 minute using a Silverson Mixer. Based on the results, it was decided to initially focus on Miglyol™ 812, Aerosil™ 200/Miglyol™ 812, Hydrokote™ 112, Sterotex™ NF, Compritol™ 888 ATO, Precirol™ ATO 5, Methocel™ K15M/Miglyol™ 812 and Methocel™ K100M/Miglyol™ 812 as the excipients for this project.

[1096] Example 6

[1097] The release profile of three initial formulations were determined by UV monitoring. Formulations prepared and tested were:

[1098]

Formula (Ref 052/149/1)	% (w/w)	mg/dose
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Sterotex™	48.92	159.00
Coconut oil	25.00	81.25
Methocel™ K15M	20.00	65.00
Aerosil™ 200	3.00	9.75
Levorphanol tartrate	3.08	10.00

[1099]

Formula (Ref 052/149/2)	% (w/w)	mg/dose
Hydrokote™ 112	78.92	256.49
Methocel™ K15M	15.00	48.75
Aerosil™ 200	3.00	9.75
Levorphanol tartrate	3.08	10.00

[1100]

Formula (Ref 052/149/3)	% (w/w)	mg/dose
Precirol™ ATO 5	78.92	256.49
Methocel™ K15M	15.00	48.75
Aerosil™ 200	3.00	9.75
Levorphanol tartrate	3.08	10.00

[1101] As shown in Figure 1, the absorbance values measured are surprisingly greatly in excess of the theoretical end absorbance. Without being bound by theory, this may be due to interference by excipients or microbial growth developing over the extended dissolution period.

[1102] Example 7

[1103] The release profile of the three analogs to the above containing only the base wax and Methocel™ was determined to observe the effects of the loss of the other excipients (coconut oil and Aerosil™). Formulations prepared and tested were:

[1104]

Formula (Ref 052/152/1)	% (w/w)	mg/dose
Sterotex™	48.92	159.00
Methocel™ K15M	20.00	65.00
Levorphanol tartrate	3.08	10.00

[1105]

Formula (Ref 052/152/2)	% (w/w)	mg/dose
Hydrokote™ 112	78.92	256.49
Methocel™ K15M	15.00	48.75
Levorphanol tartrate	3.08	10.00

[1106]

Formula (Ref 052/152/3)	% (w/w)	mg/dose
Precirol™ ATO 5	78.92	256.49
Methocel™ K15M	15.00	48.75
Levorphanol tartrate	3.08	10.00

[1107] As show in Figure 2, the measured absorbance values increase slowly for the first 34 hours and then were surprisingly found to be greatly in excess of the theoretical end absorbance. Without being bound by theory, this may be due to interference by excipients or microbial growth developing over the extended dissolution period.

[1108] Example 8

[1109] The dissolution profile of Methocel™ in combination with each of three base waxes was determined to investigate whether UV absorbance interference arose from the presence of excipients. Formulations prepared and tested were:

[1110]

Formula (Ref 052/153/1)	% (w/w)	mg/dose
Sterotex™	70.98	159.00
Methocel™ K15M	29.02	65.00

[1111]

Formula (Ref 052/153/2)	% (w/w)	mg/dose
Hydrokote™ 112	84.03	256.49
Methocel™ K15M	15.97	48.75

[1112]

Formula (Ref 052/153/3)	% (w/w)	mg/dose
Precirol™ ATO 5	84.03	256.49
Methocel™ K15M	15.97	48.75

[1113] As show in Figure 3, the absorbance values showed no significant change for the first 20-30 hours then rose greatly in excess of the theoretical end absorbance for a levorphanol containing dosage unit. Without being bound by theory, the lack of any interference from the excipients for 20-30 hours followed by the rapid increase in absorbance is strongly indicative of the interference being due to microbial growth developing over the extended dissolution period.

[1114] Example 9

[1115] Levorphanol was formulated incorporating different percentages of Methocel™. The dissolution profile was tracked by UV, as previously. Samples were also taken which were analyzed by HPLC. Plots were constructed to compare the results. Formulations prepared and tested were:

[1116]

Formula (Ref 052/156/1)	% (w/w)	mg/dose
Hydrokote™ 112	76.12	255.00
Methocel™ K15M	17.91	60.00
Aerosil™ 200	2.99	10.00
Levorphanol tartrate	2.99	10.00

[1117]

Formula (Ref 052/156/2)	% (w/w)	mg/dose
Hydrokote™ 112	78.92	256.49
Methocel™ K15M	15.00	48.75
Aerosil™ 200	3.00	9.75
Levorphanol tartrate	3.00	10.00

[1118]

Formula (Ref 052/156/3)	% (w/w)	mg/dose
Hydrokote™ 112	96.25	256.50
Levorphanol tartrate	3.75	10.00

[1119] As shown in Figure 4, the UV the absorbance values measured increase slowly for the first 30 hours then rise to in excess of the theoretical end absorbance (0.076 au). This has been

interpreted as due to interference by microbial growth developing over the extended dissolution period. During the first 30 hours the UV profiles did show a release pattern ordered in increasing content of Methocel™ but the small absorbance range exhibited made accurate quantification difficult. The HPLC analyzed data (Figure 5) show a similar release pattern, ordered in increasing content of Methocel™, but analysis shows a clear release pattern, unmodified by the interference that had occurred during UV monitoring. The release profile of levorphanol from a Hydrokote™ base formulation (no release rate modifiers incorporated; 052/156/3) shows that the release time was slow enough to meet or exceed (i.e. slower) the requirements for this project. The release rate of formulations can be accelerated by the addition of release rate modifiers but cannot be retarded beyond that of the base wax. Base formulations, without release rate, are likely to show similar release profiles for the other aqueous insoluble waxes selected.

[1120] Example 10

[1121] Hydrokote™ 112, Sterotex™, Precirol™ ATO 5 and Compritol™ 888 ATO were selected as the base wax excipients for formulations. Formulations were prepared and their release profiles determined. The formulations were then adjusted to increase or decrease the release rates towards the intended target profiles. The dissolution profiles were determined by sampling and HPLC analysis. Formulations prepared and tested were:

[1122]

Formula (Ref 111/021/1)	% (w/w)	mg/dose
Hydrokote™ 112	75.4	245.00
Methocel™ K15M	18.5	18.5
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1123]

Formula (Ref 111/021/2)	% (w/w)	mg/dose
Sterotex™	47.1	153.00
Miglyol™ 812	25.2	82.00
Methocel™ K15M	21.5	70.00
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1124]

Formula (Ref 111/021/3)	% (w/w)	mg/dose
Precirol™ ATO 5	75.4	245.00
Methocel™ K15M	18.5	60.00
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1125]

Formula (Ref 111/021/4)	% (w/w)	mg/dose
Compritol™ 888 ATO	75.4	245.00
Methocel™ K15M	18.5	60.00
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1126] Figure 6, Figure 7, Figure 8 and Figure 9 show the dissolution profiles obtained from the above example. Three capsules of each formulation were used per trial. Each two plot set shows the release profile of two sets of three capsules and the average release profiles of each three capsule set.

[1127] Example 11

[1128] Four Levorphanol ER prototype batches were prepared having a spread of release rates. Formulations prepared and tested were 111/026/1 (Hydrokote™ based), 111/026/2 (Sterotex™ based), 111/026/3 (Precirol™ based) and 111/026/4 (Compritol™ based) as described herein. All mixes were filled on a HiBar bench filling machine. T₀ dissolution profiles were run on 3 capsule samples and the batches placed on stability at 25°C/60%RH and 40°C/75%RH in sealed glass vessels. The T₀ dissolution profiles are shown in Figure 10, Figure 11, Figure 12 & Figure 13.

[1129] Example 12

[1130] The above formulations underwent a battery of abuse deterrence tests. The results are shown in Figure 14 and Figure 15 and in the Tables below. Tests were carried out to determine the general resistance with each base excipient as it was not practical to carry out the (lengthy) testing while the formulations were being modified frequently. Abuse resistance testing was carried out on the stability samples following the methods previously. The extraction into water after grinding with a mortar and pestle in water [Test 2]) initially resulted in a viscous sticky mass that would not pass through a filter, pressure fed via a syringe so no liquid could be isolated in which active could be measured.

[1131] Abuse Resistance Test 2 on Formulations 111/026/1-4 at T₀

Extraction into water Test 2) T₀ (5 ml water; 5 mins using a mortar & pestle)		
Formulation	% released	Comment
Hydrokote™ 111/026/1	0	Forms sticky viscous mix which doesn't pass through filter
Serotex™ NF 111/026/2	0	Forms sticky viscous mix which doesn't pass through filter
Precirol™ 111/038/3	0	Forms sticky viscous mix which doesn't pass through filter
Compritol™ 111/038/4	0	Forms sticky viscous mix which doesn't pass through filter

[1132] The filter type (PTFE) was changed to that which had the highest permeability (PVDF or polyvinylidene difluoride) to permit testing that could discriminate between dosage units. The results on testing using these filters on samples at the three month storage time point are shown in below. Each sample was tested in duplicate and gave satisfactory results.

[1133] Abuse Resistance Test 2 on Formulations 111/026/1-4 at T_{3 month}

Extraction into water Test 2) T_{3 month} (5 ml water; 5 mins using a mortar & pestle)		
Formulation	% released	Comment
Hydrokote™ 111/026/1	7.3; 6.4	Viscous paste with waxy lumps
Sterotex™ NF 111/026/2	6.7; 15.5	Viscous paste with waxy lumps

[1134] The Table below shows comparable data from test we undertook on an extended release tramadol (Zydol™ tablets) and on an extended release oxycodone (OxyContin™ tablets).

[1135] Abuse Resistance Test 2 on Commercial Tablets Comparators

Extraction into water Test 2 (5 ml water; 5 mins using a mortar & Pestle)		
Formulation	% released	Comment
Zydol™ (tablet)	87	Mobile easily filtered solution
OxyContin™ (tablet)	82	Mobile easily filtered solution

[1136] Example 13

[1137] This test was designed to assess the ease of powdering and percentage of resultant particles of 600 micron or less. Initial powdering tests were carried out using a laboratory stainless steel sieve of nominal 650 micron size. The sieve size used had been qualitatively determined as a size that could differentiate between the powders generated. Initially much finer sieves had been tested but were found to be too fine e.g. a 45 micron sieve was tested but this was too fine resulting in almost zero powder passing through the sieve from any samples. As a result of the initial tests, a certified sieve was obtained of 600 micron size for further trials. All of the above samples were subjected to the powdering test. All results for Hydrokote™ and Sterotex™ are acceptable.

[1138] Abuse Resistance Test 3 on Formulations 111/026/1-4 at T₀

Crush to small particles Test 3 (Freeze, grind in mortar, sieve through 600μ sieve)		
Formulation	% through sieve	Comment
Hydrokote™ 111/026/1	0	Forms sticky film on mortar
Sterotex™ NF 111/026/2	0	Forms sticky film on mortar
Precirol™ 111/026/3	66.5	Many particles pass through mesh
Compritrol™ 111/026/4	92.7	Most particles pass through mesh

[1139] Formulations 111/026/3 (Precirol™) and 111/026/4 (Compritrol™) were temporarily discontinued at this stage as being too easily powdered, however, the samples present on stability were subjected to testing at the one month timepoint.

[1140] Example 14

[1141] Figure 16, Figure 17, Figure 18, Figure 19, Figure 20, Figure 21, Figure 22 and Figure 23

show the dissolution data after storage at 40°C/75%RH for one month.

[1142] Example 15

[1143] Figures 24, Figure 25, Figure 26 and Figure 27 show month dissolution data after storage at 25°C/60%RH and 40°C/75%RH for 111/026/1 (Hydrokote™) and 111/026/2 (Sterotex™).

[1144] Example 16

[1145] Abuse resistance testing demonstrated of formulations 111/026/3 and 111/026/4 demonstrated that both formulations powdered too easily. Both formulations were modified by the inclusion of an oil to impart stickiness. Formulations prepared and tested were:

[1146]

Formula (Ref 111/038/3)	% (w/w)	mg/dose
Precirol™ ATO 5	53.2	173.00
Miglyol™ 812	25.2	82.00
Methocel™ K15M	15.4	50.00
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1147]

Formula (Ref 111/038/4)	% (w/w)	mg/dose
Compritol™ 888 ATO	53.2	173.00
Miglyol™ 812	25.2	82.00
Methocel™ K15M	15.4	50.00
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1148] Abuse Test 3 (Ease of Powdering) on Modified Precirol™ and Compritol™

Crush to small particles Test 3 (Freeze, grind in mortar, sieve through 600µ sieve)		
Formulation	% through sieve	Comment
Precirol™ 111/038/3	23.2	Few particles pass through mesh
Compritol™ 111/038/4	13.8	Few particles pass through mesh

[1149] Dissolution testing of these formulations gave the release profiles shown in Figure 28. Both formulations had very similar release profiles.

[1150] Example 17

[1151] A Hydrokote™ based formulation with a slower releasing profile than formulation 111/026/1 and a Sterotex™ based formulation with a faster releasing profile than formulation 111/026/2 were attempted. Formulations prepared and tested were:

[1152]

Formula (Ref 111/043/1)	% (w/w)	mg/dose
Hydrokote™ 112	48.9	159.00
Miglyol™ 812	24.9	81.00
Methocel™ K15M	20.0	65.00

Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1153]

Formula (Ref 111/043/2)	% (w/w)	mg/dose
Sterotex™	58.8	191.00
Miglyol™ 812	24.9	81.00
Methocel™ K15M	10.1	33.00
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1154] Dissolution testing of these formulations gave the release profiles shown in Figure 29 and Figure 30.

[1155] Example 31

[1156] Precirol™ and Compritol™ based formulations with slower release profiles than formulation 111/038/3 and 111/038/4 were attempted. Formulations prepared and tested were:

[1157]

Formula (Ref 111/045/3)	% (w/w)	mg/dose
Precirol™ ATO 5	57.7	187.50
Miglyol™ 812	25.2	81.90
Methocel™ K15M	10.0	32.50
Aerosil™ 200	4.0	13.00
Levorphanol tartrate	3.1	10.00

[1158]

Formula (Ref 111/045/4)	% (w/w)	mg/dose
Compritol™ 888 ATO	57.7	187.50
Miglyol™ 812	25.2	81.90
Methocel™ K15M	10.0	32.50
Aerosil™ 200	4.0	13.00
Levorphanol tartrate	3.1	10.00

[1159] Dissolution testing of these formulations gave the release profiles shown in Figure 31 and Figure 32.

[1160] Example 32

[1161] Abuse resistance testing on stability batches 111/026/1 and 111/026/2 was carried out at 3 months. See Figure 33 and the Tables below.

[1162] Abuse Resistance Test 2 on Formulations 111/026/1&2 at T_{3 month}

Extraction into water Test 2 T _{3 month} (5 ml water; 5 mins using a mortar & pestle)		
Formulation	% released	Comment
Hydrokote™ 111/026/1	7.3; 6.4	Viscous paste with waxy lumps
Sterotex™ NF 111/026/2	6.7; 15.5	Viscous paste with waxy lumps

[1163] Abuse Resistance Test 5 on Formulations 111/026/1&2 at T_{3 month}

Extraction into acid Test 5 T_{3 month} (5 ml dil acetic; crush & bring to boil)		
Formulation	% released	Comment
Hydrokote™ 111/026/1	0; 14.6	Thick paste with large waxy lumps. Difficult to filter
Sterotex™ NF 111/026/2	5.6; 3.0	Lumpy paste difficult to draw into syringe

[1164] Example 33

[1165] A Hydrokote™ based formulation with a faster releasing profile than formulation 111/0436/1 and a Sterotex™ based formulation with a faster releasing profile than formulation 111/043/2 were attempted. Formulations prepared and tested were:

[1166]

Formula (Ref 111/060/1)	% (w/w)	mg/dose
Hydrokote™ 112	68.8	224.00
Methocel™ K15M	25.0	81.00
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1167]

Formula (Ref 111/059/2)	% (w/w)	mg/dose
Sterotex™	53.8	175.00
Miglyol™ 812	24.9	49.00
Methocel™ K15M	15.0	33.00
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1168] The dissolution profiles determined for these formulations are shown in Figure 34 and Figure 35

[1169] Example 34

[1170] The dissolution profile of Compritol™ formulation 111/038/4 and 111/045/4 after 1 month at 25°C/60%RH and comparison with T₀ are shown in Figure 36, Figure 37, Figure 38 and Figure 39.

[1171] Example 35

[1172] Two Sterotex™ based formulations were developed and their dissolution profiles determined to examine the magnitude in the change in release rate on Methocel™ variation. Formulations prepared and tested were:

[1173]

Formula (Ref 111/068/2)	% (w/w)	mg/dose
Sterotex™	57.1	185.60
Miglyol™ 812	25.2	82.00
Methocel™ K15M	11.5	37.40
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1174]

Formula (Ref 111/099/2)	% (w/w)	mg/dose
Sterotex™	55.18	179.10
Miglyol™ 812	25.2	82.00
Methocel™ K15M	13.5	43.90
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1175] The dissolution profiles determined for these formulations are shown in Figure 40, Figure 41 and Figure 42.

[1176] Example 36

[1177] The relative dissolution profile of four R&D batches are shown in Figure 43

[1178] Example 37

[1179] Four batches were manufactured. These formulations were Hydrokote™ formulation 111/026/1, Sterotex™ formulations 111/026/2 and 111/038/4, and Compritol™ formulation 111/038/4. See Table below.

Batch number	Description	Formulation Ref
VE2470	Levorphanol Tartrate ER 10 mg in Hydrokote™ 112	111/026/1
VE2471	Levorphanol Tartrate ER 10 mg in Compritol™ 888 ATO	111/038/4
VE2472	Levorphanol Tartrate ER 10 mg in 47% Sterotex™	111/026/2
VE2473	Levorphanol Tartrate ER 10 mg in 57% Sterotex™	111/068/2

[1180] Example 38

[1181] The above batches were tested for abuse resistance as shown in Figure 44 and Figure 45, and in the four Tables below.

[1182] Example 39

Abuse Resistance Test 2 on Batches VE2470, VE2471, VE2472 & VE2473

Extraction into water Test 2 T ₀ (5 ml water; 5 mins using a mortar & pestle)		
Formulation	% released	Comment
Hydrokote™ 111/026/1 VE2470	21.4	Forms sticky viscous gel like paste with small lumps. Hard to filter
Compritol™ 111/038/4 VE2471	3.6	Forms sticky gel which is very difficult to filter
47% Sterotex™ 111/026/2 VE2472	14.1	Forms sticky paste with small waxy lumps. Mix is difficult to filter.
57% Sterotex™ 111/068/2 VE2473	27.1	Forms sticky paste with small waxy lumps. Mix is difficult to filter.
OxyContin™ 80 mg	82	Mobile easily filtered solution

[1183]

Abuse Resistance Test 3 On Batches VE2470, VE2471, VE2472 & VE2473

Crush to small particles Test 3 (Freeze, grind in mortar, sieve through 600μ sieve)		
Formulation	% through sieve	Comment
Hydrokote™ 111/026/1 VE2470	4.8	Forms sticky film on mortar. Difficult to scrape off and pass sieve.
Compritol™ 111/038/4 VE2471	16.9	Forms sticky film on mortar. Difficult to scrape off
47% Sterotex™ 111/026/2 VE2472	12.5	Forms sticky film on mortar. Difficult to scrape off a
457% Sterotex™ 111/068/2 VE2473	7.0	Forms sticky film on mortar. Difficult to scrape off a
OxyContin tablet 80 mg	66.8 %	Powders as expected

[1184]

Abuse Resistance Test 5 On Batches VE2470, VE2471, VE2472 & VE2473

Extraction into acid Test 5 T₀ (5 ml dilute acetic; crush & bring to boil)		
Formulation	% released	Comment
Hydrokote™ 111/026/1 VE2470	2.0	Opaque suspension. Very difficult to filter
Compritol™ 111/038/4 VE2471	34.3	Contents did not dissolve. Remainder filtered easily
47% Sterotex™ 111/026/2 VE2472	4.8	Opaque suspension with small waxy lumps. Very difficult to filter
457% Sterotex™ 111/068/2 VE2473	8.5	Opaque suspension with small waxy lumps. Very difficult to filter
OxyContin tablets 80 mg	90	Wax floats on mobile solution; filters easily

[1185]

Abuse Resistance Test 6 On Batches VE2470, VE2471, VE2472 & VE2473

Base excipient	Excipient mp	Formulation	Formulation molten at	Comment
Hydrokote™ 112	43-46°C	111/026/1	45°C	VE2470 Sticky mass, can suck and eject negligible material from needle
Compritol™ 888 ATO	69-74°C	111/038/4	68° C	VE2471. Sticky mass, doesn't suck into syringe, sets instantly in needle tip
Sterotex™	60-63°C	111/026/2	62°C	VE2472 Sticky mass, too viscous to be drawn into syringe needle.
Sterotex™	60-63°C	111/0686/2	62°C	VE2473 Sticky mass, too

				viscous to be drawn into syringe needle.
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[1186] Example 40

[1187] Dissolution profiles of Levorphanol ER batches after 0, 1 and two months storage at 25°C/60%RH are shown in Figure 46, Figure 47, Figure 48, Figure 49, Figure 50, Figure 51, Figure 52 and Figure 53. Formulations prepared and tested were:

[1188]

Formula (Ref 111/026/1)	% (w/w)	mg/dose
Hydrokote™ 112	75.4	245.00
Methocel™ K15M	18.5	60.00
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1189]

Formula (Ref 111/026/2)	% (w/w)	mg/dose
Sterotex™ (47%)	47.1	153.00
Miglyol™ 812	25.2	82.00
Methocel™ K15M	21.5	70.00
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1190]

Formula (Ref 111/038/4)	% (w/w)	mg/dose
Compritol™ 888 ATO	53.2	173.00
Miglyol™ 812	25.2	82.00
Methocel™ K15M	15.4	50.00
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1191]

Formula (Ref 111/068/2)	% (w/w)	mg/dose
Sterotex™ (57%)	57.1	185.60
Miglyol™ 812	25.2	82.00
Methocel™ K15M	11.5	37.40
Aerosil™ 200	3.1	10.00
Levorphanol tartrate	3.1	10.00

[1192] Example 41

[1193] Example 41 to 44 were prepared as follows: (i) ingredient (1) was dispensed into a mixer; (ii) ingredient (1) was heated until fully melted; (iii) ingredient (2) was dispensed into the same mixer; (iv) ingredient (1) and (2) were mixed until dispersed; (v) ingredient (3) was dispensed into the same mixer; (vi) ingredient (1), (2) and (3) were mixed until dispersed; (vii) ingredient (4) was dispensed into the same vessel; (viii) ingredient (1), (2), (3) and (4) were mixed thoroughly with a high shear mixer; (ix) the contents were transferred into a liquid filling machine and filled into hard gelatin capsules.

[1194] Example 41

Extended Release Levorphanol

	Ingredients	% w/w	mg/capsule
1	Hydrokote™ 112	75.38	245.0
2	Methocel™ K15M	18.46	60.0
3	Aerosil™ 200	3.08	10.0
4	Levorphanol Tartrate	3.08	10.0

[1195] Example 42

Extended Release Levorphanol

	Ingredients	% w/w	mg/capsule
1	Beeswax	70.74	237.00
2	Methocel™ K15M	23.88	80.00
3	Aerosil™ COK 84	2.39	8.00
4	Levorphanol Tartrate	2.99	10.00

[1196] Example 43

Extended Release Levorphanol

	Ingredients	% w/w	mg/capsule
1	Cithrol™ GMS	81.49	273.00
2	Methocel™ K100	11.94	40.00
3	Aerosil™ COK 84	3.58	12.00
4	Levorphanol Tartrate	2.99	10.00

[1197] Example 44

Extended Release Levorphanol

	Ingredients	% w/w	mg/capsule
1	Hydrokote™ 112	76.10	255.00
2	Methocel™ K15M	17.90	60.00
3	Aerosil™ COK 84	3.0	10.00
4	Levorphanol Tartrate	3.0	10.00

[1198] Example 45 to 48 were prepared as follows: (i) ingredient (1) was dispensed into a mixer; (ii) ingredient (1) was heated until fully melted; (iii) ingredient (2) was dispensed into the same mixer; (iv) ingredient (1) and (2) were heated until fully melted; (v) ingredient (3) was dispensed into the same mixer; (vi) ingredient (1), (2) and (3) were mixed until dispersed; (vii) ingredient (4) was dispensed into the same mixer; (viii) ingredient (1), (2), (3) and (4) were mixed until dispersed; (ix) ingredient (5) was dispensed into the same vessel; (x) ingredient (1), (2), (3), (4) and (5) were mixed thoroughly with a high shear mixer; (ix) the contents were transferred into a liquid filling

machine and filled into hard gelatin capsules.

[1199] Example 45

Extended Release Levorphanol

	Ingredients	% w/w	mg/capsule
1	Compritol™ 888 ATO	53.23	173.00
2	Miglyol™ 812	25.23	82.00
3	Methocel™ K15M	15.38	50.00
4	Aerosil™ 200	3.08	10.0
5	Levorphanol Tartrate	3.08	10.0

[1200] Example 46

Extended Release Levorphanol

	Ingredients	% w/w	mg/capsule
1	Sterotex™	47.07	153.00
2	Miglyol™ 812	25.23	82.00
3	Methocel™ K15M	21.54	70.00
4	Aerosil™ 200	3.08	10.0
5	Levorphanol Tartrate	3.08	10.00

[1201] Example 47

Extended Release Levorphanol

	Ingredients	% w/w	mg/capsule
1	Sterotex™	57.11	185.60
2	Miglyol™ 812	25.23	82.00
3	Methocel™ K15M	11.50	70.00
4	Aerosil™ 200	3.08	10.00
5	Levorphanol Tartrate	3.08	10.00

[1202] Example 48

Extended Release Levorphanol

	Ingredients	% w/w	mg/capsule
1	Sterotex™	42.09	141.00
2	Fractionated Coconut Oil	29.85	100.00
3	Methocel™ K15M	23.89	80.00
4	Aerosil™ 200	1.19	4.00

5	Levorphanol Tartrate	2.98	10.00
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[1203] Example 49

[1204] Example 49 is a capsule (or optionally tablet) formulation of oral extended release levorphanol for ileo-colonic and colonic delivery.

Delayed Onset, Extended Release Levorphanol for Ileo-colonic or Colonic Delivery

Ingredients	Qty./Unit
1. Levorphanol Tartrate	20 mg
2. HPMC 2208, USP	150 mg
3. Carnauba wax	30 mg
4. HPMC 2910, USP	15 mg
5. Magnesium Stearate	2 mg
6. Stearic acid	8 mg
7. Talc	3 mg

[1205] In Example 49, place the ingredients 1, 2 and 3 in the granulator and mix for 15 minutes. Dissolve ingredient 4 in water (mix in hot water, then cool down) and spray into the fluidized mixture. Dry to approximately 5% moisture. Sequentially add ingredient 5, 6 and 7, with mixing steps between each addition. Encapsulate the dosage form in HPMC or other suitable capsules or compress into a tablet.

[1206] For the capsule formulation, prepare a composition of aqueous Eudragit™ FS30D dispersion to coat 1.3 kg HPMC capsules: Eudragit™ FS30D 1207 g (solids, 362 g), Triethyl citrate 18 g (solids 18 g), Glyceryl monostearate 11 g (solids 11 g), Tween 80 (33%) 13 g (solids 4 g) and Distilled Water 728 g. Spray the dispersion onto the HPMC capsules using an Accela-Cota 10. The temperature of the capsule bed during the coating process is maintained between 26 and 32 °C. The mean amounts of polymer applied ranges from 5 mg/cm² to 20 mg/cm², preferably 6 mg/cm² to 10 mg/cm².

[1207] For the tablet formulation, the composition of aqueous Eudragit™ FS30D dispersion described above may be applied with a typical coating thicknesses of 10 to 30 mg polymer per cm² of tablet surface, preferably, 10 to 18 mg polymer per cm² capsule surface.

[1208] The in vitro performance of the dosage form can be tested using methods known in the art and described herein. When the capsules are tested using the USP Paddle Method in 0.1N HCl (pH 1.2) for two hours, followed by a switch to phosphate buffer pH 6.8 for one to two hours and then again, a switch to phosphate buffer pH 7.4, they remain intact and substantially non-releasing at pH 1.2 and pH 6.8 and provide substantial release at pH 7.4.

[1209] In some embodiments, oral delayed onset, extended release capsule of levorphanol for ileo-

colonic and colonic delivery in sustained release form can be made, as shown in Example 49 to 62.

[1210] Example 50 to 53 are prepared as follows: (i) dispense ingredient (1) into a mixer; (ii) heat ingredient (1) until fully melted; (iii) dispense ingredient (2) into the same mixer; (iv) mix ingredient (1) and (2) until dispersed; (v) dispense ingredient (3) into the same mixer; (vi) mix ingredient (1), (2) and (3) until dispersed; (vii) dispense ingredient (4) into the same vessel; (viii) mix ingredient (1), (2), (3) and (4) thoroughly with a high shear mixer; (ix) transfer the contents into a liquid filling machine and fill into hard gelatin capsules. Optionally, cure the capsules by setting them at room temperature for a period of 1 to 7 days.

[1211] For Example 50 to 53, prepare a composition of aqueous Eudragit™ FS30D dispersion to coat 1.3 kg HPMC capsules: Eudragit™ FS30D 1207 g (solids, 362 g), Triethyl citrate 18 g (solids 18 g), Glyceryl monostearate 11 g (solids 11 g), Tween 80 (33%) 13 g (solids 4 g) and Distilled Water 728 g. Spray the dispersion onto the HPMC capsules using an Accela-Cota 10. The temperature of the capsule bed during the coating process is maintained between 26 and 32 °C. The mean amounts of polymer applied ranges from 5 mg/cm² to 20 mg/cm², preferably 6 mg/cm² to 15 mg/cm².

[1212] The in vitro performance of the dosage form can be tested using methods known in the art and described herein. When the capsules are tested using the USP Paddle Method in 0.1N HCl (pH 1.2) for two hours, followed by a switch to phosphate buffer pH 6.8 for one to two hours and then again, a switch to phosphate buffer pH 7.4, the capsules will remain intact and substantially non-releasing at pH 1.2 and pH 6.8, and they will release the levorphanol at pH 7.4 over a prolonged period (e.g., over 12 to 48 hours).

[1213] Example 50

Delayed Onset, Extended Release Dosage for Ileo-colonic or Colonic Release

	Ingredients	% w/w	mg/capsule
1	Hydrokote™ 112	75.38	245.0
2	Methocel™ K15M	18.46	60.0
3	Aerosil™ 200	3.08	10.0
4	Levorphanol Tartrate	3.08	10.0

[1214] Example 51

Delayed Onset, Extended Release Dosage for Ileo-colonic or Colonic Release

	Ingredients	% w/w	mg/capsule
1	Beeswax	70.74	237.00
2	Methocel™ K15M	23.88	80.00
3	Aerosil™ COK 84	2.39	8.00

4	Levorphanol Tartrate	2.99	10.00
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[1215] Example 52

Delayed Onset, Extended Release Dosage for Ileo-colonic or Colonic Release

	Ingredients	% w/w	mg/capsule
1	Cithrol™ GMS	81.49	273.00
2	Methocel™ K100	11.94	40.00
3	Aerosil™ COK 84	3.58	12.00
4	Levorphanol Tartrate	2.99	10.00

[1216] Example 53

Delayed Onset, Extended Release Dosage for Ileo-colonic or Colonic Release

	Ingredients	% w/w	mg/capsule
1	Hydrokote™ 112	75.38	253.00
2	Methocel™ K15M	18.46	60.00
3	Aerosil™ COK 84	3.08	12.00
4	Levorphanol Tartrate	3.08	10.00

[1217] Example 54 to 57 are prepared as follows: (i) dispense ingredient (1) into a mixer; (ii) heat ingredient (1) until fully melted; (iii) dispense ingredient (2) into the same mixer; (iv) heat ingredient (1) and (2) until fully melted; (v) dispense ingredient (3) into the same mixer; (vi) mix ingredient (1), (2) and (3) until dispersed; (vii) dispense ingredient (4) into the same mixer; (viii) mix ingredient (1), (2), (3) and (4) until dispersed; (ix) dispense ingredient (5) into the same vessel; (x) mix ingredient (1), (2), (3), (4) and (5) thoroughly with a high shear mixer; (ix) transfer the contents into a liquid filling machine and fill into hard gelatin capsules.

[1218] For Example 54 to 57, prepare a composition of aqueous Eudragit™ FS30D dispersion to coat 1.3 kg HPMC capsules: Eudragit™ FS30D 1207 g (solids, 362 g), Triethyl citrate 18 g (solids 18 g), Glyceryl monostearate 11 g (solids 11 g), Tween 80 (33%) 13 g (solids 4 g) and Distilled Water 728 g. Spray the dispersion onto the HPMC capsules using an Accela-Cota 10. The temperature of the capsule bed during the coating process is maintained between 26 and 32 °C. The mean amounts of polymer applied ranges from 5 mg/cm² to 20 mg/cm², preferably 6 mg/cm² to 15 mg/cm².

[1219] The in vitro performance of the dosage form can be tested using methods know in the art and described herein. When the capsules are tested using the USP Paddle Method in 0.1N HCl (pH 1.2) for two hours, followed by a switch to phosphate buffer pH 6.8 for one to two hours and then again, a switch to phosphate buffer pH 7.4, the capsules will remain intact and substantially non-

releasing at pH 1.2 and pH 6.8, and they will release the levorphanol at pH 7.4 over a prolonged period (e.g., over 12 to 48 hours).

[1220] Example 54

Delayed Onset, Extended Release Dosage for Ileo-colonic or Colonic Release

	Ingredients	% w/w	mg/capsule
1	Compritol™ 888 ATO	52.23	173.00
2	Miglyol™ 812	25.23	82.00
3	Methocel™ K15M	15.38	50.00
4	Aerosil™ 200	3.08	10.0
5	Levorphanol Tartrate	3.08	10.0

[1221] Example 55

Delayed Onset, Extended Release Dosage for Ileo-colonic or Colonic Release

	Ingredients	% w/w	mg/capsule
1	Sterotex™	47.07	153.00
2	Miglyol™ 812	25.23	82.00
3	Methocel™ K15M	21.54	70.00
4	Aerosil™ 200	3.08	10.0
5	Levorphanol Tartrate	3.08	10.00

[1222] Example 56

Delayed Onset, Extended Release Dosage for Ileo-colonic or Colonic Release

	Ingredients	% w/w	mg/capsule
1	Sterotex™	57.11	185.60
2	Miglyol™ 812	25.23	82.00
3	Methocel™ K15M	11.50	70.00
4	Aerosil™ 200	3.08	10.00
5	Levorphanol Tartrate	3.08	10.00

[1223] Example 57

Delayed Onset, Extended Release Dosage for Ileo-colonic or Colonic Release

	Ingredients	% w/w	mg/capsule
1	Sterotex™	42.09	141.00
2	Fractionated Coconut Oil	23.88	80.00
3	Methocel™ K15M	29.85	100.00

4	Aerosil™ COK 84	1.194	4
5	Levorphanol Tartrate	2.99	10.00

[1224] Examples 58 and 59 are oral delayed onset, extended release tablets of levorphanol for ileo-colonic and colonic delivery in sustained release.

[1225] The core tablet of levorphanol is prepared using the composition shown in the Tables for Examples 58 and 59 using the following procedure: (i) Mix 1, 2, (and 3), and 5 and pass through #20 mesh; (ii) Dissolve 4 in 7; (iii) Granulate the powder from (i) using a fluid bed granulator and then dry; (iv) Pass the dry granules through #20 mesh; (v) Mix the granules with 6; (vi) Compress to tablet using plain/plain tooling. Prepare a coating solution comprising: (a) Ethylcellulose (Ethocel PR100), 9.0 to 15 mg per tablet; (b) Polyvinylpyrrolidone (Kollidon™ 90F), 3.0 to 7.0 mg per tablet; (c) Dibutyl Sebacate, 2.0 to 4.0 mg per tablet; (d) Denatured Alcohol 150 to 300 mg per tablet (evaporates during process). Spray coating solution using coating pan until desired in vitro release is achieved as described herein. Adjust coating solution composition or coating weight/thickness as required. The coating weight is usually approximately 5 to 40% w/w. For the initial trial, prepare one coating comprising : (a) Ethylcellulose (Ethocel PR100), 9.2 mg per tablet; (b) Polyvinylpyrrolidone (Kollidon™ 90F), 4.15 mg per tablet; (c) Dibutyl Sebacate, 2.70 mg per tablet; (d) Denatured Alcohol 170 mg per tablet (evaporates during process). Prepare another coating comprising: (a) Ethylcellulose (Ethocel PR100), 14.15 mg per tablet; (b) Polyvinylpyrrolidone (Kollidon™ 90F), 5.1 mg per tablet; (c) Dibutyl Sebacate, 3.85 mg per tablet; (d) Denatured Alcohol 245 mg per tablet (evaporates during process).

[1226] Example 58

Delayed Onset, Extended Release Levorphanol Tartrate Tablets for Slow Ileo-colonic or Colonic Release

Ingredients	Quantity (mg)
1. Levorphanol Tartrate	40.00
2. Microcrystalline Cellulose	90.00
3. HPMC (low viscosity grade)	46.00
4. Polyvinyl Alcohol	2.00
5. Colloidal Silicon Dioxide	1.00
6. Sodium Stearyl Fumarate	1.00
7. Purified Water *	As needed to form granules

* Evaporated during process

[1227] Example 59

Delayed Onset, Extended Release Levorphanol Tartrate Tablets for Slow Ileo-colonic or Colonic Release

Ingredients	Quantity (mg)
1. Levorphanol Tartrate	10.00
2. Microcrystalline Cellulose	90.00
3. HPMC (low viscosity grade)	---
4. Polyvinyl Alcohol	2.00
5. Colloidal Silicon Dioxide	1.00
6. Sodium Stearyl Fumarate	1.00
7. Purified Water *	41.60 (to form granules)

* Evaporated during process

[1228] Alternatively, Examples 58 and 59 may be coated with a suitable amount of Eudragit™ S 100, or Eudragit™ S 12.5, or Eudragit™ FS 30D

[1229] Example 60

[1230] Example 60 provides a method for manually sealing the overlapping region of the HPMC capsule body and cap using a process called banding. The banding solution is prepared as follows: (i) prepare the banding solution with 18 g of 4.5 cps HPMC along with 33 g of water and heated to 80 °C in a beaker; (ii) stir the mixture until the HPMC is well dispersed in the water; (iii) to completely solubilize the HPMC, add 50 mL of absolute alcohol and sonicate for 10 minutes; (iv) seal capsules using equipment such as the Lab band sealing machine (LBS 100) or the Qualicaps™ Lab-Top Capsule Band-Sealer (S-1); (v) apply banding solution uniformly to the external edge of the gap of the capsule to be sealed to form a liquid ring around the circumference of the capsule and remove excess sealing liquid from the exterior of the capsule; (vi) dry the capsules by applying thermal energy, such as hot air and a controlled temperature oven. For larger scale banding, automated equipment such as the Qualicaps S-40 or S-100 capsule band-sealing machine or the Hermetica™ is a capsule banding machine may be used to seal filled, two-piece capsules with a single or double band of substances such as gelatin or hypromellose at the joined portion of the cap and body.

[1231] Example 61

[1232] Example 61 provides an alternative method of coating small batches of capsules to provide ileo-colonic or colonic deliver of the oral levorphanol dosage form for slow release. This method can be used in place of other described enteric coating methods. The method can be readily modified by those skilled in the art to coat tablet dosage forms. In this example, coating is carried out using 45% suspension of Eudragit™ FS30D. Coating solution is prepared by homogenizing talc and triethyl citrate in water for 10 minutes. This suspension is poured into Eudragit™ FS 30 D dispersion under stirring. This spray suspension is transferred through 0.5 mm sieve. Coating suspension is spread by spray gun on a moving capsule bed. The process is carried out in

conventional coating pan (see Table below). The coating solution may be further modified to achieve targeted GI delivery or release in or distal to the duodenum, jejunum, ileum, ileo-cecal junction, ileo-colonic region or colon, using methods known in the art and those described herein.

Composition of Coating Solution

Ingredients	Enteric coating
Eudragit™ FS 30 D	150 g
Talc	22.5 g
Triethyl citrate	2.5 g
Water	175 g

[1233] The coating process parameters like the coating pan, baffles, inlet air temperature, product temperature, exhaust and spray air pressure are shown in Table below.

Coating Process Parameters

Coating pan	12 inch
Baffles	Present
Silicone tube od/id	2 mm
Inlet air temperature	40 °C
Product Temperature	30 °C
Exhaust	ON
Blower	ON
Spray air pressure	2 bar

[1234] Example 62

[1235] Example 62 provides an alternative method of coating small batches of capsules to provide ileo-colonic or colonic delivery of the oral levorphanol dosage form for slow release. This method can be used in place of other described enteric coating methods. The method can be readily modified by those skilled in the art to coat tablet dosage forms. The coating solution may be further modified to achieve targeted GI delivery or release in or distal to the duodenum, jejunum, ileum, ileo-cecal junction, ileo-colonic region or colon, using methods known in the art and those described herein. An initial coating solution is provided in the Table below. This can be modified further to achieve the desired delivery profile:

S. No.	Ingredients	% w/w
1	Eudragit™ S 100	6.1
2	Triethyl citrate	0.9
3	Talc	3.0
4	Isopropyl alcohol	85.0
5	Water	5.0

[1236] The procedure for preparation of the above coating solution is: (a) dissolve Eudragit™ in 70% of total IPA and 100 % of water; (b) homogenize talc and triethyl citrate in 30% of remaining IPA; (c) add talc and triethyl citrate dispersion to Eudragit™ solution and stir gently. Apply the coat by dip coating using the ProCoater™ (Torpac, New Jersey), with the method recommended by the manufacturer or preferably described by described by Dodds and Podczeck (Tablets & Capsules, January 2008, CSC Publishing Inc). Once dry, check weight gain. Additional coating may be applied to provide further weight gain. Batches with polymer target weight gains of about 10 mg/cm² to about 20 mg/cm² are prepared (for example, 10 mg/cm² or 15 mg/cm² and 20 mg/cm²). The approximate surface area of Capsule Size 00, 0, 1 and 2 are 6.16 cm², 5.07 cm², 4.06 cm², and 3.43 cm², respectively (see Jones, Tablets & Capsules, January 2009 and April 2009, CSC Publishing Inc). This provides a target weight gain range shown below:

Capsule		Total Capsule Weight Gain		
Size	Surface Area	10 mg/cm ²	15 mg/cm ²	20 mg/cm ²
00	6.16 cm ²	60 mg	90 mg	120 mg
0	5.07 cm ²	50 mg	75 mg	100 mg
1	4.06 cm ²	40 mg	60 mg	80 mg
2	3.43 cm ²	35 mg	50 mg	70 mg

[1237] To determine if the desired target delivery or release has been achieved, a disintegration tester is used (e.g. manually with the ERWEKA™ ZT 120, ZT 120, ZT 220, or ZT 320, or using the automated ZT 850). Alternatively, an orbital shaker or a beaker with an agitator (or magnetic stirrer at moderate or high speed) is used, first in 0.1N HCl for two hours, then with a change in media to water at pH >7 (or other suitable pH). The capsules shell remains intact in 0.1 N HCL (pH 1.2) for two hours and disintegrates or ruptures at the desired pH (e.g., pH 7) usually after 5 to 90 minutes (the higher the weight gain, the longer they stay intact at pH 7). For delayed onset, extended release dosage forms intended to provide targeted GI delivery (e.g., ileo-colonic or colonic delivery) for subsequent slow or sustained release, the capsule shell will rupture, disintegrate, or dissolve but the contents may remain intact (depending on the dosage form used).

[1238] A more specific and reliable method to determine coating integrity and attainment of target GI delivery (which does not rely on visual inspection of capsules) for delayed onset, extended release forms is the use of a dissolution methods where the drug release is quantified. When such the capsules are tested using the USP Paddle Method in 0.1N HCl (pH 1.2) for 2 hours at 37 °C, the capsules (or tablets) remain intact and substantially non-releasing. Following a switch to the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at the target pH, the dosage form begins to provide rapid or slow release of the drug usually after 5 to 90 minutes.

[1239] The optimal coating solution composition, weight gain and process parameters to achieve the desired target delivery or release is achieved by simultaneously testing the coated dosage form dosage form at various pH using the USP Paddle Method in 0.1N HCl (pH 1.2) for 2 hours at 37 °C, followed by a switch to the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water (time = 0 hour begins here) at 37 °C at the target pH (e.g., pH 6.5, pH 6.8, pH 7.0, pH 7.5). For delayed onset, extended release dosage forms intended to provide targeted GI delivery distal to the stomach, preferably less than 10% of drug should be released at pH 1.2 at 1 or 2 hours, using the method shown above.

[1240] Various alternative small and large scale methods of organic and aqueous coating of tablets and capsules have been described or referenced herein, or are known those skilled in the art. Enteric coatings may also be applied over tablet and capsule osmotic delivery dosage forms of oral levorphanol, including push pull osmotic pumps, monolithic osmotic delivery systems and controlled porosity osmotic pumps to provide targeted delivery in the GI tract.

[1241] Example 63

A matrix tablet formulation of extended release levorphanol is prepared using the method described here: (i) the Polyox and MCC are passed through a 44# sieve and then weighed; (ii) levorphanol tartrate is weighed and milled in mortar-pestle to make fine powder; (iii) the mixture of step (i) is mixed with step (ii) to provide a homogeneous mixture. Uniform mixture is achieved through sieving several times and mixing geometrically; (iv) the lubricants are added and passed through 25 # sieve in above mixture by sieving them with step (iii); (v) The mixture is well mixed and sieved through a 25# sieve twice and homogenized in a polybag; (vi) tablets are compressed using a standard concave 9 mm punch on single punch compression machine.

[1242] **Extended Release Levorphanol Tablets**

	Drug Layer	mg/Tablet	%w/w
1	Levorphanol Tartrate	10.0	5.0
2	Polyox WSR 301	100.0	50.0
3	MCC 101	80.0	40.0
4	Talc	3.0	1.5
5	Mg. Stearate	3.0	1.5
6	SiO ₂	4.0	2

[1243] The tablet dissolution is evaluated in 900 mL of pH 1.2 for 2 hours, followed by a switch to pH 6.8 phosphate buffer using the USP paddle method at 50 to 100 rpm, and in 900 mL of pH 6.8 phosphate buffer using the USP paddle method at 100 rpm and.

[1244] Example 64

A matrix tablet formulation of oral extended release levorphanol is prepared using the method described here: (i) the Polyox, HPMC K100M CR and MCC are passed through a 44 # sieve and then weighed; (ii) levorphanol tartrate is weighed and passed through a 25# sieve; (iii) the mixture of step (i) is mixed with step (ii) to provide a homogeneous mixture. Uniform mixture is achieved

through sieving several times and mixing geometrically; (iv) the lubricants are added and passed through 100 # sieve in above mixture by sieving them with step (iii); (v) the mixture is well mixed and sieved through a 25# sieve twice and homogenized in a polybag; (vi) tablets are compressed using a standard concave 9 mm punch on single punch compression machine.

[1245] Extended Release Levorphanol Tablets

	Drug Layer	mg/Tablet	%w/w
1	Levorphanol Tartrate	10.0	5.0
2	Polyox WSR 301	50.0	25.0
3	HPMC K100M CR	50.0	25.0
4	MCC 101	80.0	40.0
5	Talc	3.0	1.5
6	Mg. Stearate	3.0	1.5
7	SiO ₂	4.0	2

[1246] The tablet dissolution is evaluated in 900 mL of pH 1.2 for 2 hours at 50 to 100 rpm, followed by a switch to 900 mL pH 6.8 phosphate buffer using the USP paddle

[1247] A controlled porosity osmotic pump (CPOP) dosage form of oral levorphanol is prepared using the method described here.

[1248] Core Tablet: (i) levorphanol tartrate is mixed with lactose and sodium chloride after passing through 40# sieve; (ii) the mixture of step (1) is added to PVP K 30 solution in IPA; (iii) the mass is well mixed to achieve a homogeneous mixture; (iv) the mass is dried in a dryer at 50°C for 10 minutes; (v) the mass is passed through a #18 sieve once for granulation; (vi) the granules are further dried; (vii) magnesium stearate and talc are then added and mixed; (viii) the tablets are compressed using a standard concave 9 mm punch on single punch compression machine.

[1249] Coating Solution: (i) cellulose acetate is dissolved in acetone; (ii) D-sorbitol is dissolved in water half quantity; (iii) PEG is dissolved in rest of the one fourth of water; (iv) step (ii) is mixed with step (1) with high stirring; (v) step (iii) is mixed with the mixture of step (i) and step ii); (vi) the solution is stirred to homogenize; (vii) dip the tube of the coating solution dispenser into the product of step (vi).

[1250] Extended Release Osmotic Dosage Form Core Tablet

	Drug Layer	mg/Tablet	%w/w
1	Levorphanol Tartrate	10.0	4.3
2	Sodium Chloride	100.0	43.5
3	Lactose	100.0	43.5
4	PVP K 30 in IPA 3 mL	12.0	5.2
5	Mg. Stearate	3.0	1.3
6	Talc	3.0	1.3
7	Aerosil™ 200	2.0	0.87

[1251] Extended Release Osmotic Dosage Form Coating Solution

	Coating Formula	mg/Tablet	% w/w
1	Cellulose Acetate	22.95	2.39
2	D -Sorbitol	4.05	0.42
3	PEG - 400	4.05	0.42
4	Acetone	855.00	88.97
5	Water	75.00	7.80

[1252] **Extended Release Osmotic Dosage Form Coating Process Parameters**

Coating Parameters	
Solvent	Acetone : Water (90 : 10)
Solids content (%w/w)	4 % (3.23 %)
Weight gain (%)	15 % Target / 13.71 Achieved
Inlet air temperature (°C)	50 - 55 °C (Set) 49 ° Actual
Out let air temperature (°C)	45-50 °C (Set) 40° Actual
Inlet air CFM	32
Outlet air CFM	43
Tablet surface bed temp (°C)	40-42 °C
Pre-warm tablet bed (°C)	41-43 °C
Load	175 gm
Atomizing air pressure (kg/cm ²)	3.0 kg/cm ²
Gun-to-bed distance (inches)	Three to Four inch
Spray rate (g/min)	4.5 to 5.5 g\min
Baffles	6
Pan speed (rpm)	3.0 RPM
Peristaltic Pump RPM	10 RPM
Fluid nozzle (mm)	1.5
Spray equipment	Solace
Spray pan size	12 “

[1253] The tablet dissolution is evaluated in 900 mL of pH 6.8 phosphate buffer using the USP paddle method at 50 to 100 rpm after application of coating in the following w/w% amounts: (i) 5.7%; (ii) 9.6%; and (13.7%).

[1254] Example 65

[1255] A push-pull osmotic pump (PPOP) dosage form of extended release levorphanol is prepared using the method described below. Ingredients 1, 2 and 3 of drug layer are sifted (through BSS 22), dry mixed, and granulated with IPA. The granules, after drying and sifting (through BSS 22) are lubricated with ingredients 4 to 6 (passed through 30 BSS) of drug layer blend. Similarly, ingredients 1, 2, 3 and 4 of push layer are granulated with IPA. The granules, after drying and sifting are lubricated with ingredients 5 to 7. Bilayer tablets are compressed on a single punch compression machine using 8 mm punch. First the push layer is filled into die cavity and pressed lightly followed by addition of drug layer and mass is compressed to obtain tablets having minimum hardness of 4.5 kg/cm². A 4% w/v solution containing cellulose acetate and PEG 4000 in ratio of 90:10 is used for the coating of the bilayer tablets. Cellulose acetate and PEG 4000 are dissolved in acetone, stirred and sonicated to obtain clear transparent solution. Coating is done until the weight gain of 20-22 % w/w which takes around 2.5 hrs. Coated tablets are dried in the oven for

16 to 20 hours; 55 °C. Coated tablets are drilled using 8.0 mm drill at the centre of tablet on the drug layer side to create an appropriate orifice.

[1256] Extended Release Osmotic Dosage Form Drug Layer

	Drug Layer	mg/Tablet	%w/w
1	Levorphanol Tartrate	10	6.45
2	Polyox WSR N 80	136	87.74
3	HPMC E5	7	4.51
4	Magnesium Stearate	1	0.65
5	Colloidal Silicon Dioxide	0.5	0.32
6	Talc	0.5	0.32

[1257] Extended Release Osmotic Dosage Form Push Layer

	Push Layer	mg/Tablet	%w/w
1	Polyethylene oxide (Polyox WSR Coagulant)	63	63
2	Sodium Chloride	29	29
3	HPMC E5	5	5
4	Red Ferric Oxide	1	1
5	Magnesium Stearate	0.8	0.8
6	Colloidal Silicon Dioxide	0.7	0.7
7	Talc	0.5	0.5

[1258] The tablet dissolution is evaluated in 900 mL of pH 6.8 phosphate buffer using the USP paddle method at 50 to 100 rpm.

[1259] Example 66

[1260] A push-pull osmotic pump (PPOP) dosage form of extended release levorphanol is prepared using the method described below. Ingredients 1, 2 and 3 of drug layer are sifted (through BSS 22), dry mixed, and granulated with IPA. The granules, after drying and sifting (through BSS 22) are lubricated with ingredients 4 to 6 (passed through 30 BSS) of drug layer blend. Similarly, ingredients 1, 2, 3 and 4 of push layer are granulated with IPA. The granules, after drying and sifting are lubricated with ingredients 5 to 7. Bilayer tablets are compressed on a single punch compression machine using 8 mm punch. First the push layer is filled into die cavity and pressed lightly followed by addition of drug layer and mass is compressed to obtain tablets having minimum hardness of 7.5 kg/cm². A 4% w/v solution containing cellulose acetate and PEG 4000 in ratio of 95:5 is used for the coating of the bilayer tablets. Cellulose acetate and PEG 4000 are dissolved in acetone, stirred and sonicated to obtain clear transparent solution. Coating is done until the weight gain of 20-22 % w/w which takes around 2.5 hrs. Coated tablets are drilled using 8.0 mm drill at the centre of tablet on the drug layer side to create an appropriate orifice.

[1261] Extended Release Osmotic Dosage Form Drug Layer

	Drug Layer	mg/Tablet	%w/w
1	Levorphanol Tartrate	10	6.45
2	(Polyox WSR N 80)	136	87.74

3	HPMC E5	7	4.51
4	Magnesium stearate	1	0.65
5	Colloidal silicon dioxide	0.5	0.32
6	Talc	0.5	0.32

[1262] Extended Release Osmotic Dosage Form Push Layer

	Push Layer	mg/Tablet	%w/w
1	Polyethylene oxide (Polyox WSR Coagulant)	63	63
2	Sodium Chloride	29	29
3	HPMC E5	5	5
4	Red Ferric Oxide	1	1
5	Magnesium Stearate	0.8	0.8
6	Colloidal Silicon Dioxide	0.7	0.7
7	Talc	0.5	0.5

[1263] The tablet dissolution is evaluated in 900 mL of pH 6.8 phosphate buffer using the USP paddle method at 50 to 100 rpm.

[1264] Example 67

[1265] A push-pull osmotic pump (PPOP) dosage form of extended release levorphanol is prepared using the method described below. Ingredients 1, 2 and 3 of drug layer are sifted (through BSS 22), dry mixed, and granulated with IPA. The granules, after drying and sifting (through BSS 22) are lubricated with ingredients 4 to 6 (passed through 30 BSS) of drug layer blend. Similarly, ingredients 1, 2, 3 and 4 of push layer are granulated with IPA. The granules, after drying and sifting are lubricated with ingredients 5 to 7. Bilayer tablets are compressed on a single punch compression machine using 8 mm punch. First the push layer is filled into die cavity and pressed lightly followed by addition of drug layer and mass is compressed to obtain tablets having minimum hardness of 6.5 kg/cm². A 4% w/v solution containing cellulose acetate and PEG 4000 in ratio of 90:10 is used for the coating of the bilayer tablets. Cellulose acetate and PEG 4000 is dissolved in acetone, stirred and sonicated to obtain clear transparent solution. Coating is done until the weight gain of 20-22 % w/w which takes around 2.5 hrs. Coated tablets are drilled using 8.0 mm drill at the centre of tablet on the drug layer side to create an appropriate orifice.

[1266] Extended Release Osmotic Dosage Form Drug Layer

	Drug Layer	mg/Tablet	%w/w
1	Levorphanol Tartrate	10	6.45
2	(Polyox WSR N 80)	136	87.74
3	HPMC E5	7	4.51
4	Magnesium stearate	1	0.65
5	Colloidal silicon dioxide	0.5	0.32
6	Talc	0.5	0.32

[1267] Extended Release Osmotic Dosage Form Push Layer

	Push Layer	mg/Tablet	% w/w
1	Polyethylene oxide (Polyox WSR Coagulant)	63	63
2	Sodium Chloride	29	29
3	HPMC E5	5	5
4	Red Ferric Oxide	1	1
5	Magnesium Stearate	0.8	0.8
6	Colloidal Silicon Dioxide	0.7	0.7
7	Talc	0.5	0.5

[1268] The tablet dissolution is evaluated in (i) 900 mL of pH 6.8 phosphate buffer and in and (ii) at pH 1.2 for 2 hrs, followed by pH 6.8 phosphate buffer for the remaining time using the USP paddle method at 50 to 100 rpm.

[1269] Example 68

[1270] A matrix dosage form of extended release levorphanol is prepared using the method described below. 1. Weigh the levorphanol tartrate, HPMC E15 LV, HPMC K15 M CR, MCC, ascorbic acid, citric acid, sodium citrate, EDTA and colloidal silicon dioxide. 2. Sift ingredients of step 1 using mesh ASTM # 40. 3. Blended step 2 ingredients for 10 minutes. 4. Weigh PVP K30 and alpha-tocopherol acetate and put in IPA and prepare binder solution. 5. Granulate step 3 blend using step 4 binder solution. 6. Dry step 5 granules in oven at 50 °C. 7. Sift dry granules through mesh ASTM # 25. 8. Weigh and sift magnesium stearate through mesh # 60. 9. Lubricate step 7 granules using pre-sifted magnesium stearate for 5 minutes in a polybag. 10. Compress the granules using 7.5 mm round standard concave punches.

[1271]

Components	mg/Tablet
Levorphanol Tartrate	10
HPMC E 15 LV	13.3
HPMC K 15 M CR	26.7
MCC (Avicel™ PH 102)	56.4
Ascorbic Acid	2.5
Alpha-tocopherol Acetate	0.5
Citric Acid Anhydrous	4
Sodium Citrate Trihydrate	4
PVP K30	3
EDTA	0.1
Aerosil™	3
Magnesium stearate	1.5
Isopropyl Alcohol	qs

[1272] The tablet dissolution is evaluated in (i) 600 mL of pH 6.8 phosphate buffer and in and (ii) in pH 1.2 (0.1 N HCl) for 24 hours using the USP paddle method at 50 to 100 rpm.

[1273] Example 69

Tablets Composition of Extended Release Levorphanol

Ingredients	Qty./Unit
1. Levorphanol Tartrate	20 mg
2. HPMC 2208, USP	150 mg
3. Carnauba wax	30 mg
4. HPMC 2910, USP	15 mg
5. Magnesium Stearate	2 mg
6. Stearic acid	8 mg
7. Talc	3 mg

[1275] In Example 69, place the ingredients 1, 2 and 3 in the granulator and mix for 15 minutes. Dissolve ingredient 4 in water (mix in hot water, then cool down) and spray into the fluidized mixture. Dry to approximately 5% moisture. Sequentially add ingredient 5, 6 and 7, with mixing steps between each addition. Compress using capsule shaped tooling.

[1276] Example 70

Tablets Composition of Extended Release Levorphanol

Ingredients	Amt/Unit (mg)
Levorphanol Tartrate	30
Spray Dried Lactose	60
Povidone	5
Eudragit RS30D (solids)	10
Triacetin	2
Stearyl Alcohol	25
Talc	2.5
Magnesium Stearate	1.25
Opadry Pink Y-S-14518A	4.0

[1277] In Example 70: 1. Granulation: Spray the Eudragit/Triacetin dispersion onto the Levorphanol, Spray Dried Lactose and Povidone using a fluid bed granulator. 2. Milling: Discharge the granulation and pass through a mill. 3. Waxing: Melt the stearyl alcohol and add to the milled granulation using a mixer. Allow to cool. 4. Milling: Pass the cooled granulation through a mill. 5. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer. 6. Compression: Compress the granulation into tablets using a tablet press. 7. Film coating: Apply an aqueous film coat to the tablets.

[1278] Example 71

Capsule Composition of Extended Release Levorphanol

Ingredients	Amt/Unit (mg)
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Levorphanol Tartrate	20
Eudragit RSPO	76
Eudragit RLPO	4
Stearyl Alcohol	25

[1279] In Example 71: 1. Blend milled Stearyl Alcohol, Eudragit RLPO, Levorphanol Tartrate, and Eudragit RSPO using a Hobart Mixer. 2. Extrude the granulation using a Powder Feeder, Melt Extruder (equipped with the 6 x 1 mm die head), Conveyor, Lasermike, and Pelletizer. Powder feed rate-40 g/min; vacuum-about 980 mBar; Conveyor, such that diameter of extrudate is 1 mm, Pelletizer, such that pellets are cut to 1 mm in length. Screen pellets using #16 mesh and #20 mesh screens. Collect material that passes through the #16 mesh screen and is retained on the #20 mesh screen. 4. Fill capsules with the pellets.

[1280] Example 72

Capsule Composition of Extended Release Levorphanol

Ingredients	Amt/Unit (mg)
Levorphanol Tartrate	12
Eudragit RSPO	77
Ethocel	4.5
Stearic acid	27

[1281] In Example 72: 1. Blend milled Stearic acid, ethocel, Levorphanol Tartrate, and Eudragit RSPO using a V-blender. 2. Extrude the mixture using a Powder Feeder, Melt Extruder (equipped with the 6 x 1 mm die head), Conveyor, Lasermike, and Pelletizer. Powder feed rate, 1.2 kg/hr; vacuum, about 980 mBar; Conveyor, such that diameter of extrudate is 1 mm; Pelletizer, such that pellets are cut to 1 mm in length. 3. Screen pellets using #16 mesh and #20 mesh screens. Collect material that passes through the #16 mesh screen and is retained on the #20 mesh screen. Fill pellets in capsules.

[1282] Example 73

Capsule Composition of Extended Release Levorphanol

Steps	Ingredients	Amt/unit (mg)
1	Levorphanol tartrate	12
	Non-pareil beads (30/35 mesh)	45
	Opadry Clear	2.5
2	Eudragit RS3-D (dry)	7.2
	Eudragit RL30D (dry)	0.4
	Triethyl citrate	1.5
	Cabosil	0.4
3	Opadry Clear (HPMC)	1.9
	Cabosil	0.28

[1283] In Example 73: 1. Dissolve Levorphanol tartrate and Opadry (HPMC) in water. Spray the

drug solution onto nonpareil beads in a fluid bed coater with Wurster insert. 2. Disperse Eudragit RS, Eudragit RL, triethyl citrate, and Cabosil in water. Spray the dispersion onto the beads in the fluid bed coater. 3. Dissolve Opadry in water. Spray the solution onto the beads in the fluid bed coater. 4. Cure the beads at 60.degree. C. for 24 hours.

[1284] Example 74

Tablet Composition of Extended Release Levorphanol

Ingredient	Amt/unit (mg)
Levorphanol Tartrate	15
Anhydrous Dicalcium Phosphate (Powdered)	44
Microcrystalline Cellulose	62
Glyceryl Behenate	62
Magnesium Stearate	20
Opadry Red	2
Purified Water	10
	57*

*Remains in product as residual moisture only.

[1285] In Example 74: 1. Pass the Stearyl Alcohol flakes through an oscillating mill. 2. Mix the Levorphanol Tartrate, milled Stearyl Alcohol, Anhydrous Dicalcium Phosphate, Microcrystalline Cellulose, and Glyceryl Behenate in a twin shell blender. 3. Continuously feed the blended material into a twin screw extruder and collect the resultant heated material on a conveyor. 4. Allow the extrudate to cool on the conveyor. 5. Mill the cooled extrudate using an oscillating mill. 6. Blend the milled extrudate and Magnesium Stearate. 7. Compress the resultant granulation using a tablet press, preferably into a caplet. 8. Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet.

[1286] Example 75

Tablet Composition of Extended Release Levorphanol

Ingredient	Amt/unit (mg)
Levorphanol Base	10
Spray Dried Lactose	60
Povidone	5
Eudragit RS 30D (dry wt.)	10
Triacetin	2
Stearyl Alcohol	25
Talc	2.5
Magnesium Stearate	1.25
Opadry Pink	6
Purified Water	34*

*Remains in product as residual moisture only.

[1287] In Example 75: Plasticize the Eudragit with Triacetin by mixing. 2. Place the Levorphanol Base, Spray Dried Lactose, and Povidone into a fluid bed granulator and apply the above solution.

3. Pass the granulation through a rotating impeller mill. 4. Dry granulation if moisture content is too high. 5. Melt Stearyl Alcohol and wax the above granulation by adding melted Stearyl Alcohol onto granulation while mixing. 6. Cool the waxed granulation in a fluid bed dryer. 7. Pass the cooled waxed granulation through a rotating impeller mill. 8. Blend the milled waxed granulation, Talc and Magnesium Stearate. 9. Compress the resultant granulation using a tablet press. 10. Prepare a film coating solution by dispersing the Opadry in Purified Water and applying it to the tablet.

[1288] Example 76

Capsule Composition of Extended Release Levorphanol

Ingredient	Amt/unit (mg)
Levorphanol Tartrate	8
Eudragit RSPO	76.5
Ethylcellulose	4.5
Stearyl Alcohol	27

[1289] In Example 76: 1. Pass Stearyl Alcohol flakes through an impact mill. 2. Mix the Levorphanol Tartrate, Eudragit, Ethylcellulose and milled Stearyl Alcohol in a twin shell blender. 3. Continuously feed the blended material into a twin screw extruder and collect the resultant strands on a conveyor. 4. Allow the strands to cool on the conveyor. 5. Cut the cooled strands into pellets using a Pelletizer. 6. Screen the pellets and collect desired sieve portion. 7. Fill the extruded pellets into capsules.

[1290] Example 77 to 88 may be prepared as follows: (i) Dispense the specified hydrophobic controlled release material (e.g., hydrogenated Type I vegetable oil, hydrogenated Type II vegetable oil, polyoxyethylene stearates, polyoxyethylene distearates, glycerol monostearate, poorly water soluble, or high melting point waxes) into a mixer; (ii) Heat until fully melted; (iii) dispense the hydroxypropyl methyl cellulose (HPMC) into the mixer; (iv) Mix until dispersed; (v) Dispense the Aerosil into the same vessel; (vi) Mix until dispersed; (vii) Dispense levorphanol into the same vessel; (viii) Stir thoroughly with a high shear mixer; (ix) Transfer the mix into a liquid filling machine; (x) Fill into hard gelatin (or HPMC) capsule; (xi) Optionally, transfer the capsules to a banding machine and band the capsules. (xii) Optionally, dispense (i), (iii) and (v) into a mixer, then continue heat the mixture of (i), (iii) and (v) simultaneously until fully melted, then continue from (vii). Optionally, dispense (i), (iii), (v) and (vii) into a mixer, then continue heat the mixture until (i), (iii) and (v) have until fully melted, then continue from (viii).

[1291] Example 77

Capsule Composition of Extended Release Levorphanol

Ingredients	Quantity (mg)/Dose
Sterotex® NF	200
Fractionated coconut oil	70

Methocel® K 15M	81
Aerosil® COK 84	4
Levorphanol Tartrate	5

[1292] Example 78

Capsule Composition of Extended Release Levorphanol

Ingredients	Quantity (mg)/Dose
Beeswax	200
HPMC, K15M	80
Aerosil COK 84	8
Levorphanol Tartrate	5

[1293] Example 79

Capsule Composition of Extended Release Levorphanol

Ingredients	Quantity (mg)/Dose
Sterotex NF	150
HPMC, K15M	75
Coconut oil	75
Aerosil COK 84	5
Levorphanol Tartrate	10

[1294] Example 80

Capsule Composition of Extended Release Levorphanol

Ingredients	Quantity (mg)/Dose
Cithrol GMS	275
HPMC, K100M	40
Aerosil COK 84	10
Levorphanol Tartrate	5

[1295] Example 81

Capsule Composition of Extended Release Levorphanol

Ingredients	Quantity (mg)/Dose
Hydrokote 112	250
HPMC, K15M	60
Aerosil COK 84	10
Levorphanol Tartrate	10

[1296] Example 82

Capsule Composition of Extended Release Levorphanol

Ingredients	Quantity (mg)/Dose
Beeswax	200
HPMC, Pharmacoat 606	62.5
Aerosil COK 84	7.5
Levorphanol Tartrate	5

[1297] Example 83

Capsule Composition of Extended Release Levorphanol

Ingredients	Quantity (mg)/Dose
Gelucire 50/02	190
Methocel K 100M	35
Aerosil COK 84	10
Levorphanol Tartrate	5

[1298] Example 84

Capsule Composition of Extended Release Levorphanol

Ingredients	Quantity (mg)/Dose
Cetyl alcohol	280
Methocel K 100M	50
Aerosil COK 84	10
Levorphanol Tartrate	10

[1299] Example 85

Capsule Composition of Extended Release Levorphanol

Ingredients	Quantity (mg)/Dose
Sterotex NF	320
Methocel K 15M	60
Aerosil COK 84	10
Levorphanol Tartrate	10

[1300] Example 86

Capsule Composition of Extended Release Levorphanol

Ingredients	Quantity (mg)/Dose
Cithrol GMS	320
Methocel K 100M	55
Aerosil COK 84	15

Levorphanol Tartrate	10
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[1301] Example 87

Capsule Composition of Extended Release Levorphanol

Ingredients	Quantity (mg)/Dose
Sterotex® NF	100
Fractionated coconut oil	70
Beeswax	100
Methocel® K 15M	81
Aerosil® COK 84	4
Levorphanol Tartrate	10

[1302] Example 88

Capsule Composition of Extended Release Levorphanol

Ingredients	Quantity (mg)/Dose
Glyceryl behenate	135
Fractionated coconut oil	50
Methocel® K 15M	60
Aerosil® COK 84	3
Levorphanol Tartrate	5

[1303] Example 89

Tablet Composition of Extended Release Levorphanol

Ingredients	Quantity (mg)/Dose
Lactose (spray dried)	230
Eudragit™ RS PM	60
Purified water	q.s.*
Stearyl Alcohol	90
Talc	8
Magnesium Stearate	4
Levorphanol Tartrate	5

*Remains in product as residual moisture only.

[1304] In Example 89: The required quantities of levorphanol tartrate, spray-dried lactose, and Eudragit™ RS PM are transferred into an appropriate-size mixer, and mixed for approximately 5 minutes. While the powders are mixing, the mixture is granulated with enough water to produce a moist granular mass. The granules are then dried in a fluid bed dryer at 60 °C, and then passed

through an 8-mesh screen. Thereafter, the granules are re-dried and pushed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60 to 70 °C, and while the granules are mixing, the melted stearyl alcohol is added. The warm granules are returned to the mixer. The coated granules are removed from the mixer and allowed to cool. The granules are then passed through a 12-mesh screen. Then granulate is then lubricated by mixing the required quantity of talc and magnesium stearate in a suitable blender. Tablets are compressed on a suitable tableting machine.

PHARMACOLOGIC EVALUATION

[1307] The in vitro pharmacologic profile of levorphanol was evaluated using standard methods. The results were analyzed and expressed as shown below.

[1308] Binding Assays

[1309] The specific ligand binding to the receptors was defined as the difference between the total binding and the nonspecific binding determined in the presence of an excess of unlabelled ligand. The results were expressed as a percent of control specific binding ((measured specific binding/control specific binding) x 100) and as a percent inhibition of control specific binding (100 - ((measured specific binding/control specific binding) x 100)) obtained in the presence of the test compounds. The IC₅₀ values (concentration causing a half-maximal inhibition of control specific binding) and Hill coefficients (nH) were determined by non-linear regression analysis of the competition curves generated with mean replicate values using Hill equation curve fitting ($Y = D + [(A - D)/(1 + (C/C_{50})^{nH})]$, where Y = specific binding, D = minimum specific binding, A = maximum specific binding, C = compound concentration, C₅₀ = IC₅₀, and nH = slope factor). This analysis was performed using validated proprietary software. The inhibition constants (K_i) were calculated using the Cheng Prusoff equation $K_i = IC_{50}/(1+(L/K_D))$, where L = concentration of radioligand in the assay, and K_D = affinity of the radioligand for the receptor). A scatchard plot was used to determine the K_d.

[1310] In Vitro Pharmacology: Cellular Functional Assays

[1311] The results were expressed as a percent of control specific agonist response ((measured specific response/control specific agonist response) x 100) and as a percent inhibition of control specific agonist response (100 - ((measured specific response/control specific agonist response) x 100)) obtained in the presence of the test compounds. The EC₅₀ value (conc. producing a half-maximal specific response) and IC₅₀ value (conc. causing a half-maximal inhibition of the control specific agonist response) were determined by non-linear regression analysis of the conc. response curves generated with mean replicate values using Hill equation curve fitting ($Y = D + [(A - D)/(1 + (C/C_{50})^{nH})]$, where Y = specific response, D = minimum specific response, A = maximum specific response, C = compound concentration, and C₅₀ = EC₅₀ or IC₅₀, and nH = slope factor). This analysis was performed using validated proprietary software. For the antagonist, the apparent

dissociation constant (K_B) was calculated using the modified Cheng Prusoff equation ($K_B = IC_{50}/(1+(A/EC_{50}A))$), where A = concentration of reference agonist in the assay, and $EC_{50}A = EC_{50}$ value of the reference agonist).

[1312] Enzyme Assays

[1313] The results were expressed as a percent of control specific activity ((measured specific activity/control specific activity) x 100) and as a percent inhibition of control specific activity (100 – ((measured specific activity/control specific activity) x 100)) obtained in the presence of the test compounds. The IC_{50} values (concentration causing a half-maximal inhibition of control specific activity) and Hill coefficients (nH) were determined by non-linear regression analysis of the inhibition curves generated with mean replicate values using Hill equation curve fitting ($Y = D + [(A - D)/(1 + (C/C_{50})^{nH})]$), where Y = specific activity, D = minimum specific activity, A = maximum specific activity, C = compound concentration, $C_{50} = IC_{50}$ and nH = slope factor). This analysis was performed using validated proprietary software.

[1314] Example 90

[1315] Example 90 provides a brief summary of the experimental conditions for assessment of NMDA antagonism. Testing was done using an adaptation of the method described by Vignon et al, Brain Research, 1986;378:133-41. Levorphanol Tartrate provided 91% inhibition of control specific binding at concentration of 1×10^{-6} M levorphanol tartrate, equal to 5.8×10^{-6} M levorphanol base.

Assay	Origin	Ligand	Conc.
NMDA (antagonist radioligand)	rat cerebral cortex	[³ H]TCP	10 nM
Kd	Non Specific	Incubation	Detection Method
13 nM	MK 801 (10 μ M)	120 min 37°C	Scintillation counting

[1316] Example 91

[1317] Example 91 provides a brief summary of the experimental conditions for assessment of 5-HT uptake assay. Testing was done using an adaptation of the method described by Perovic and Muller, Arzneim-Forsch Drug Res 1995;45:1145-48. Levorphanol tartrate provided an IC_{50} of 5.2×10^{-8} M levorphanol tartrate, equal to 3.02×10^{-8} M levorphanol base. See Figure 83.

Origin	Assay	Substrate/Tracer
rat brain synaptosomes	5-HT uptake	[³ H]5-HT (0.2 μ Ci/ml)
Reaction Product	Incubation	Method of Detection
[³ H]5-HT incorporation into synaptosomes	15 min 37°C	Scintillation counting

[1318] Example 92

[1319] Example 92 provides a brief summary of the experimental conditions for assessment of norepinephrine uptake assay. Testing was done using an adaptation of the method described by

Perovic and Muller, *Arzneim-Forsch Drug Res* 1995;45:1145-48. Levorphanol tartrate provided an IC_{50} of 2.1×10^{-6} M levorphanol tartrate, equal to 1.22×10^{-6} M levorphanol base. See Figure 84.

Assay	Origin	Substrate/Tracer
rat hypothalamus synaptosomes	norepinephrine uptake	[³ H]NE (0.2 μCi/ml)
Incubation	Reaction Product	Method of Detection
[³ H]NE incorporation into synaptosomes	20 min 37°C	Scintillation counting

[1320] The in vivo pharmacologic profile of levorphanol was evaluated using standard methods. The results were analyzed and expressed as shown below.

[1321] Example 93

[1322] Objectives: To evaluate the efficacy and potency of levorphanol in a model of inflammatory pain and to correlate its potency relative to that of morphine.

[1323] Methods: Male Sprague-Dawley rats (200-300 grams) were used. Peripheral inflammation was induced by subdermal injection of 0.05 ml of a 0.6% carrageenan suspension into the plantar aspect of lightly ether-anesthetized rats. This procedure reliably produces a marked inflammatory response within 3 hours of carrageenan injection which is indicated by swelling of the hindpaw, edema, rubor and hyperalgesia and tactile allodynia. Drugs were administered 150 minutes after carrageenan-induced inflammation. Behavioral tests were performed 2, 3 and 4 hours after induction of inflammation. Tactile hyperesthesia was measured by determining the withdrawal threshold of the hindpaw to probing the plantar aspect with a series of von Frey filaments. A significant ($p < 0.05$) reduction in paw withdrawal threshold indicated tactile hyperesthesia. Responses to thermal nociception were determined by placing rats within plexiglass enclosures on a clear glass plate. After an acclimatization period, an infrared source was focused onto the plantar surface of the hindpaw. Paw withdrawal was detected by a motion sensor that halted the IR source and the timer, indicating paw withdrawal latency. Thermal hyperalgesia was indicated by a significant ($p < 0.05$) reduction in paw withdrawal latency and antinociception was indicated by a significant increase in latency. The levorphanol data for mechanical allodynia and thermal hyperalgesia were compared to historical morphine data. In order to analyze dose-effect relationships, the data were converted to % Maximal Possible Effect (%MPE) by the formula: % MPE = $100 \times (\text{test value} - \text{basal value}) / (\text{cut-off} - \text{basal value})$. Dose-response curves along with A_{50} values and confidence intervals were determined from linear regression analysis of the log dose-effect curves. Significant shifts in the dose-effect curves were indicated by Student's t-statistic applied to the A_{50} values obtained for levorphanol and morphine.

[1324] Conclusions: Carrageenan injected into the hindpaw produced behavioral sensitivity to tactile and thermal stimuli and increased paw volume within 3 hours, indicating that inflammation

was successfully induced. Levorphanol was more potent than morphine at all times for reversal of tactile hyperalgesia occurring in the inflamed hind paw and for paw withdrawal after noxious radiant heat. Surprisingly levorphanol base (which is approximately 58% of the active amount of tested material, levorphanol tartrate dihydrate) was only approximately 2 to 3 times more potent than morphine base for reversal of tactile hyperalgesia and 4 to 5 times more potent than morphine base for paw withdrawal after noxious radiant heat. When compared in the way the dose is expressed in pharmaceutical compositions (levorphanol is dosed by as mg of levorphanol tartrate dihydrate, while morphine is dose morphine as mg of morphine base), levorphanol was surprisingly only approximately 1.2 to 1.7 times more potent than morphine for reversal of tactile hyperalgesia and 2.3 to 2.9 times more potent than morphine base for paw withdrawal after noxious radiant heat.

[1325] Example 94

[1326] Objective: To evaluate the efficacy and potency of levorphanol and to compare its potency relative to that of morphine in a model of thermal nociception (hot-plate test).

[1327] Methods: Male Sprague-Dawley rats (200-300 grams) were used. Antinociceptive activity was determined by the 53°C hot-plate test. The rat is placed on a metal plate heated to 53°C, and the latency to withdrawing or shaking or licking of a paw, or escape attempts by jumping were documented. A cut-off latency of 15 sec was employed. Drugs were prepared administered after baseline measurements were performed. Behavioral testing was performed 30, 45 and 60 minutes after dosing. The levorphanol data for were compared to historical morphine data. In order to analyze dose-effect relationships, the data were converted to % Maximal Possible Effect (%MPE) by the formula: $\% \text{ MPE} = 100 \times (\text{test latency} - \text{basal latency}) / (15 \text{ sec} - \text{basal latency})$. Dose-response curves along with A_{50} values (i.e., dose calculated to produce a 50% MPE) and confidence intervals were determined from linear regression analysis of the log dose-effect curves. Significant differences in potency between 2 dose-response curves were determined by applying the Student's t-statistic to variances of the A_{50} values obtained for each dose-response curve. The antinociceptive effect of levorphanol was determined in the 53°C rat hot-plate test 30, 45 and 60 minutes after dosing. Hot-plate latencies for each time-point were compared to the mean baseline response by ANOVA followed by the *post-hoc* Fisher's Least Significant Difference test.

[1328] Conclusions: Levorphanol produced dose-dependent antinociception in rats in the classic 53°C rat hot-plate test of antinociception. Levorphanol was more potent than morphine at all times. Surprisingly, levorphanol base (which is approximately 58% of the active amount of tested material, levorphanol tartrate dihydrate) was only approximately 1.9 to 4.7 times more potent than morphine base in the hot-plate test of antinociception. When compared in the way the dose is expressed in pharmaceutical compositions (levorphanol is dosed by as mg of levorphanol tartrate dihydrate, while morphine is dose morphine as mg of morphine base), levorphanol was surprisingly only approximately 1.1 to 2.7 times more potent than morphine as an analgesic in this pain model.

Perhaps more surprising, the duration of analgesic action of levorphanol was shorter than that of morphine, which supports the development of extended release dosage forms of levorphanol.

[1329] Example 95

[1330] Objective: To evaluate the efficacy and potency of levorphanol and to compare its potency relative to that of morphine in a model of thermal nociception (tail flick test).

[1331] Methods: Male Sprague-Dawley rats (200-300 grams) were used. Antinociceptive activity was determined by a significant increase in the latency to a reflexive flicking of the tail away from a radiant heat (infrared) source projected onto a small area on the ventral aspect of the tail. Baseline tail flick latencies were determined prior to any drug administration. The antinociceptive effect of levorphanol was determined 30, 45 and 60 minutes after dosing. The levorphanol data for were compared to historical morphine data. Tail flick latencies for each time-point were compared to the mean baseline response by ANOVA followed by the *post-hoc* Fisher's Least Significant Difference test. A significant increase from the baseline was considered antinociceptive. In order to analyze dose-effect relationships, the data were converted to % Maximal Possible Effect (%MPE) by the formula: $\% \text{ MPE} = 100 \times (\text{test latency} - \text{basal latency}) / (15 \text{ sec} - \text{basal latency})$. Dose-response curves along with A_{50} values (i.e., dose calculated to produce a 50% MPE) and confidence intervals were determined from linear regression analysis of the log dose-effect curves. Significant differences in potency between 2 dose-response curves were determined by applying the Student's t-statistic to variances of the A_{50} values obtained for each dose-response curve.

[1332] Conclusions: Levorphanol produced dose-dependent antinociception in rats in the classic tail flick model of antinociception. Levorphanol was more potent than morphine at all times. Surprisingly, levorphanol base (which is approximately 58% of the active amount of tested material, levorphanol tartrate dihydrate) was only approximately 3.6 to 5.8 times more potent than morphine base in the tail flick test of antinociception. When compared in the way the dose is expressed in pharmaceutical compositions (levorphanol is dosed by as mg of levorphanol tartrate dihydrate, while morphine is dose morphine as mg of morphine base), levorphanol was surprisingly only approximately 2.1 to 3.4 times more potent than morphine as an analgesic in this pain model. Perhaps more surprising, the duration of analgesic action of levorphanol was shorter than that of morphine, which supports the development of extended release dosage forms of levorphanol.

HUMAN STUDIES

[1333] Example 96

[1334] This study was a 5-way, analytically masked, single-dose crossover bioavailability study of four formulations of extended release (ER) levorphanol tartrate relative to immediate release (IR) levorphanol tartrate tablets in 15 subjects. Eligible subjects reported to the clinical unit in the evening, at least 13 hours prior to dosing in each treatment period. All subjects fasted for ≥ 12

hours prior to dosing. Water was restricted for 2 hours pre-levorphanol dosing to 2 hours post-levorphanol dosing. A single dose of levorphanol was administered. Subjects took their study medication in each treatment period with 240 mL of water and received a standardized meal four hours after dosing. All subjects remained in the unit until the completion of the last scheduled study procedure in each treatment period (approximately 48 hours post-dose). There was a minimum of 7 and up to 14 day washout period between each of the 5 dosing periods. Since the doses of levorphanol ER in the treatment groups were different, as was the dose of levorphanol IR, the plasma concentration data were normalized to the same dose to allow comparisons between treatments. Physical examination, vital signs, 12-lead ECG, clinical laboratory tests were performed at the screening visit and at the beginning and again upon exit from the study. Vital signs including respiratory rate, blood pressure and pulse will be obtained at screening, at pre-dose, 4-hours post-dose (prior to ambulation) and prior to the last blood collection in each study period. Vital signs at Screening, at pre-dose and at 4-hours post dose were taken in a sitting and standing position. Other scheduled vital signs were obtained after the subject had been in a sitting position for five minutes. Spontaneous reporting of adverse events was monitored during the course of the study. In the Levorphanol ER treatment periods, blood samples were collected for levorphanol at 0.0 (pre-dose) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0, 24.0, 28.0, 36.0, and 48.0 hours post-dose (21 samples). In the Levorphanol IR treatment, blood samples were collected for levorphanol at 0.0 (pre-dose) and at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0, 24.0, 36.0, and 48.0 hours post-dose (21 samples). Harvested plasma samples was stored at -70°C and subsequently processed for bioanalysis for levorphanol. The assay for levorphanol in plasma was done with a sensitive, specific, robust and validated analytical method. Data from 15 subjects were included in the pharmacokinetic and statistical analyses. Full precision concentration data (not rounded to three significant figures) and actual sample times were used for all pharmacokinetic and statistical analyses. Data from 15 subjects were included in the pharmacokinetic and statistical analyses. Concentration-time data were transferred from Watson LIMS directly to WinNonlinTM Enterprise Edition (Version 4.0, Pharsight Corporation) using the Custom Query Builder option for analysis. Data were analyzed by noncompartmental methods in WinNonlin. Data were also analyzed using compartmental models. The results of this study confirm that various tested prototypes of levorphanol ER provide an extended release profile, when compared with Levorphanol IR, as evidenced by the time of peak concentration, mean residence times, mean absorption time, W_{50} and HVD. Figure 58, Figure 59, Figure 60 and Figure 61 show the mean levorphanol plasma concentration time profile obtained with the prototypes of Levorphanol ER in this example. Figure 62, Figure 63, Figure 64 and Figure 65 show the surprising relationship between the release rate of levorphanol and the plasma concentration time profile. Levorphanol ER provides a prolonged in vitro dissolution rate that is

substantially longer than the dosing interval in vivo. Levorphanol ER continues to robustly release drug in vitro well past the dosing interval, even when plasma concentrations are declining. Figure 66, Figure 67, Figure 68 and Figure 69 show a superior extended release human pharmacokinetic profile for various dosages of Levorphanol ER described in this example, when compared with a brand name multiparticulate extended release once-daily morphine (Morphine ER), making the Levorphanol ER dosage form suitable for up to once a day dosing (e.g., twice-a-day [Q12H or Q12H PRN] or once-a-day [QD, Q24H or Q24H PRN]. To allow meaningful comparison (and preserve the overall shape of the plasma-concentration time profile), the plasma concentration of each Levorphanol ER dosage form has been put on the same scale as the Morphine ER (“normalized”) by applying a fixed ratio of mean AUC_{0-inf} of Morphine ER to Levorphanol ER for each plasma concentration.

[1335] The results of the study are summarized in part below.

Parameter	Levo ER (1)	Levo ER (2)	Levo ER (3)	Levo ER (4)	Levo IR
T_{max} (hr)	10.36	12.29	9.15	11.53	2.40
λ_z (hr^{-1})	0.0658	0.0575	0.0557	0.0541	0.0649
$T_{1/2}$ (hr)	10.93	14.11	13.65	14.35	10.85
K_{01}	0.264	0.5458	0.4621	0.4977	1.3543
K_{10}	0.0662	0.0292	0.0379	0.0269	0.1304
T_{lag}	1.35	1.56	1.08	1.46	0.51
MRT_{last} (hr)	19.06	21.39	20.30	22.27	12.44
$MRTINF_{obs}$ (hr)	22.93	28.96	27.19	29.50	14.76
MAT (hr)	5.14	3.39	3.24	3.47	1.25
W_{50} (hr) (6 hour dosing)	-	-	-	-	4.5
W_{50} (hr) (8 hour dosing)	-	-	-	-	6.0
W_{50} (hr) (12 hour dosing)	7.8	8.6	8.8	8.4	6.6
W_{50} (hr) (24 hour dosing)	16.5	19.9	20.00	20.4	6.6
HVD (hr)	20.0	29.6	24.3	32.1	6.6

[1336] Example 97

[1337] The pharmacokinetics of a prototype dosage form of extended release levorphanol (Levorphanol ER) was compared with immediate release levorphanol (Levorphanol IR) in 15 fasted medically supervised subjects. Eligible subjects reported to the clinical unit the evening prior to dosing in each treatment period and all subjects fasted for ≥ 12 hours prior to dosing. Water was restricted for 2 hours pre-levorphanol dosing to 2 hours post-levorphanol dosing. Levorphanol ER and levorphanol IR were given as a single administration using a randomized crossover design with an intervening washout period between the treatments. Subjects took the total study dose with 240 mL of water and receive a standardized meal four hours after dosing. All subjects remained in the

unit until the completion of the last scheduled study procedure (approximately 48 hours post-dose). Physical examination, vital signs, 12-lead ECG, clinical laboratory tests were performed at the screening visit and at the beginning and again upon exit. A screen for drugs of abuse was performed at screening and prior to dosing. An ethanol breath test was performed prior to dosing. Vital signs including respiratory rate, blood pressure and pulse were obtained at screening, at pre-dose, 4-hours post-dose and prior to the last blood collection. Adverse events were monitored during the course of the study. Blood samples were collected for levorphanol at 0.0 (pre-dose) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0, 24.0, 28.0, 36.0, and 48.0 hours post-dose (21 samples). Harvested plasma samples were stored at -70°C and subsequently processed for bioanalysis for levorphanol. The assay for levorphanol in plasma was done with a sensitive, specific, robust and validated analytical method. A total of 14 subjects completed the Levorphanol ER treatment (one subject was excluded due to non-compliance with study procedures) and all 15 subjects completed the Levorphanol IR treatment. All completed subjects were included in the pharmacokinetic and statistical analyses. Bioavailability parameters based on actual dose (assayed dose) are presented below. The time of peak plasma concentration, terminal elimination apparent half life, HVD and W_{50} are reported as median values. To allow meaningful comparison, C_{max} and AUC data are reported per mg of levorphanol dose. The results of the study (summarized in the Table below) show that levorphanol ER provided robust extended release properties, full bioavailability compared to Levorphanol IR. The dosage form is suitable for Q12H or Q24H dosing.

Parameter	Levorphanol ER	Levorphanol IR
C_{max} (pg/mL/mg)	407	838
AUC _{inf} (hr*pg/mL/mg)	10440	10710
T_{max} (hr)	10.00	2.00
$T_{1/2}$ (hr)	10.63	10.68
W_{50} (hr) (6 hour dosing)	-	4.5
W_{50} (hr) (8 hour dosing)	-	6.0
W_{50} (hr) (12 hour dosing)	8.0	6.0
W_{50} (hr) (24 hour dosing)	19.0	6.0
HVD (hr)	23.0	6.0
Relative Bioavailability	ER (Test)	IR (Reference)
C_{max} Ratio (ER/IR)	50.15	-
AUC _{inf} Ratio (ER/IR)	99.27	-

[1338] A wide variety of materials can be used for preparing the dosage form according to this invention. This invention therefore contemplates the use of materials other than those specifically disclosed herein, including those which may hereafter become known to the art to be capable of performing the necessary functions. In all instances wherein prophetic examples are provided, these compositions are intended to be exemplary and it should be understood that the specific procedures,

constituents, amounts thereof and the like can be varied in order to obtain a composition possessing desired properties. The percent loading of the levorphanol onto the dosage form will depend on the physiochemical and pharmaceutical properties of levorphanol API (base or salt, type of salt, particle size), choice and amount of excipient, desired route (e.g., orally ingested, sublingual), desired tablet or capsule size, and the desired release profile. Levorphanol, its pharmaceutically salts or mixture thereof, and any incorporated excipients in the above examples may require milling to assure that they meet the particle size requirements of some embodiments of the invention. The choice of particle size will vary depending on the desired properties of the dosage form. The dosage form may comprise any pharmaceutically acceptable excipients, in any desired amounts and with any desired physicochemical or mechanical properties (e.g., particle size, melting point, viscosity). Preferably, the pharmaceutical excipient is about 0.0001% to about 99.5%, more preferably, about 0.001% to about 95%, and even more preferably, about 0.01% to about 90%.

[1339] Levorphanol and the any excipients comprising the dosage form may be incorporated in any desired order to prepare the dosage form. Levorphanol, and any incorporated excipients may be processed (e.g., cured, milled, co-mingled, heated, made into a liquid, adjusted for moisture content, purified) prior to incorporation into the dosage form and the dosage form may also be further processed after manufacture (e.g., cured at ambient temperature, cured at a specified temperature, film coated, enteric coated) prior to packaging and sale. The ingredients used for the preparation of the levorphanol dosage form agent may be modified. In some embodiments, a change in the dose or amount levorphanol will not require a significant change in amount of other ingredients. In other embodiments, a proportional change in the amount of other ingredients is required to maintain the desired properties. In yet other embodiments, a change in the dose or amount levorphanol necessitates a change in the nature and/or amount of ingredients to provide the required characteristics of the levorphanol (e.g., onset of effect, duration of effect, rate and extent of absorption, therapeutic concentrations and effect, etc.).

[1340] These and other embodiments of the present invention will readily occur to those of ordinary skill in the art in view of the disclosure herein. The included examples are illustrative but not limiting of the methods and composition of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention. Additionally, it is understood that each of the various embodiments of the pharmaceutical compositions described herein may be used with each of the various embodiments of the described method of the present invention as described herein. Furthermore, it is understood that each of the embodiments disclosed herein may alternatively be described as "consisting of" or "consisting essentially of" the listed components. All patents literature (e.g., patents and patent applications) and non-patent literature (e.g., textbooks, textbook chapters, journal articles, other publications, references, software, data and databases)

cited herein are incorporated by reference in their entirety for all purposes.

[1341] Having now fully described the invention, it will be understood to those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof.

WHAT IS CLAIMED IS:

1. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing a C_{max} of levorphanol from 1 ng/mL to 70 ng/mL after first administration and sequential venous sampling to 48 hours.
2. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing a C_{max} of levorphanol of up to 70 ng/mL after first administration and sequential venous sampling to 48 hours
3. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage after first administration and sequential venous sampling to 48 hours providing a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve to 48 hours post-dose (AUC_{0-48}) of 4 ng.hr/mL to 2480 ng.hr/mL.
4. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C from 0% to 47.5% at 1 hour, from 10% to 65% at 2 hours, from 15% to 70% at 4 hours, from 25% to 77.5% at 6 hours, from 35% to 87.5% at 9 hours, and greater than 65% at 12 hours.
5. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C from 0% to about 20% at 1 hour, from about 10% to about 40% at 4 hours, from about 10% to about 50% at 6 hours, from about 20% to about 60% at 9 hours, from about 45% to about 75% at 17 hours, from about 45% to about 80% at 21 hours, from about 50% to about 85% at 25 hours, from about 55% to about 90% at 29 hours, from about 55% to about 95% at 33 hours, from about 60% to about 100% at 41 hours, and from about 65% to about 100% at 45 hours.
6. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage

- form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C from 0% to about 40% at 4 hours, from about 10% to about 60% at 9 hours, from about 30% to about 80% at 17 hours, from about 30% to about 85% at 21 hours, from about 40% to about 95% at 17 hours, from about 45% to about 95% at 25 hours, from about 50% to about 95% at 32 hours, from about 55% to about 95% at 41 hours, and from about 60% to about 98% at 45 hours.
7. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C from 0% to about 50% at 4 hours, from about 10% to about 90% at 8 hours, from about 20% to about 95% at 17 hours, from about 25% to about 95% at 25 hours, from about 30% to about 95% at 32 hours, from about 35% to about 100% at 45 hours.
 8. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C from 2% to about 50% at 4 hours, from about 10% to about 70% at 8 hours, from about 30% to about 85% at 17 hours, from about 30% to about 90% at 24 hours, from about 50% to about 95% at 33 hours and greater than 60% at 45 hours.
 9. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C from about 2% to about 40% at 4 hours, from about 5% to about 50% at 8 hours, from about 20% to about 85% at 16 hours, from about 25% to about 90% at 20 hours, from about 30% to about 95% at 24 hours, from about 50% to about 98% at 25 hours, and greater than 65% at 32 hours.
 10. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C

from about 5% to about 60% at 8 hours, from about 20% to about 80% at 16 hours, from about 25% to about 95% at 24 hours, from about 40% to about 95% at 32 hours, greater than about 60% at 40 hours, and greater than about 70% at 48 hours.

11. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C between 0% to about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 3% and about 95% at 4 hours and between about 10% and about 100% at 8 hours.
12. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C between about 10% and about 65% at 1 hour, between about 20% and about 75% at 2 hours, between about 30% and about 95% at 4 hours and between about 40% and about 100% at 8 hours.
13. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C between about 10% to about 65% at 2 hours, between about 15% to about 70% at 4 hours, between about 25% to about 77.5% at 6 hours, between about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours.
14. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C between about 5% and about 50% at 1 hour, between about 10% and about 75% at 2 hours, between about 20% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, greater than about 50% at 12 hours, greater than about 70% at 18 hours, and greater than about 80% at 24 hours.
15. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage

form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C between about 5% and about 50% at 1 hour, between about 10% and about 75% at 2 hours, between about 20% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, greater than about 50% at 12 hours, greater than about 70% at 18 hours, and greater than about 80% at 24 hours.

16. A solid oral dosage form comprising a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer at a pH of between 1.6 and 7.2 at 37 °C between 0% to about 30% at 1 hour, between about 10% to about 65% at 4 hours, between about 20% to about 70% at 8 hours, between about 25% to about 80% at 12 hours, between about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours.
17. A method of providing therapeutic effect in a human patient in need of levorphanol therapy comprising solid oral dosage form comprising administering a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing a C_{max} of levorphanol from 1 ng/mL to 70 ng/mL after first administration and sequential venous sampling to 48 hours. A method of providing therapeutic effect in a human patient in need of levorphanol therapy comprising solid oral dosage form comprising administering a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing a C_{max} of levorphanol of up to 70 ng/mL after first administration and sequential venous sampling to 48 hours
18. A method of providing therapeutic effect in a human patient in need of levorphanol therapy comprising solid oral dosage form comprising administering a therapeutically effective amount of levorphanol or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage after first administration and sequential venous sampling to 48 hours providing a systemic exposure as assessed by the mean levorphanol area under the plasma concentration time curve to 48 hours post-dose (AUC_{0-48}) of 4 ng.hr/mL to 2480 ng.hr/mL.
19. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material

- to render said dosage form suitable for extended release, said dosage form providing delayed onset of levorphanol release.
20. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing delayed onset of levorphanol release, said delayed release rendering said dosage form abuse resistant.
 21. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing delayed onset of levorphanol release, said dosage form abuse resistant compared with immediate release oral levorphanol.
 22. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing first release of levorphanol from the dosage form at a point distal to the stomach.
 23. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing first release of levorphanol from the dosage form at a point distal to the duodenum.
 24. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing first release of levorphanol from the dosage form at a point distal to the jejunum
An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing first release of levorphanol from the dosage form at a point distal to the ileum.
 25. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said composition suitable for extended release, said dosage form after a single administration providing first release of levorphanol from the dosage form not less than about 2 hours after oral ingestion.
 26. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said composition suitable for extended release, said dosage form after a single administration providing first release of levorphanol from the dosage form not less than about 3

hours after oral ingestion.

27. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said composition suitable for extended release, said dosage form after a single administration providing first release of levorphanol from the dosage form not less than about 4 hours after oral ingestion.
28. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said composition suitable for extended release, said dosage form after a single administration providing first release of levorphanol from the dosage form at a pH of about ≥ 5 .
29. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said composition suitable for extended release, said dosage form after a single administration providing first release of levorphanol from the dosage form at a pH of about ≥ 5.5 .
30. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said composition suitable for extended release, said dosage form after a single administration providing first release of levorphanol from the dosage form at a pH of about ≥ 6 .
31. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said composition suitable for extended release, said dosage form after a single administration providing first release of levorphanol from the dosage form at a pH of about ≥ 6.5 .
32. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said composition suitable for extended release, said dosage form releasing substantially all of the levorphanol distal to the stomach for subsequent systemic absorption and therapeutic effect.
33. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said composition suitable for extended release, said dosage form releasing substantially all of the levorphanol distal to the duodenum for subsequent systemic absorption and therapeutic effect.
34. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said composition suitable for extended release, said dosage form releasing substantially all of the levorphanol in the ileum and/or the colon for subsequent systemic absorption and

therapeutic effect.

35. A method of improving treatment compliance and deterring episodic, as needed, or PRN use in a population which includes subjects that can be expected to at least occasionally be non-compliant with around-the-clock or scheduled use oral extended release levorphanol comprising administering a delayed onset, extended release dosage form of levorphanol.
36. A method of rendering an oral extended release dosage form of levorphanol therapeutically ineffective or suboptimally effective when taken on an as needed or PRN basis comprising administering a delayed onset, extended release dosage form of levorphanol. by rendering the dosage A method of rendering an oral levorphanol dosage form abuse resistant in a population which includes subjects that can be expected to at least occasionally abuse the dosage form by rendering the dosage substantially devoid of mood altering or pleasurable effects when taken intermittently or occasionally, comprising administering a delayed onset, extended release dosage form of levorphanol.
37. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing delayed onset of levorphanol release, said dosage form providing an in-vitro levorphanol release rate, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water at 37 °C which is substantially pH dependent in that a difference, at 2 hours between the amount of levorphanol released at a pH of ≤ 5 , and an amount released at a pH of ≥ 6 is more than about 25%.
38. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing delayed onset of levorphanol release, said dosage form providing an in-vitro levorphanol release rate, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL of distilled water at 37 °C which is substantially pH dependent in that a difference, at 2 hours between the amount of levorphanol released at a pH of ≤ 5 and an amount released at a pH of ≥ 7 is more than about 25%.
39. A solid oral dosage form comprising a therapeutically effective amount of levorphanol, racemorphan or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer of between 0% to about 30% at 1 hour, and greater than about 15% at 2 hours, said release rate measured following pretreatment of the dosage form using the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water at a pH of ≤ 5 for two hours at 37 °C before a switch to said aqueous buffer at 37 °C at a pH ≥ 6 , , whereupon the clock is reset to time equal to 0.

40. A solid oral dosage form comprising a therapeutically effective amount of levorphanol, racemorphan or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer of between 0% and about 60% at 1 hour, between about 0% and about 80% at 2 hours, between about 3% and about 95% at 4 hours and between about 10% and about 100% at 8 hours, said release rate measured following pretreatment of the dosage form using the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water at a pH of ≤ 5 for two hours at 37 °C before a switch to said aqueous buffer at 37 °C at a pH ≥ 6.5 , whereupon the clock is reset to time equal to 0.
41. A solid oral dosage form comprising a therapeutically effective amount of levorphanol, racemorphan or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer of between 10% and about 65% at 1 hour, between about 20% and about 75% at 2 hours, between about 30% and about 95% at 4 hours and between about 40% and about 100% at 8 hours, said release rate measured following pretreatment of the dosage form using the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water at a pH of ≤ 4.5 for two hours at 37 °C before a switch to said aqueous buffer at 37 °C at a pH ≥ 6 , whereupon the clock is reset to time equal to 0.
42. A solid oral dosage form comprising a therapeutically effective amount of levorphanol, racemorphan or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer of between 0% to about 47.5% at 1 hour, from about 10% to about 65% at 2 hours, from about 15% to about 70% at 4 hours, from about 25% to about 77.5% at 6 hours, from about 35% to about 87.5% at 9 hours, and greater than about 65% at 12 hours, said release rate measured following pretreatment of the dosage form using the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water at a pH of ≤ 5 for two hours at 37 °C before a switch to said aqueous buffer at 37 °C at a pH ≥ 7 , whereupon the clock is reset to time equal to 0.
43. A solid oral dosage form comprising a therapeutically effective amount of levorphanol, racemorphan or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer of between 5% and

about 50% at 1 hour, between about 10% and about 75% at 2 hours, between about 20% and about 95% at 4 hours, between about 40% and about 100% at 8 hours, greater than about 50% at 12 hours, greater than about 60% at 18 hours, and greater than about 65% at 24 hours, said release rate measured following pretreatment of the dosage form using the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water at a pH of ≤ 4.5 for two hours at 37 °C before a switch to said aqueous buffer at 37 °C at a pH ≥ 6 , whereupon the clock is reset to time equal to 0.

44. A solid oral dosage form comprising a therapeutically effective amount of levorphanol, racemorphan or a pharmaceutically acceptable salt thereof, and controlled release material to render said dosage form extended release and suitable for up to once-a-day administration to a human patient; said dosage form providing an in-vitro release rate of levorphanol, when measured by the USP Basket or Paddle Method at 100 rpm in 900 mL aqueous buffer of between 0% to about 30% at 1 hour, from about 10% to about 65% at 4 hours, from about 20% to about 70% at 8 hours, from about 25% to about 80% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 65% at 24 hours, said release rate measured following pretreatment of the dosage form using the USP Basket or Paddle Method at 100 rpm in 900 mL distilled water at a pH of ≤ 5 for two hours at 37 °C before a switch to said aqueous buffer at 37 °C at a pH ≥ 6 , whereupon the clock is reset to time equal to 0.
45. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing delayed onset of levorphanol release, said dosage form providing less nausea than oral immediate release levorphanol given at a dose less than or equal to 50% of the extended release dose, said nausea measured after single dose administration to opioid naïve subjects.
46. An oral dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing delayed onset of levorphanol release, said dosage form providing less drowsiness than oral immediate release levorphanol given at a dose less than or equal to 50% of the extended release dose, said drowsiness measured after single dose administration to opioid naïve subjects.
47. A method of treatment for human patient in need of levorphanol comprising administering: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form suitable for every 12 hour administration.
48. A method of treatment for a human patient in need of levorphanol comprising administering: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for

extended release, said dosage form suitable for every 24 hour administration.

49. A method of improving treatment compliance in a human subject and deterring episodic, occasional, intermittent, periodic, as needed, or PRN use of the dosage form in subjects requiring around the clock, scheduled or time contingent oral levorphanol therapy by rendering the dosage form therapeutically ineffective or suboptimally effective when taken episodically, intermittently, occasionally, periodically, on an as needed basis, or PRN, said dosage form therapeutically effective in a substantial number of subjects when taken around the clock, on scheduled basis or on time contingent basis, comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing delayed onset of levorphanol release when given orally.
50. A method of improving treatment compliance in a human subject and deterring episodic, occasional, intermittent, periodic, as needed, or PRN use of the dosage form in subjects requiring chronic or prolonged oral levorphanol therapy by rendering the dosage form therapeutically ineffective or suboptimally effective when taken episodically, intermittently, occasionally, periodically, on an as needed basis, or PRN, said dosage form therapeutically effective in a substantial number of subjects when taken around the clock, on scheduled basis or on time contingent basis, comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing delayed onset of levorphanol release when given orally.
51. A method of deterring abuse and misuse of oral levorphanol in a human subject by rendering the dosage form devoid of or substantially devoid of euphoria, pleasurable effects, drug liking and mood alerting effects when taken episodically, intermittently, occasionally, periodically, on an as needed basis, or PRN, said dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing delayed onset of levorphanol release when given orally.
52. A method of deterring abuse and misuse of oral levorphanol in a human subject by delaying or substantially delaying or reducing euphoria, pleasurable effects, drug liking and mood alerting effects when taken regularly or when taken episodically, intermittently, occasionally, periodically, on an as needed basis, or PRN, said dosage form comprising: (i) a therapeutically effective amount of levorphanol, a pharmaceutically acceptable salt thereof, or a mixture thereof, and (ii) controlled release material to render said dosage form suitable for extended release, said dosage form providing delayed onset of levorphanol release when given orally.

Figure 1

10mg Levorphanol in Sterotex, Hydrokote 112 & Precirol, 052/149/1-3

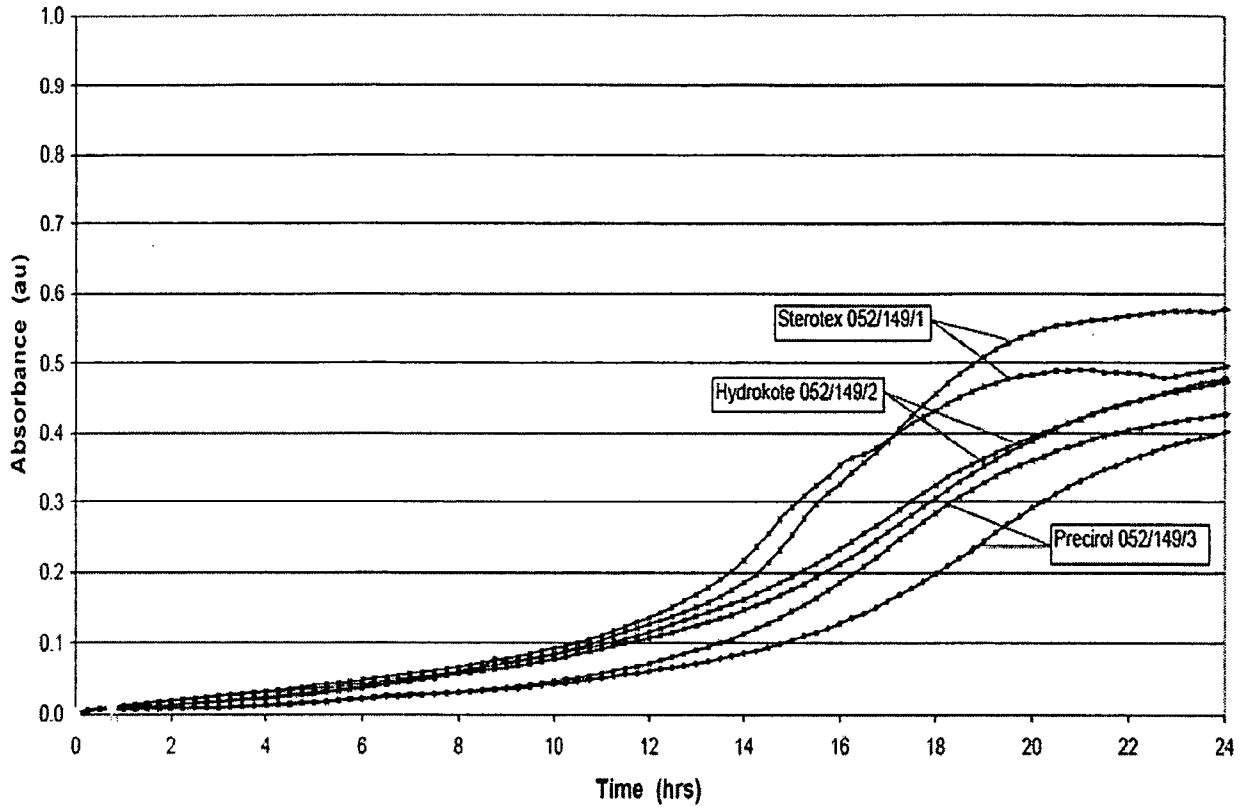


Figure 2

10mg Levorphanol Tartrate in Sterotex, Hydrokote 112 & Precirol base mixes 052/152/1-3

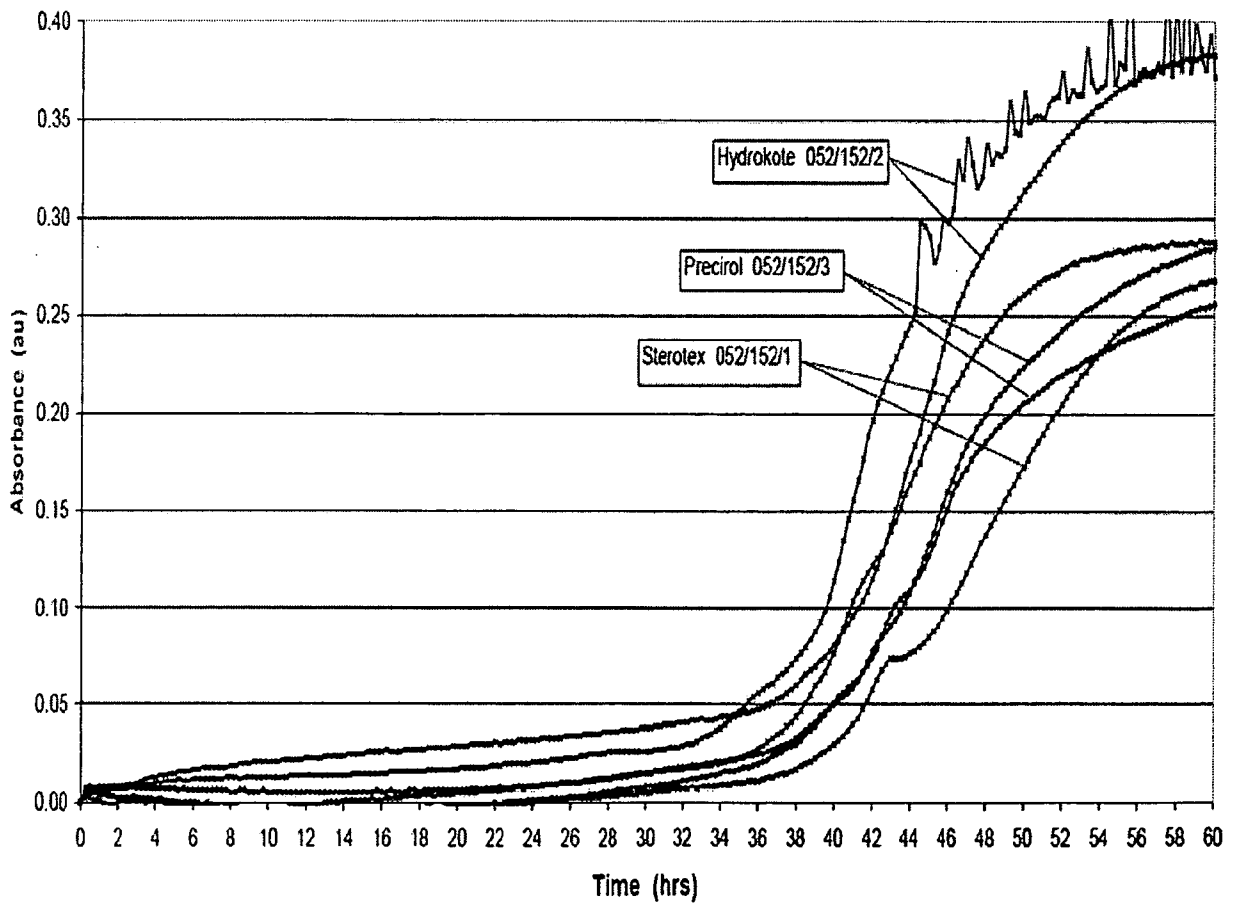


Figure 3

Sterotex, Hydrokote 112 & Precirol base mixes (without levorphanol) 052/153/1-3

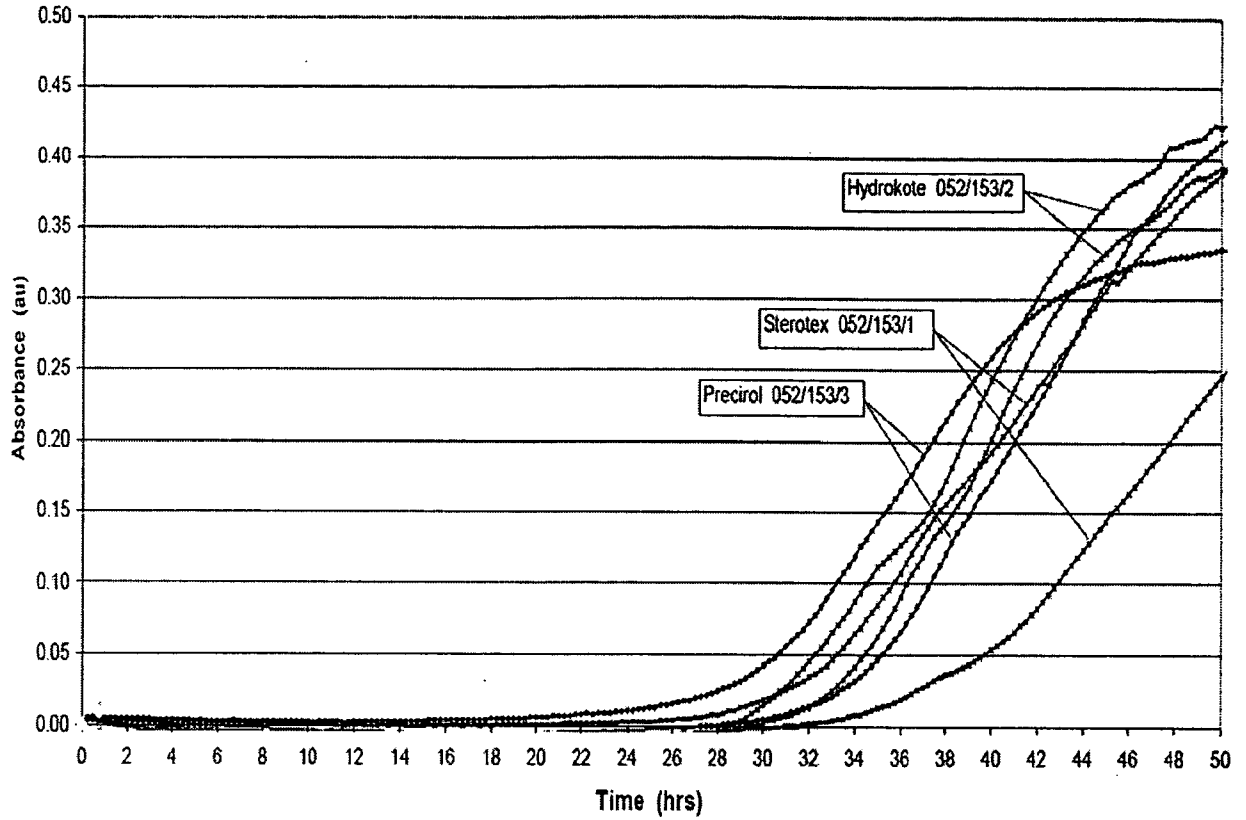


Figure 4

10mg Levorphanol Tartrate in Hydrokote 112 formulae 052/156/1, 052/156/2 & 052/157/3

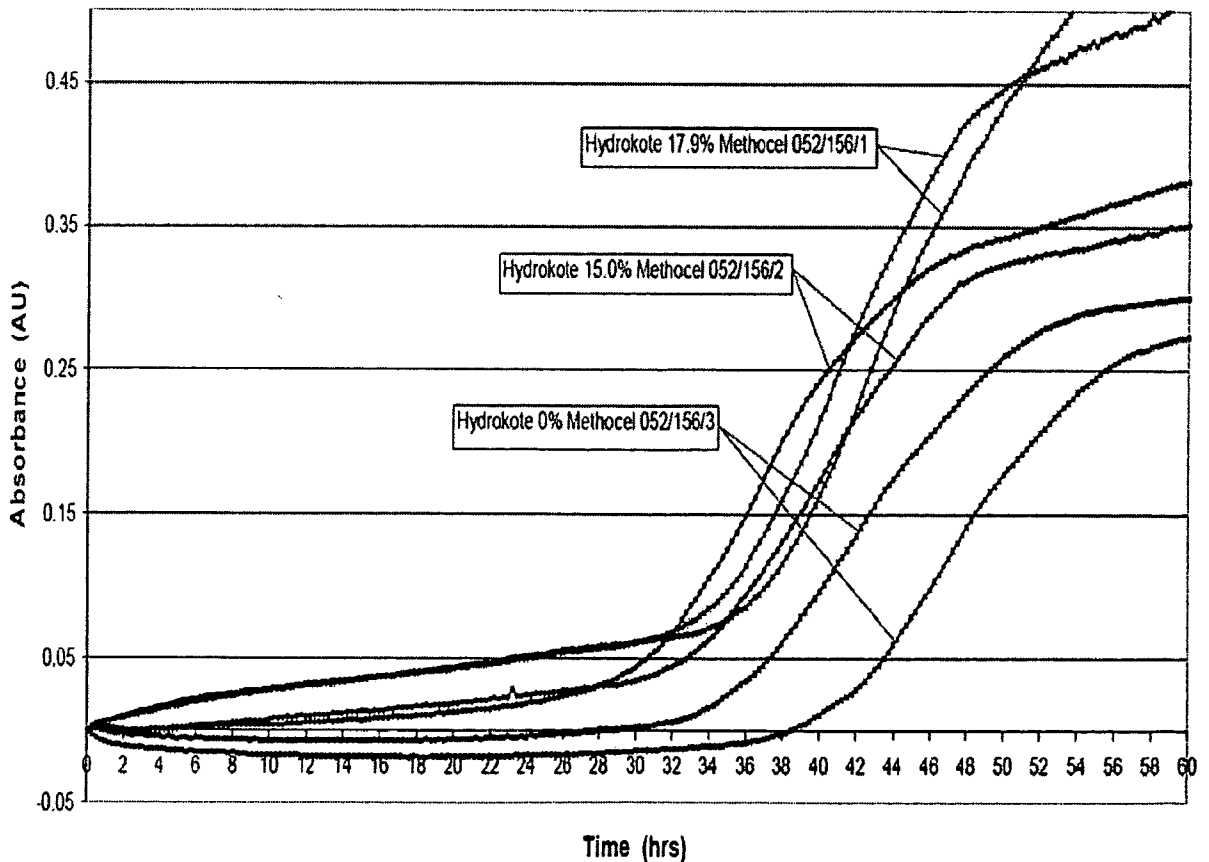


Figure 5

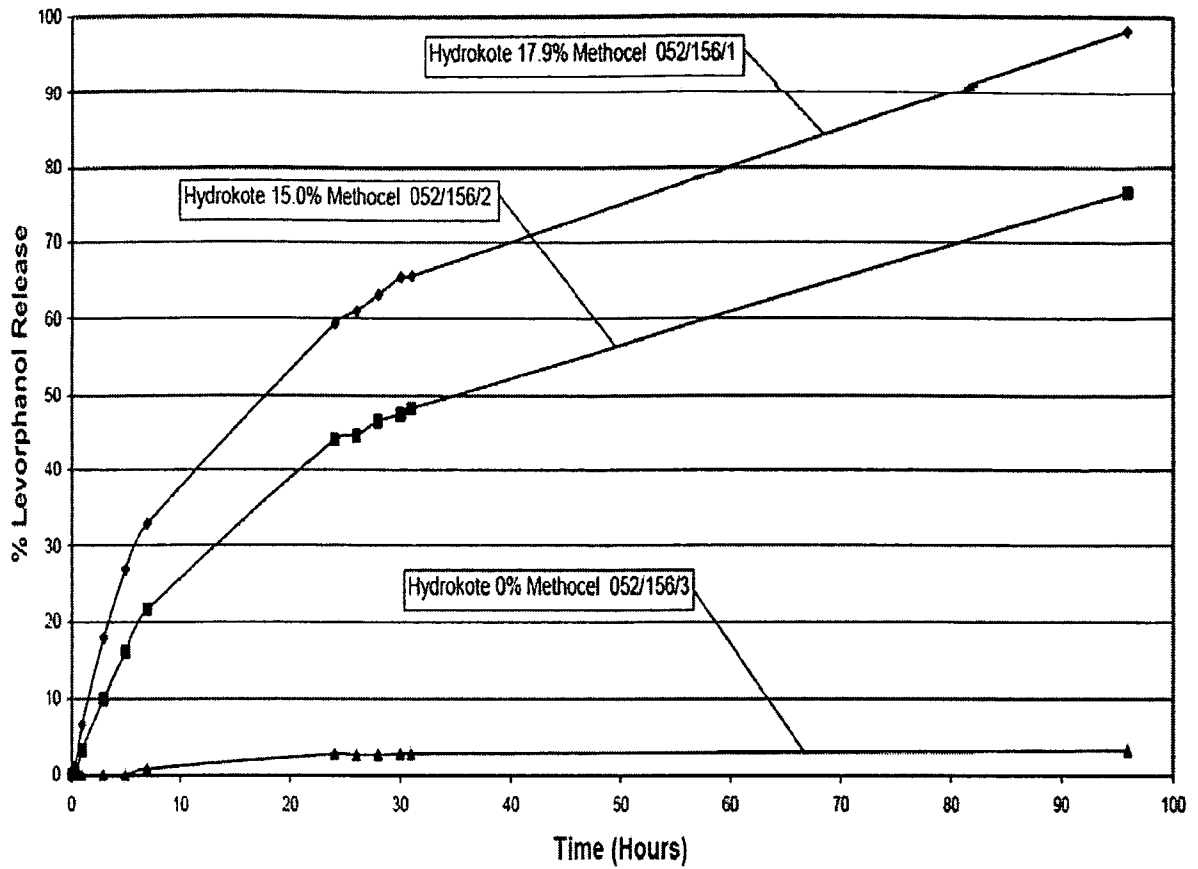


Figure 6

Levorphanol release versus time for Hydrokote & Sterotex 111/021/1 & 111/021/2

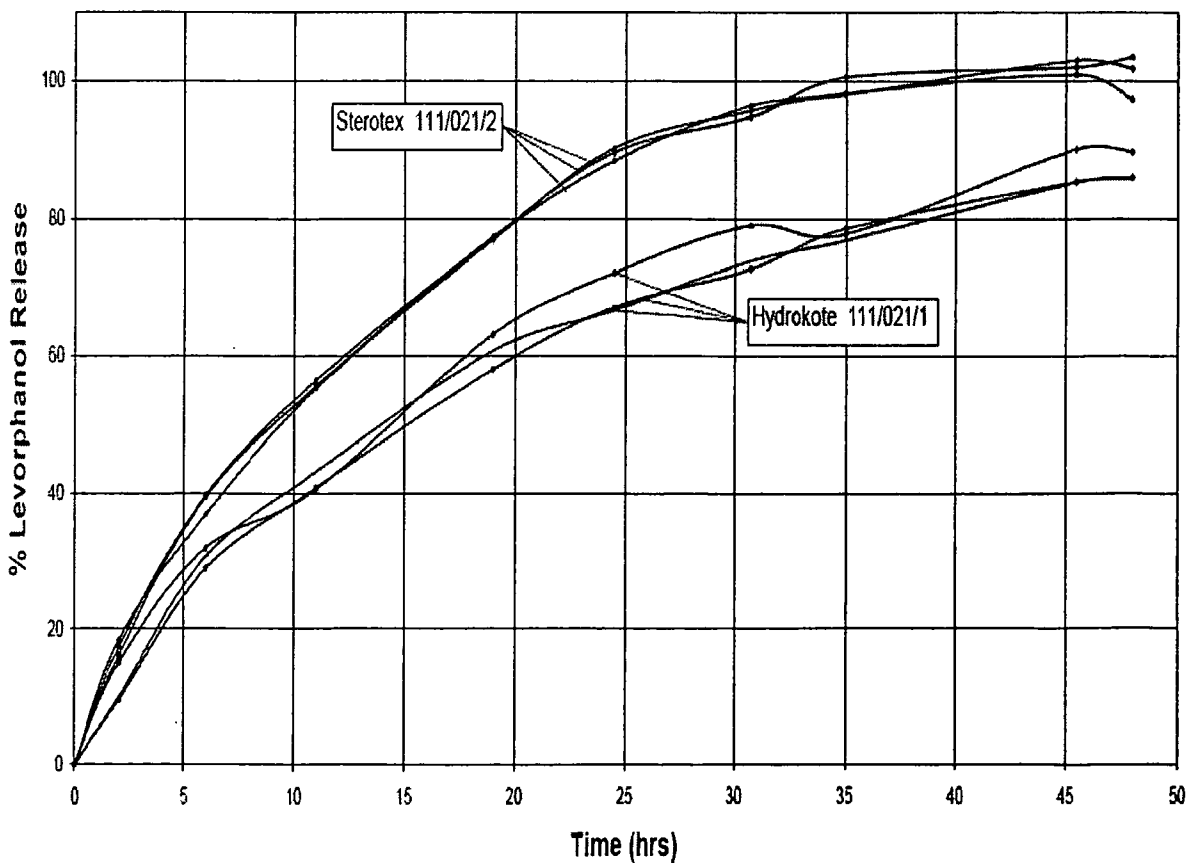


Figure 7
Mean Percentage Levorphanol release versus time for Hydrokote & Sterotex 111/021/1 & 111/021/2

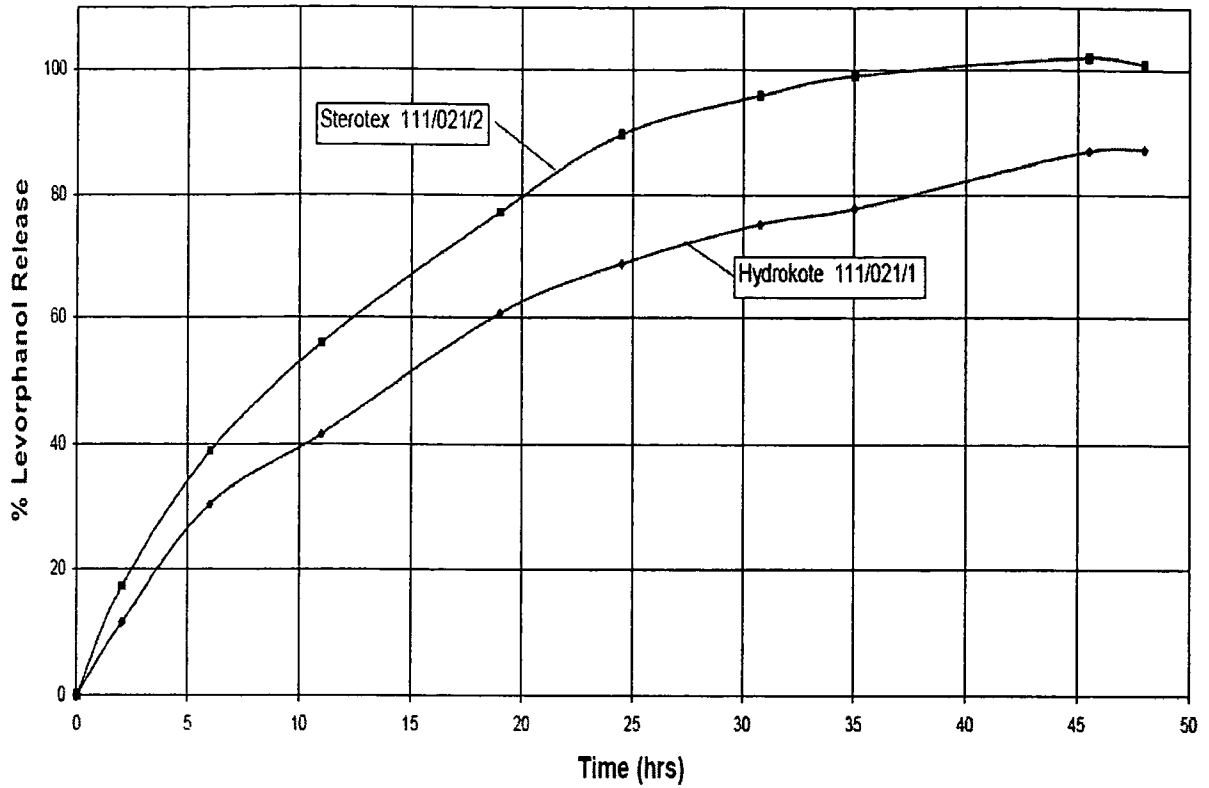


Figure 8
Percentage levorphanol release versus time from Precirol & Compritol 111/021/3 & 111/021/4

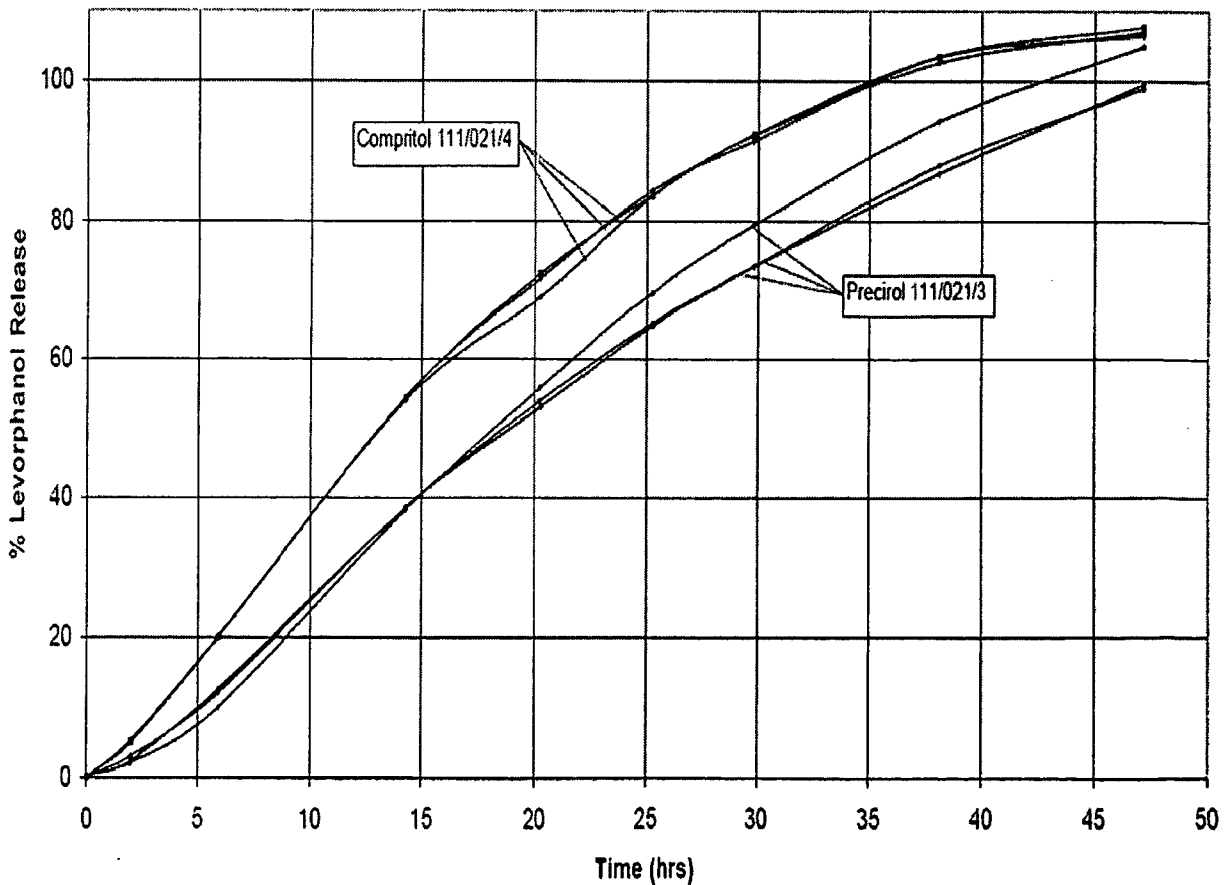


Figure 9
Mean Percentage Levorphanol Release versus time for Precirol & Compritol 111/021/3 & 111/021/4

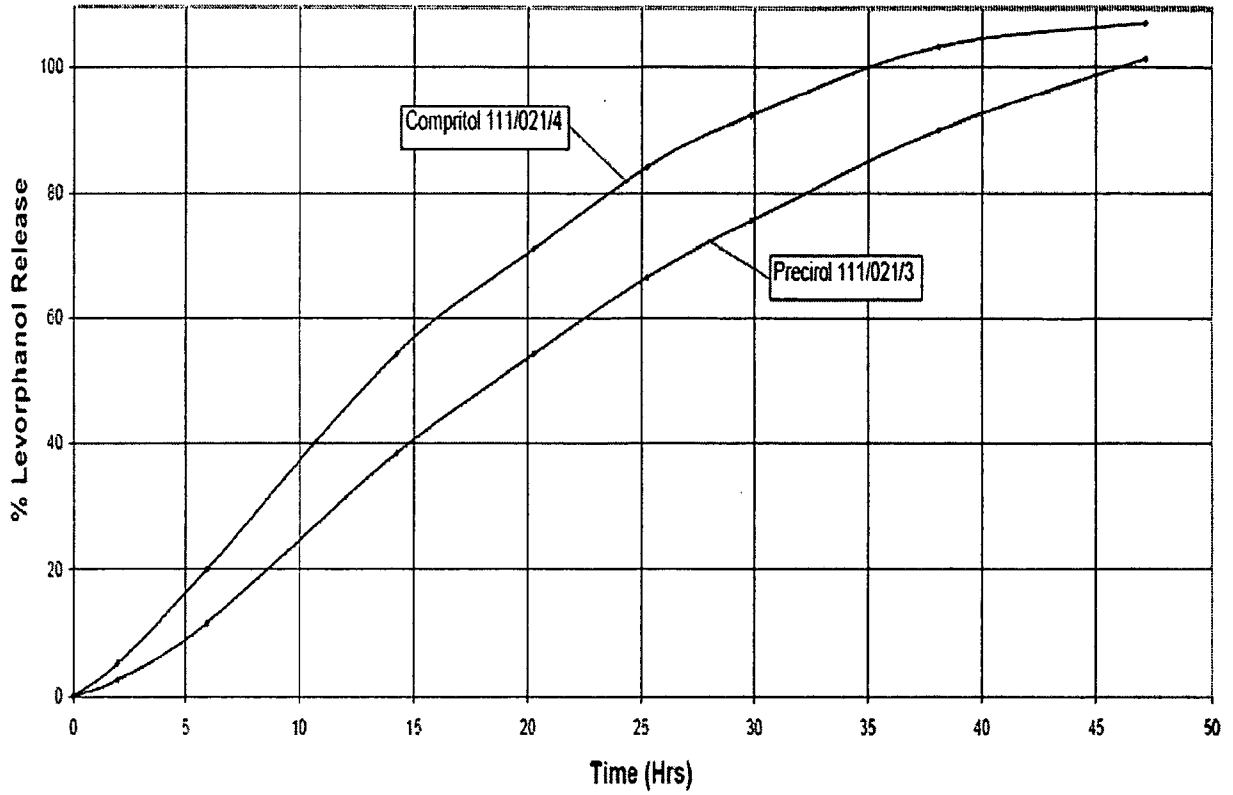


Figure 10
Percentage levorphanol release from 111/026/1, Hydrokote 112, versus time
 T_0 sample at 25°C

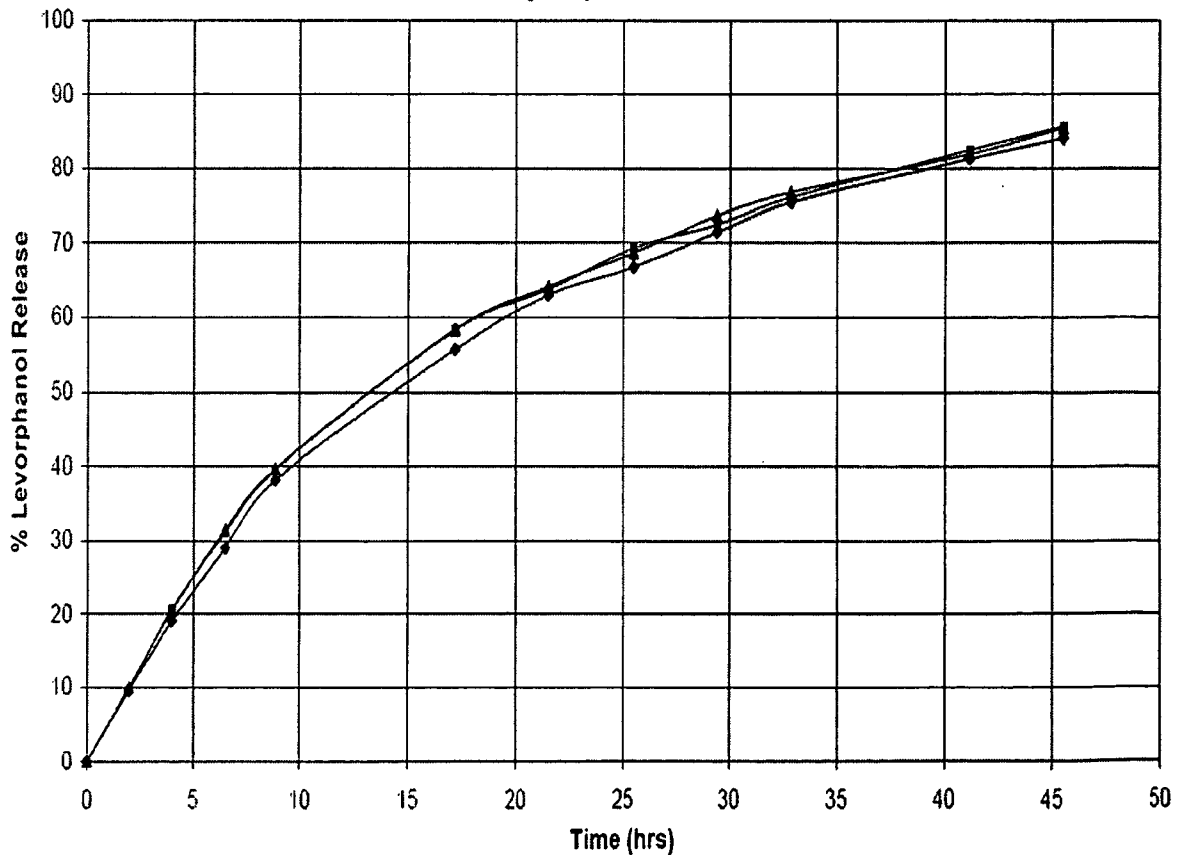


Figure 11
Percentage levorphanol release from 111/026/2, 47% Sterotex, versus time.
T₀ sample at 25°C

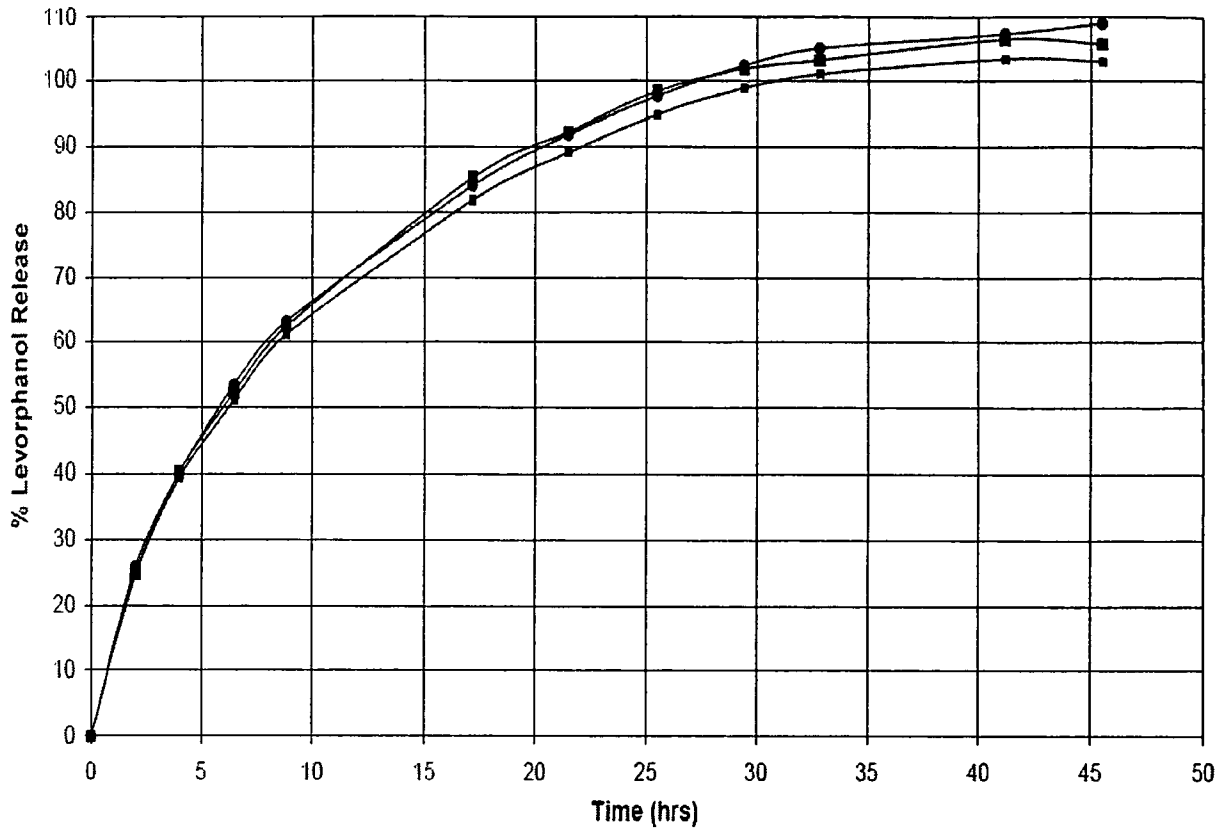


Figure 12
Percentage Levorphanol Release from 111/026/03, Precirol ATO 5, versus time

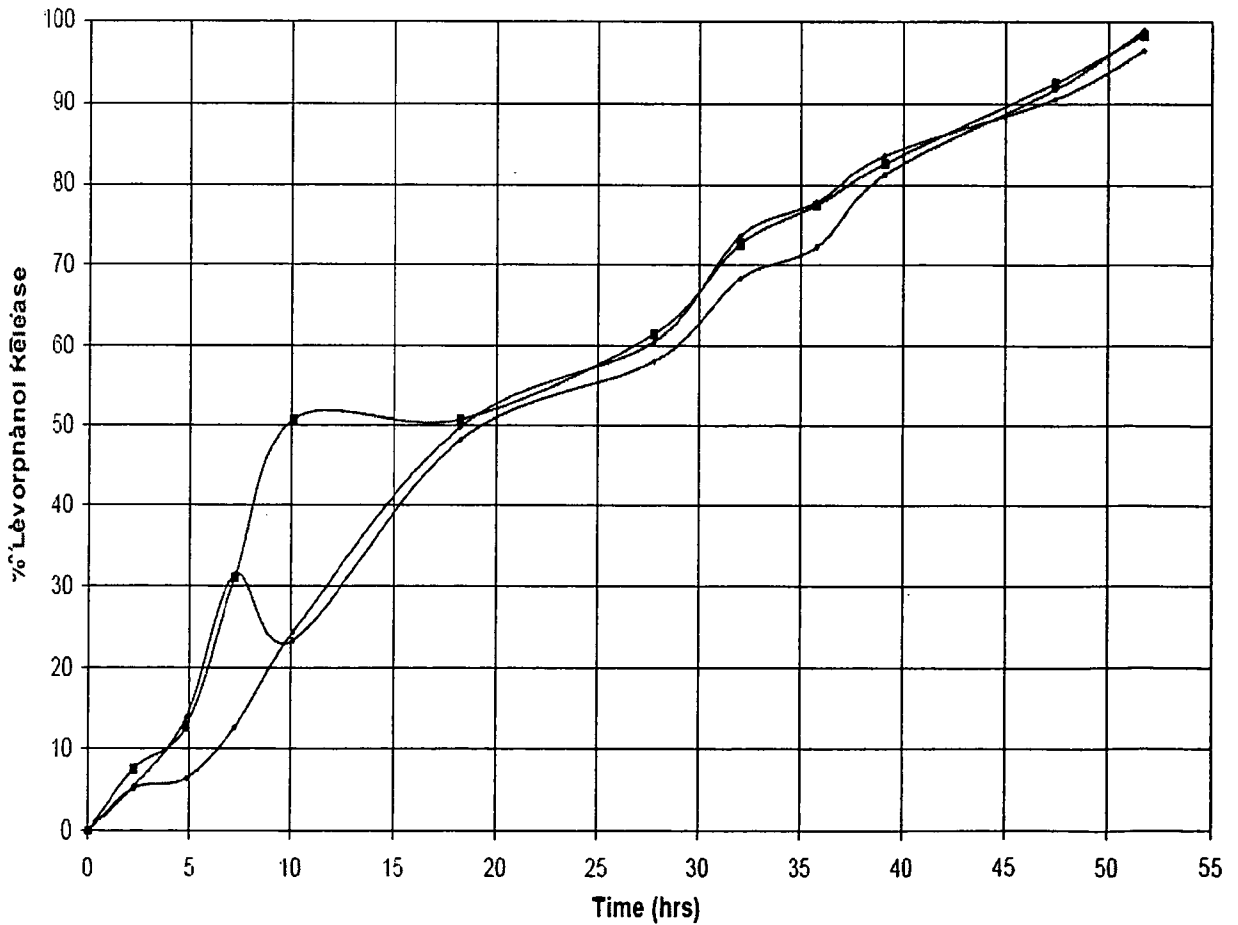


Figure 13
Percentage Levorphanol Release from 111/026/4, Compritol, versus time

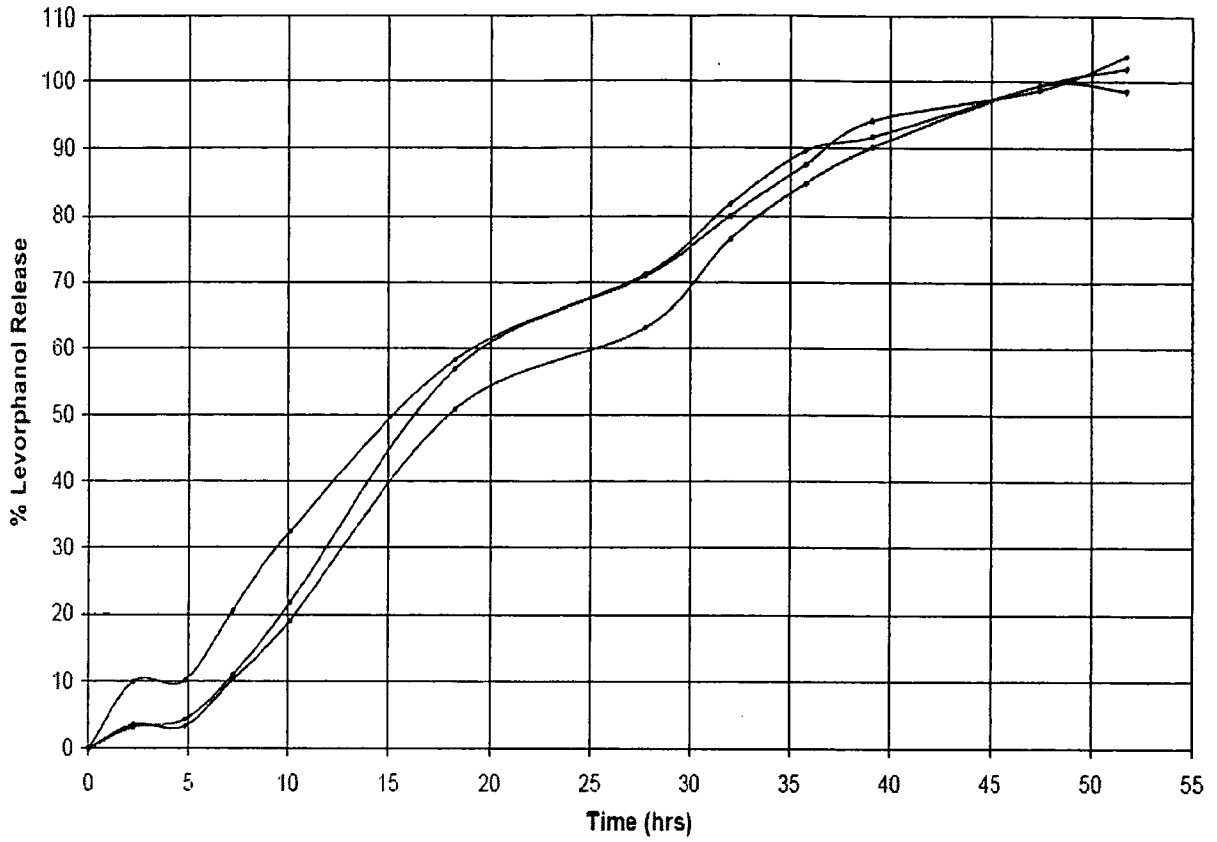


Figure 14
Abuse resistance; EtOH extraction, Test 1 (intact dosage units) at T_0

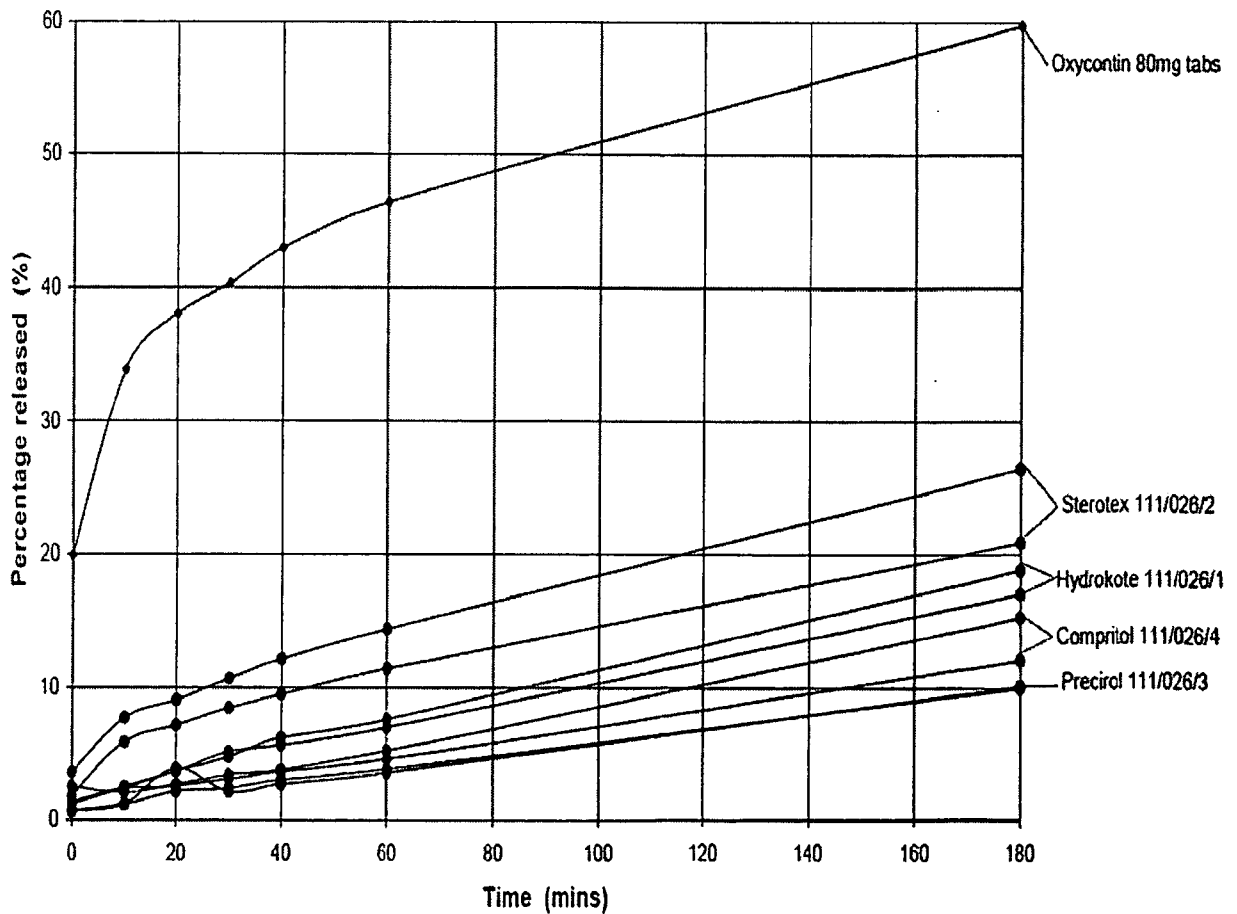


Figure 15

Abuse resistance; EtOH extraction, Test 1a (single crush of dosage unit) at T₀

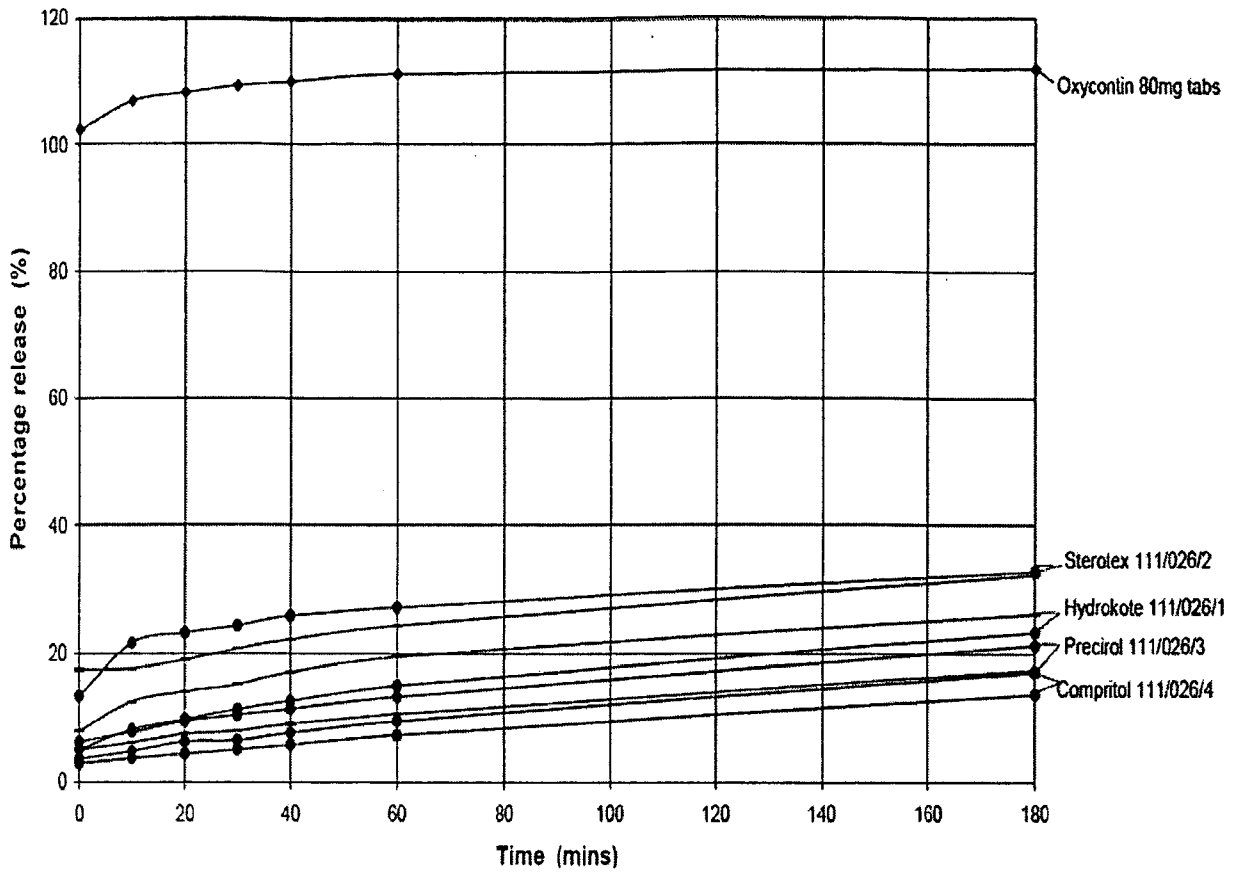


Figure 16

1 Month at 40°C Levorphanol percentage release versus time in 111/026/1 (Hydrokote 112) and 111/026/2 (Sterotex)

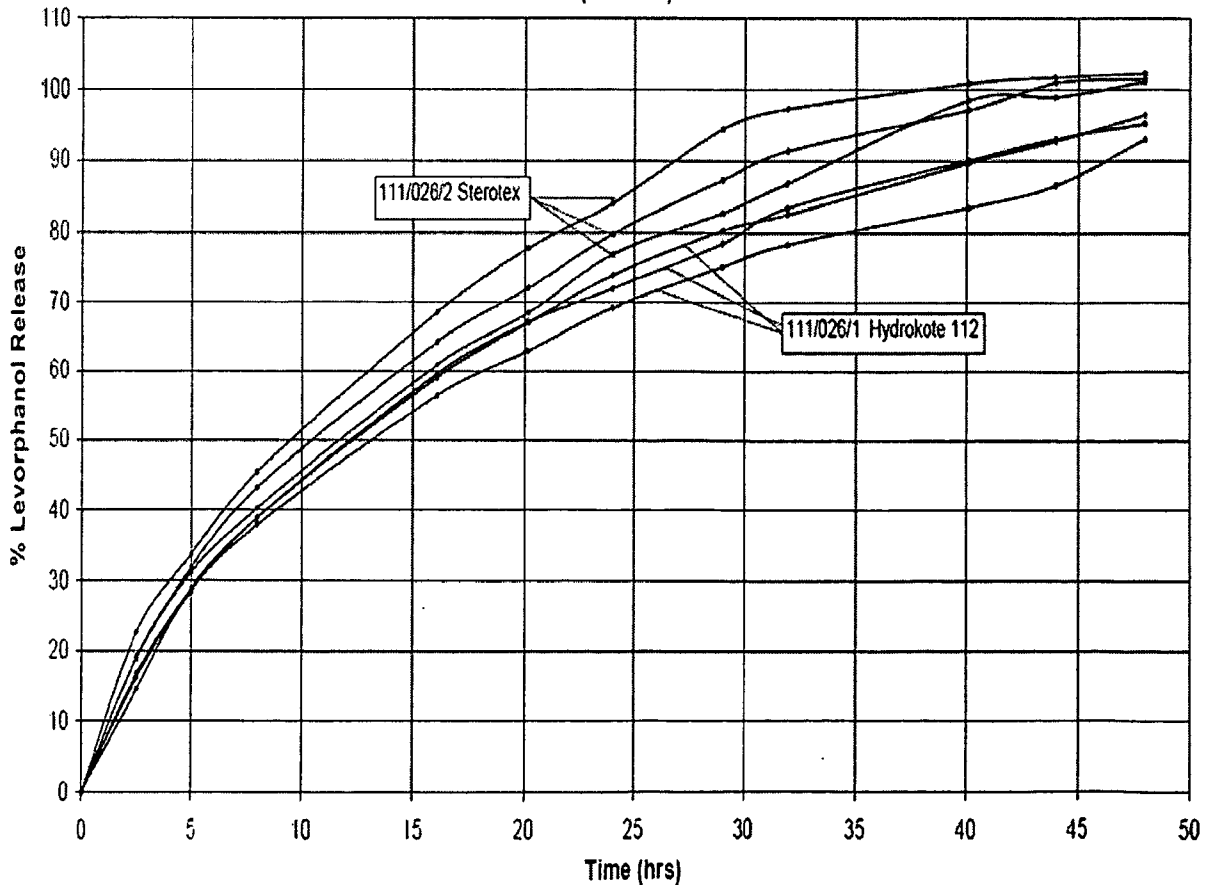


Figure 17

1 Month at 40°C Average levorphanol percentage release versus time 111/026/1 (Hydrokote 112) and 111/026/2 (Sterotex)

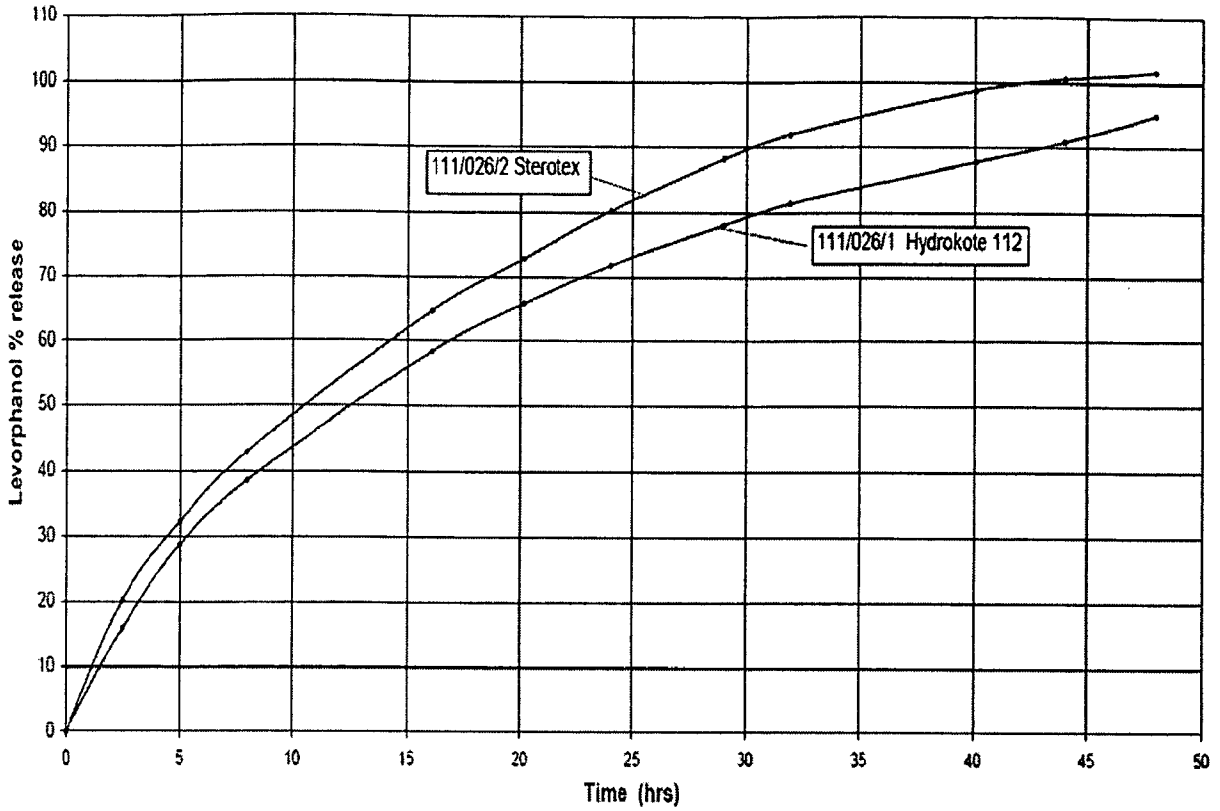


Figure 18

T₀ and 1 Month at 40°C Average levorphanol percentage release versus time 111/026/1 (Hydrokote 112)

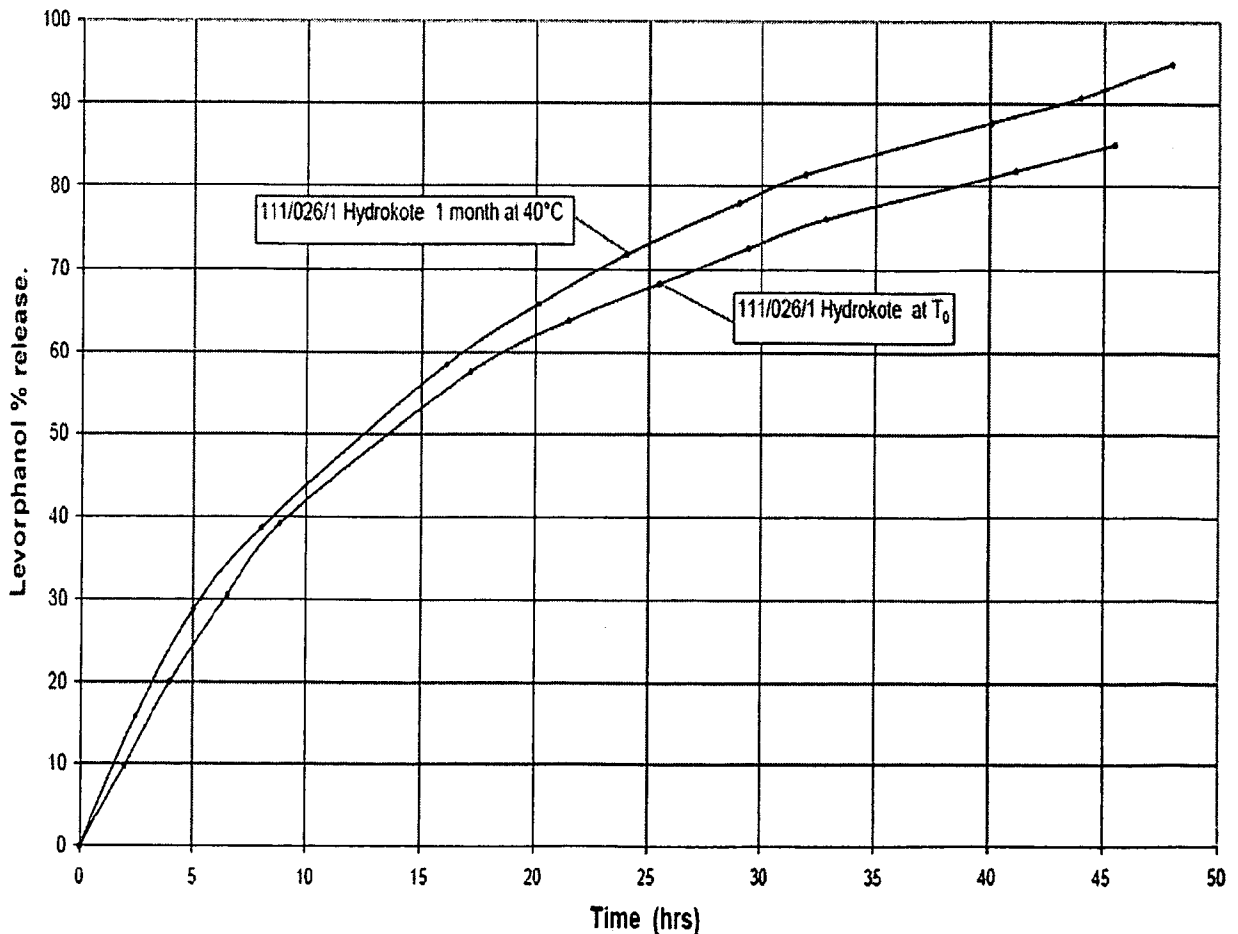


Figure 19

T₀ and 1 Month at 40°C Average levorphanol percentage release versus time 111/026/2 (Sterotex)

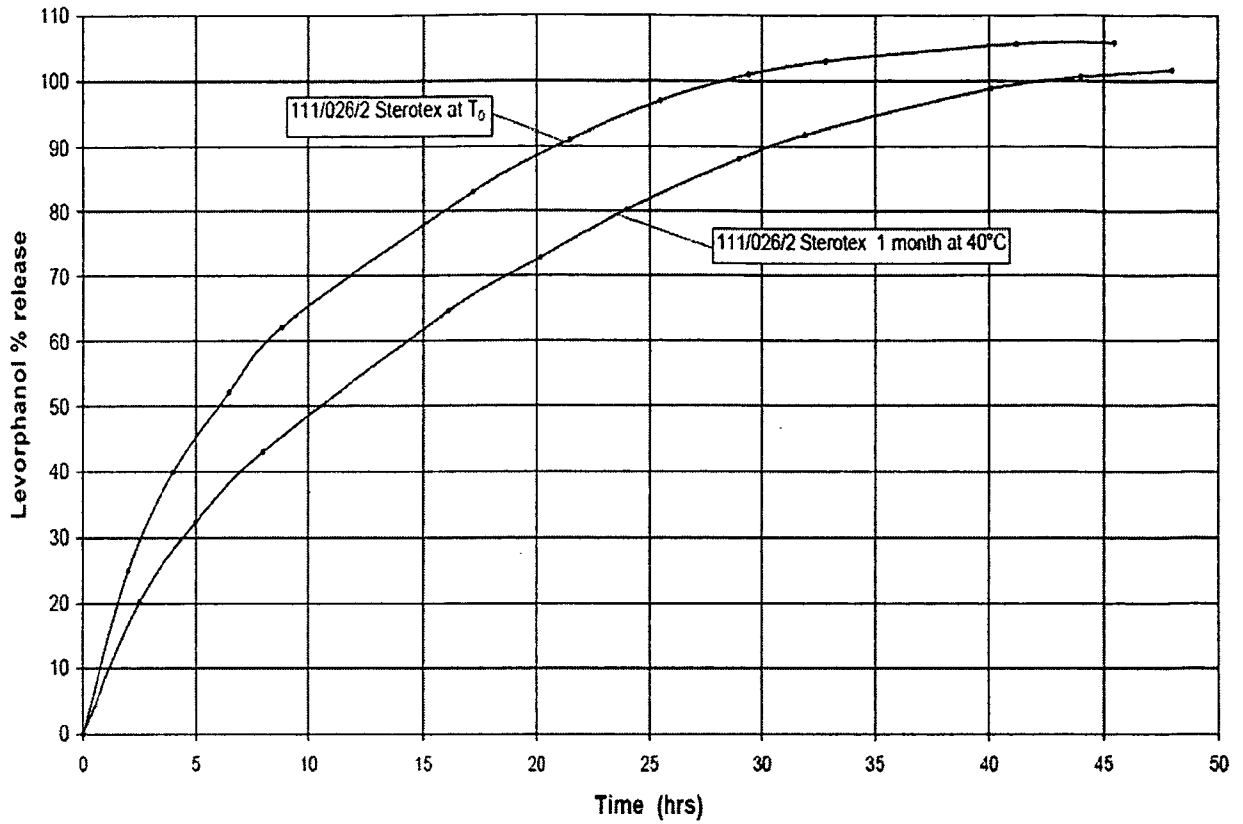
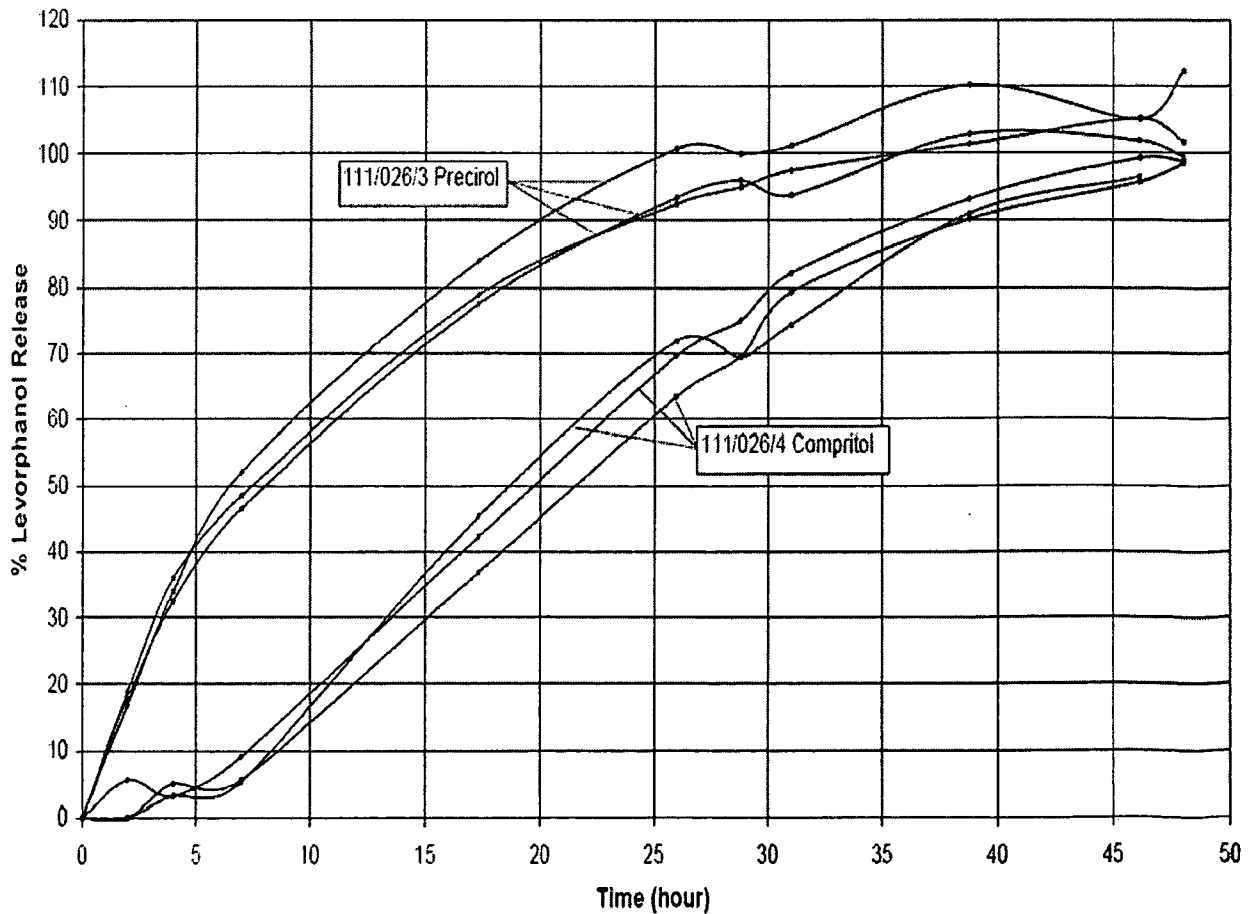


Figure 20

1 Month at 40°C Levorphanol percentage release versus time in 111/026/3 (Precirol) and 111/026/4 (Compritol)



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Figure 21
1 Month at 40°C Mean Percentage Levorphanol Release versus time from 111/026/3 (Precirol) and 111/026/4 (Compritol)

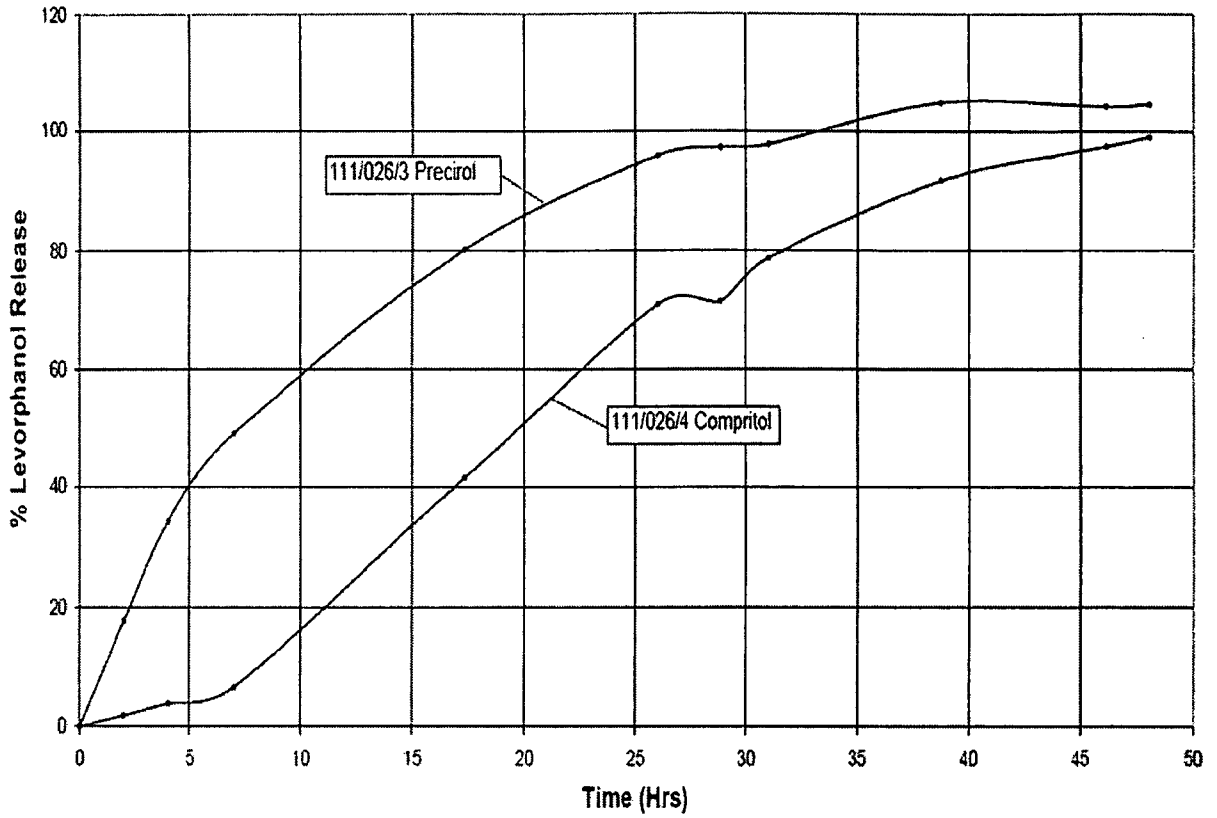


Figure 22

T₀ and 1 Month at 40°C Mean Percentage Levorphanol Release versus time from 111/026/3 (Precirol)

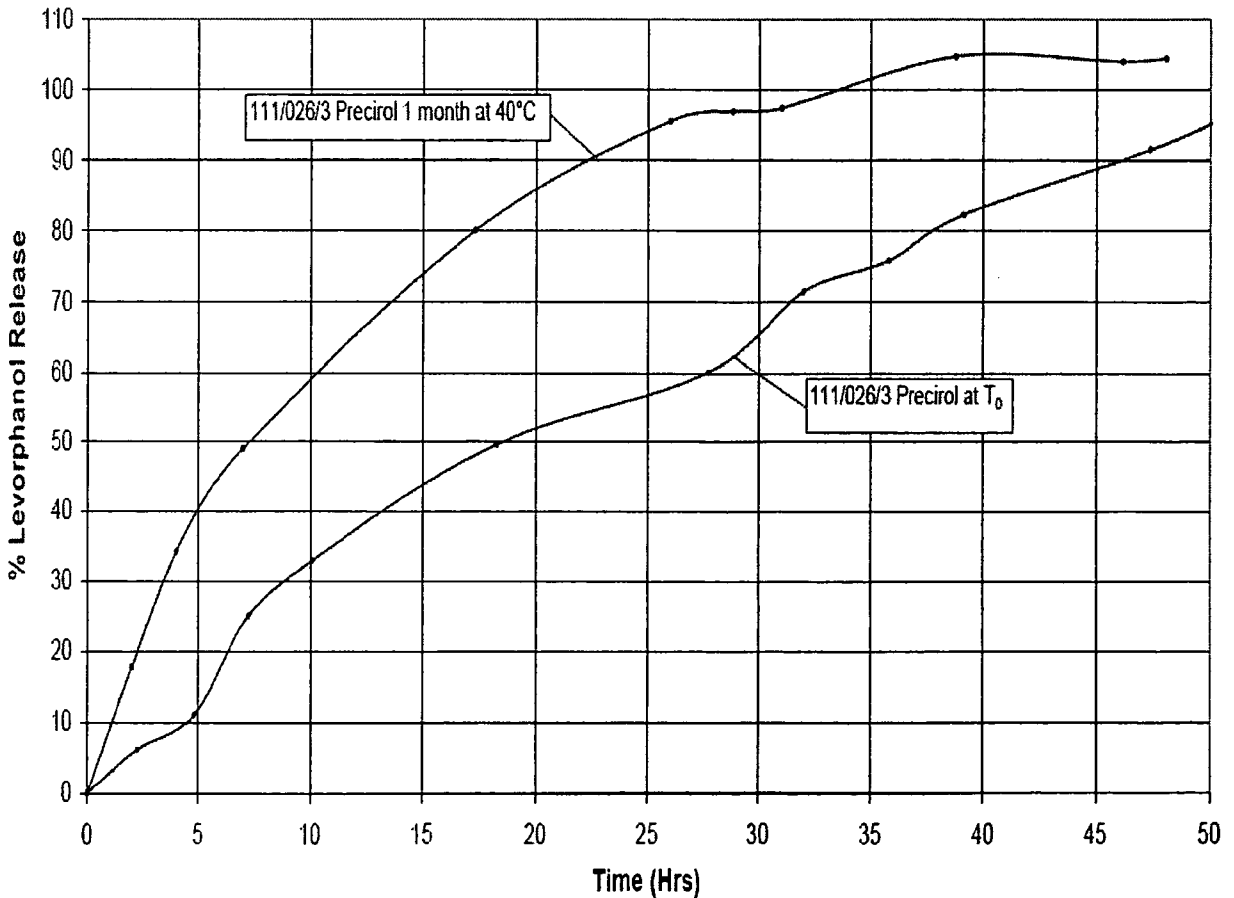


Figure 23

T₀ and 1 Month 40°C Mean Percentage Levorphanol Release versus time from 111/026/4 (Compritol)

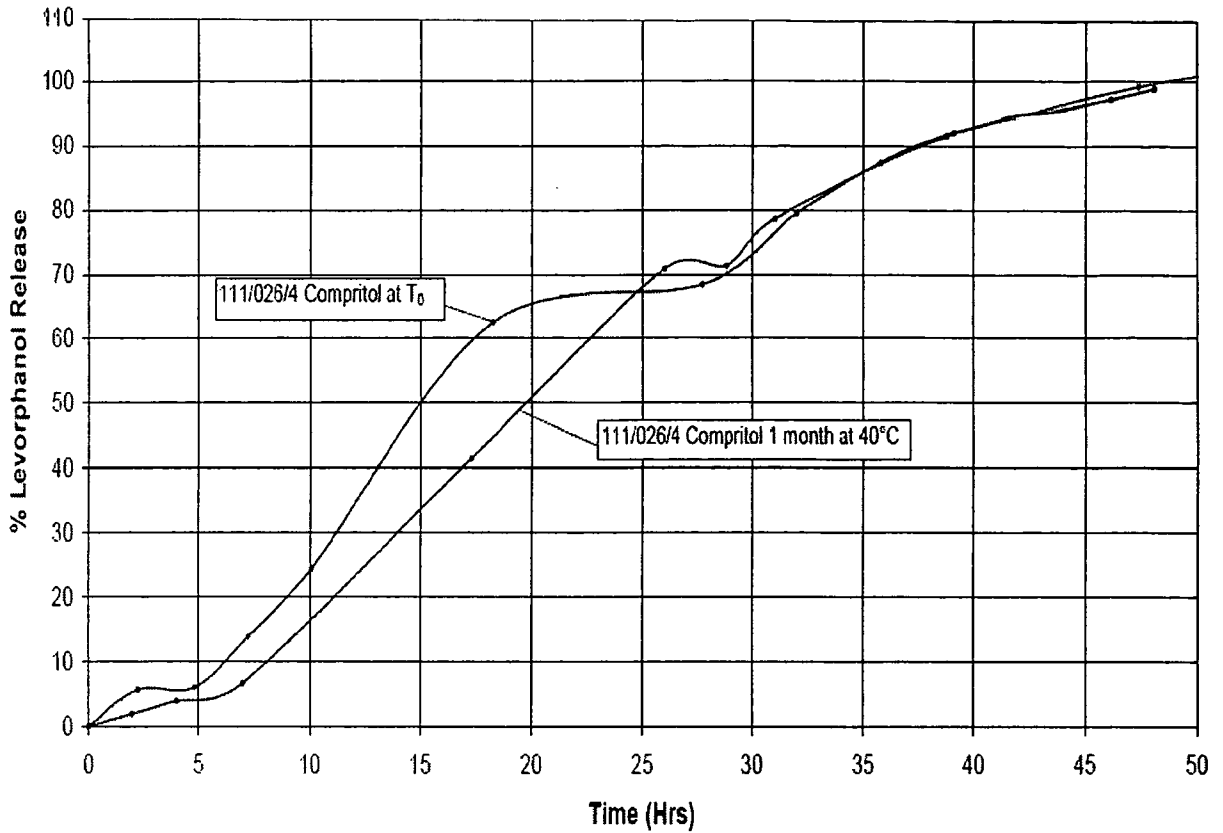


Figure 24

Levorphanol in Hydrokote release rate after 2 months at 25°C and 40°C 111/026/1

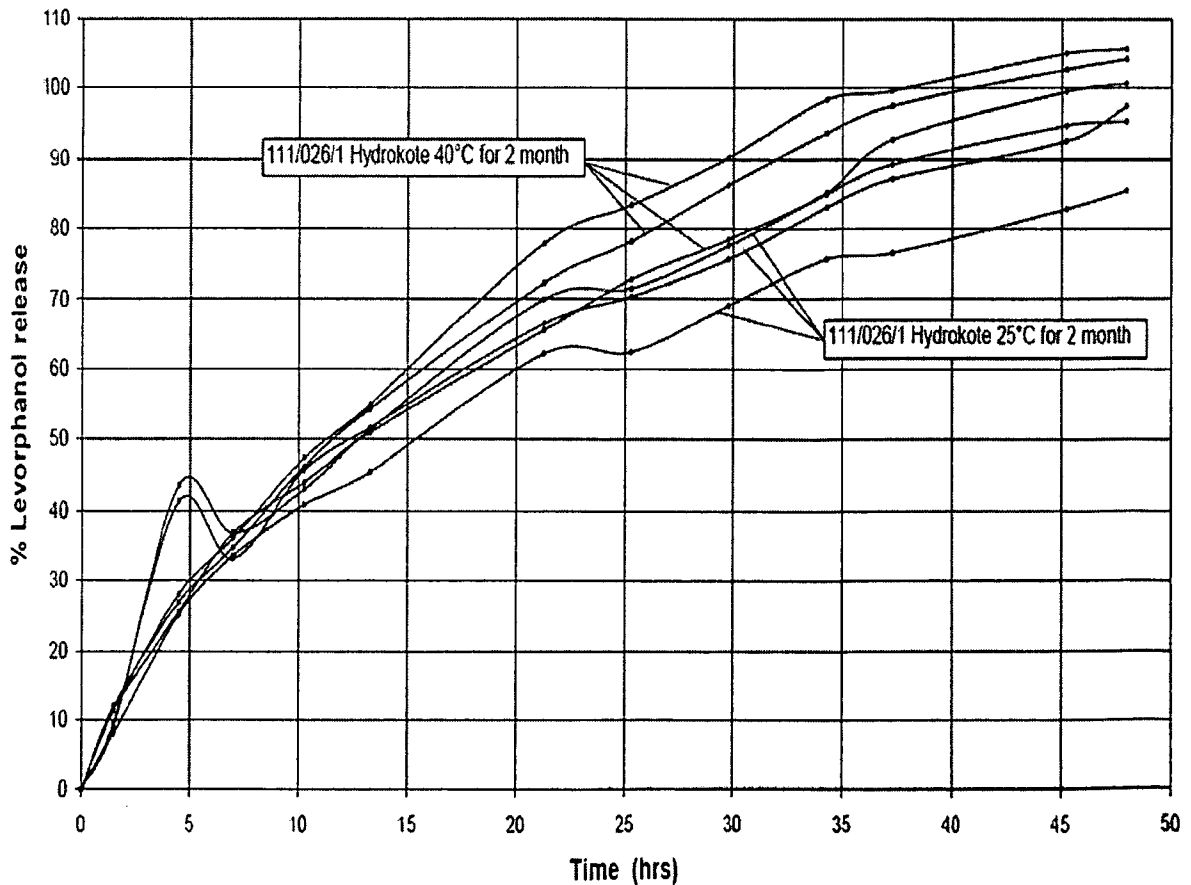


Figure 25
Average Levorphanol in Hydrokote release rate at T_0 , 1 month & 2 months at 25 and 40°C 111/026/1

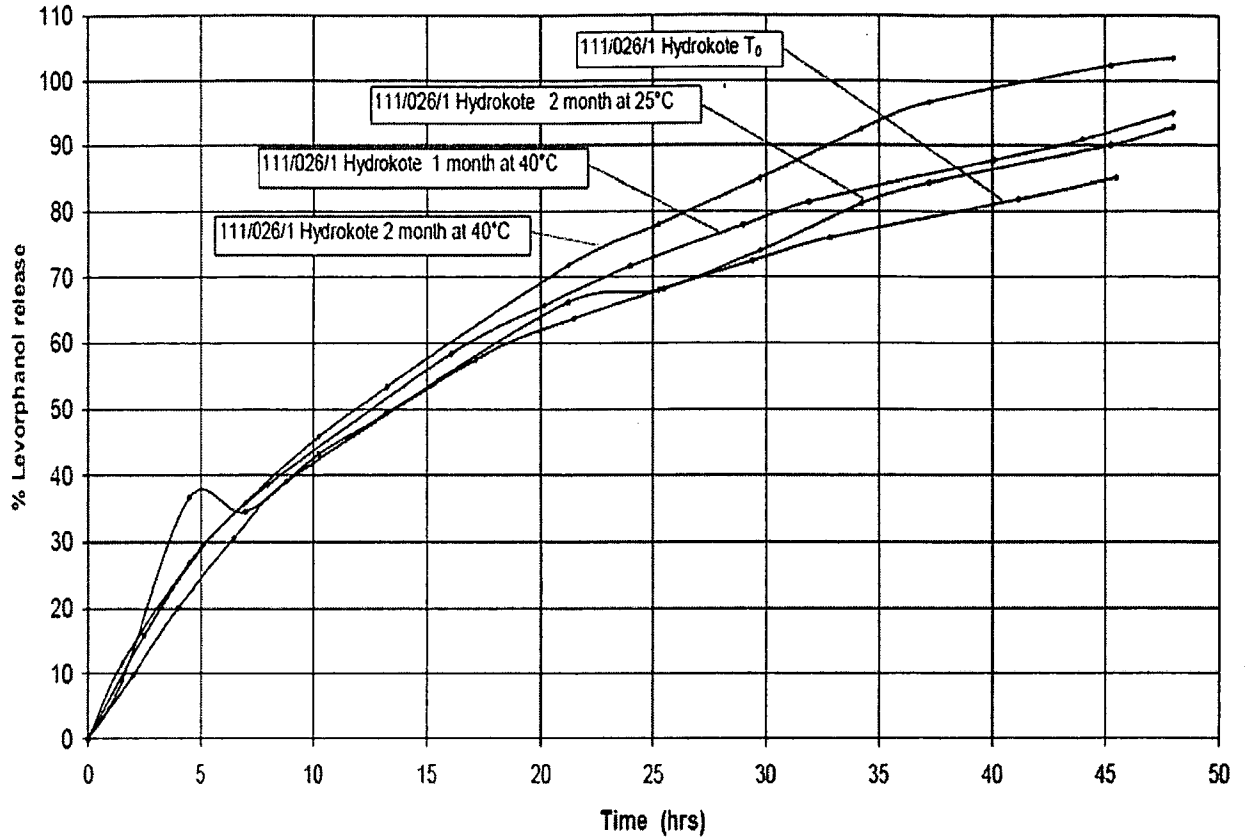


Figure 26
Levorphanol in Sterotex release rate after 2 months at 25 and 40 deg 111/026/2

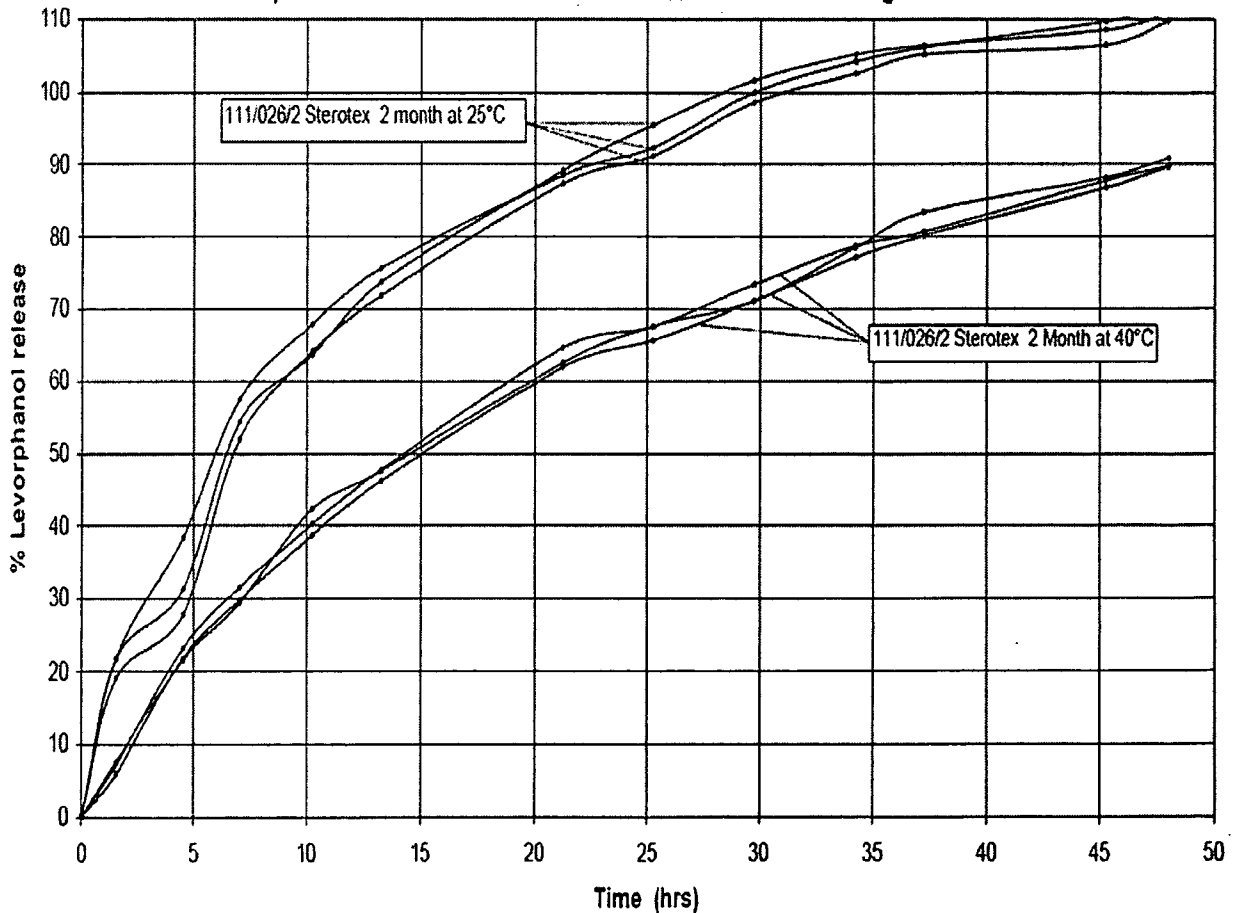


Figure 27

Average Levorphanol in Sterotex release rate at T_0 , 1 month & 2 months at 25 and 40 deg 111/026/2

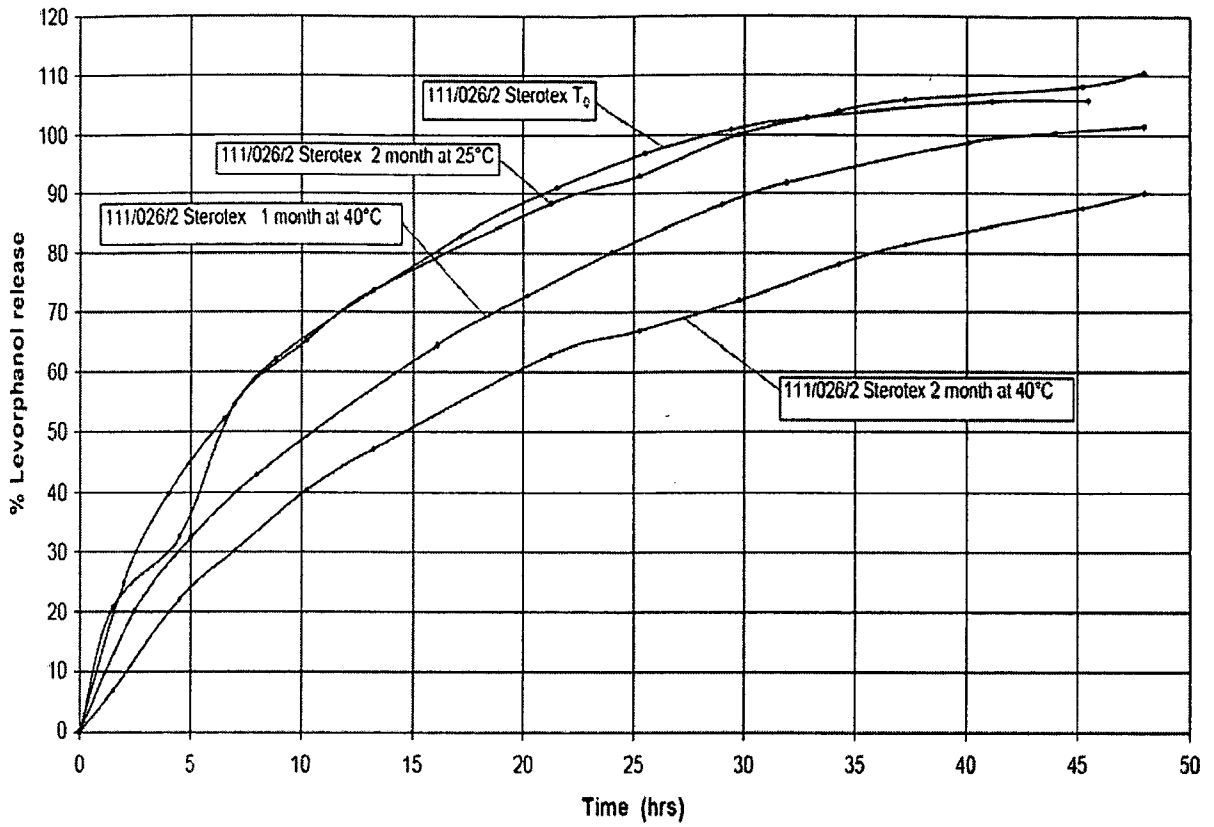


Figure 28

Percentage levorphanol release versus time from Precirol & Compritol formulations with 20% Miglyol 111/038/3 & 111/038/4

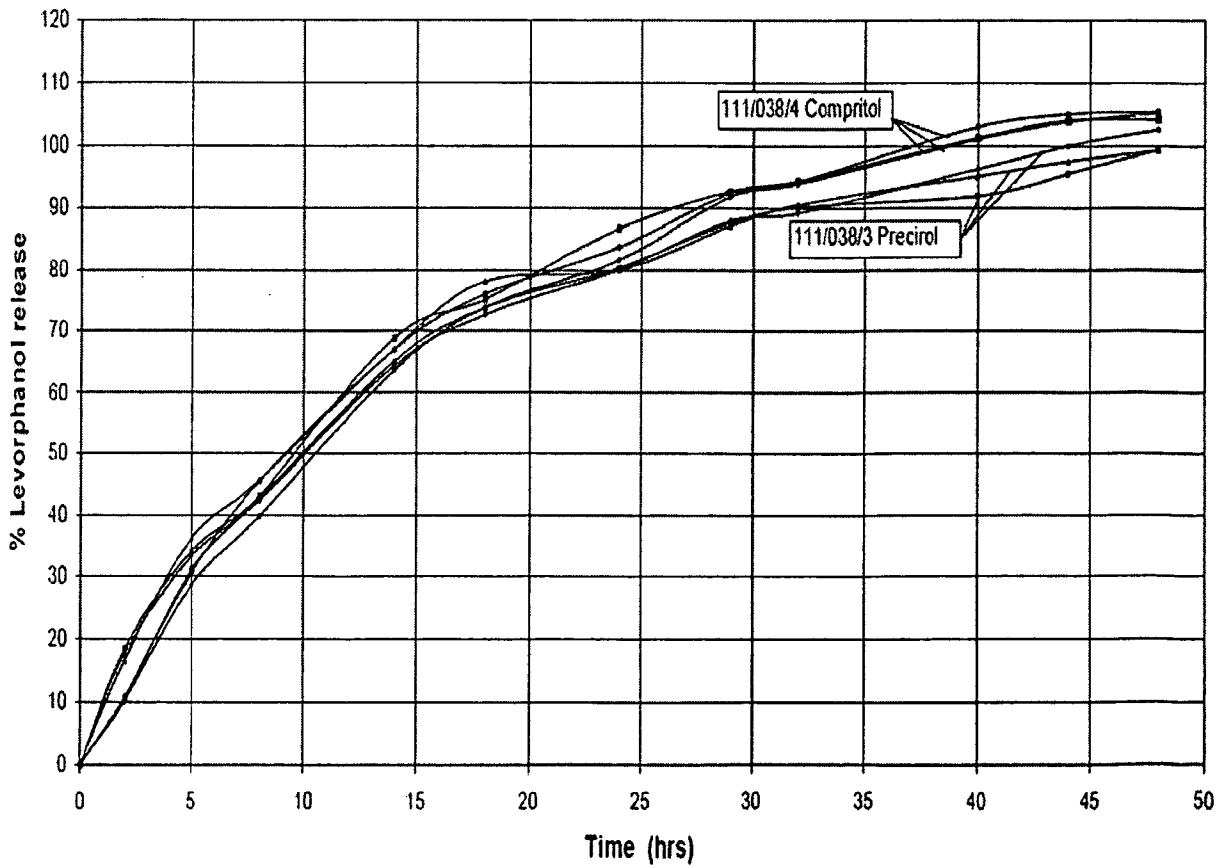


Figure 29
Percentage Levorphanol Release versus time from 111/043/1 (Hydrokote) & 111/043/2 (Sterotex)

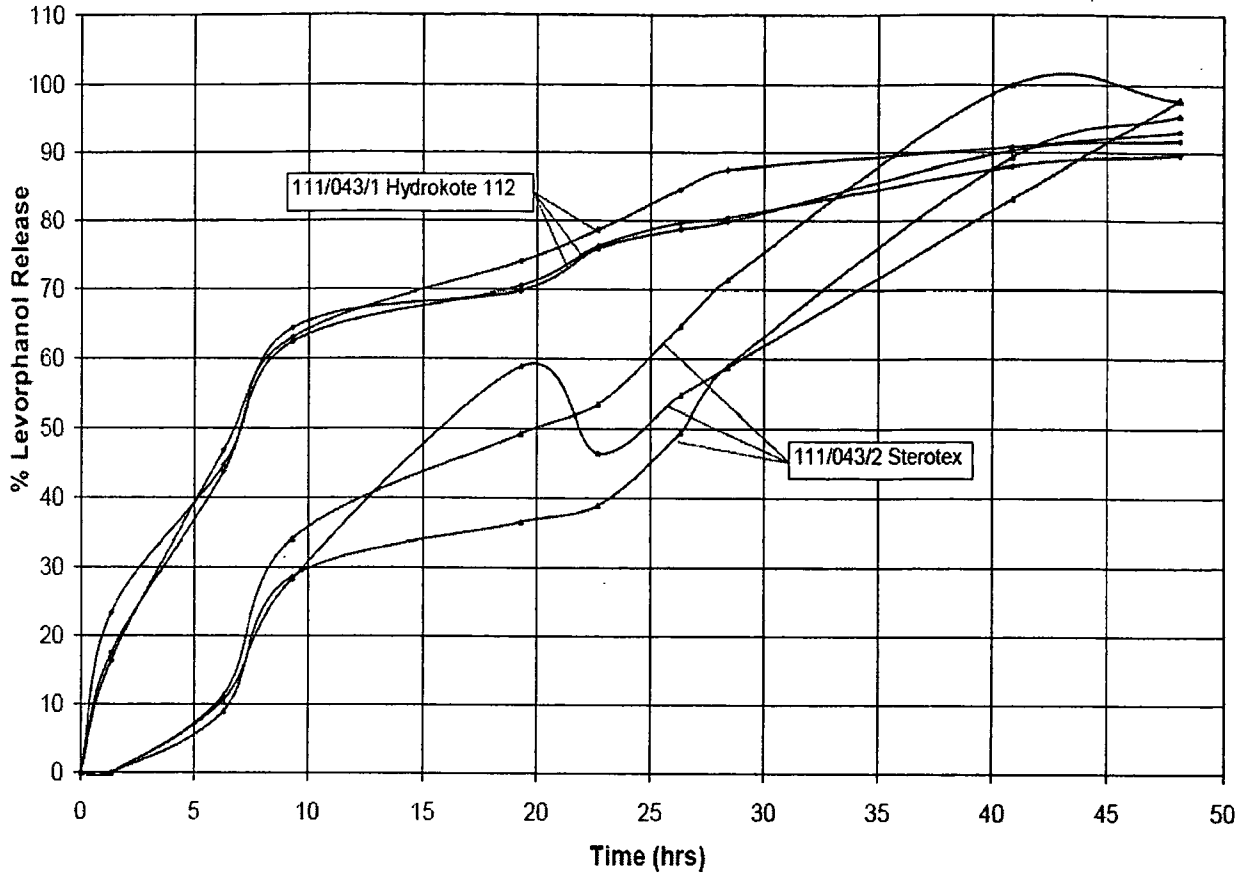


Figure 30
Mean percentage Levorphanol Release versus time from 111/043/1 (Hydrokote) & 111/043/2 (Sterotex)

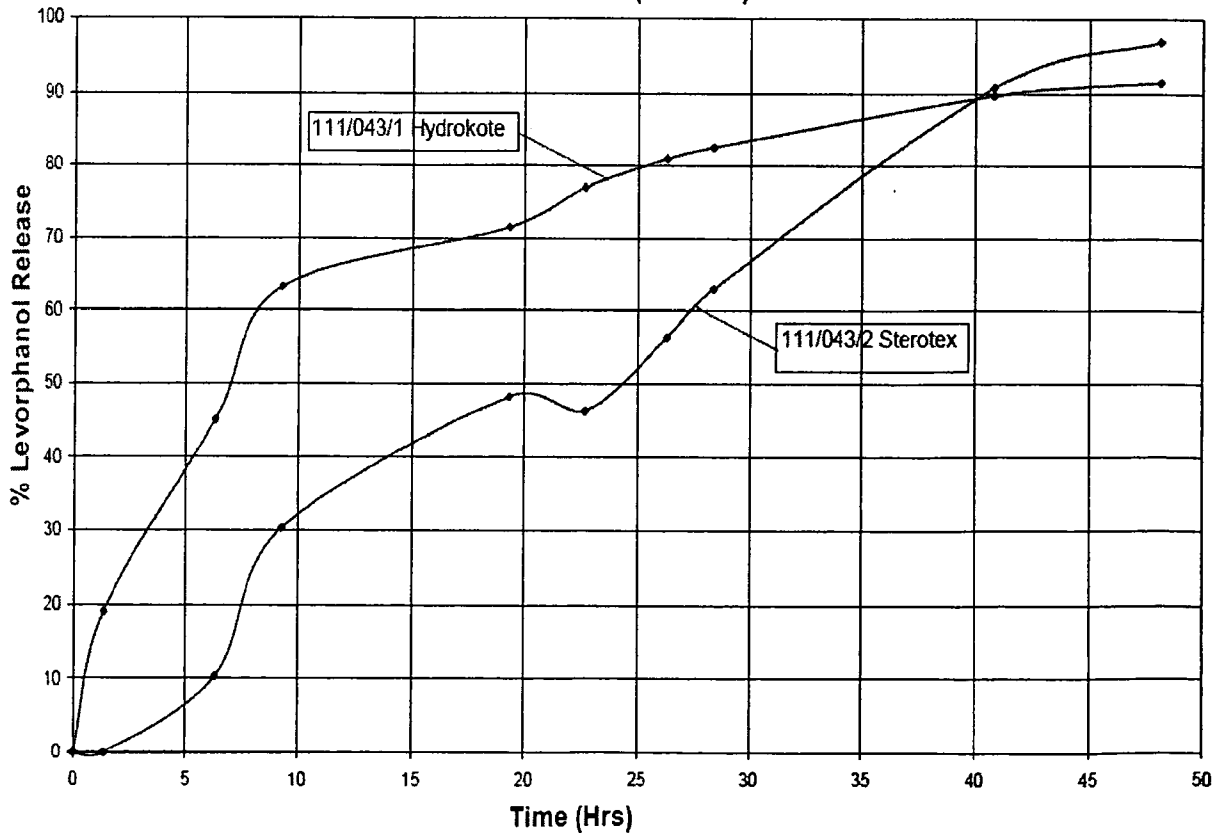


Figure 31
Percentage Levorphanol Release versus time from 111/045/3 (Precirol) & 111/045/4 (Compritol)

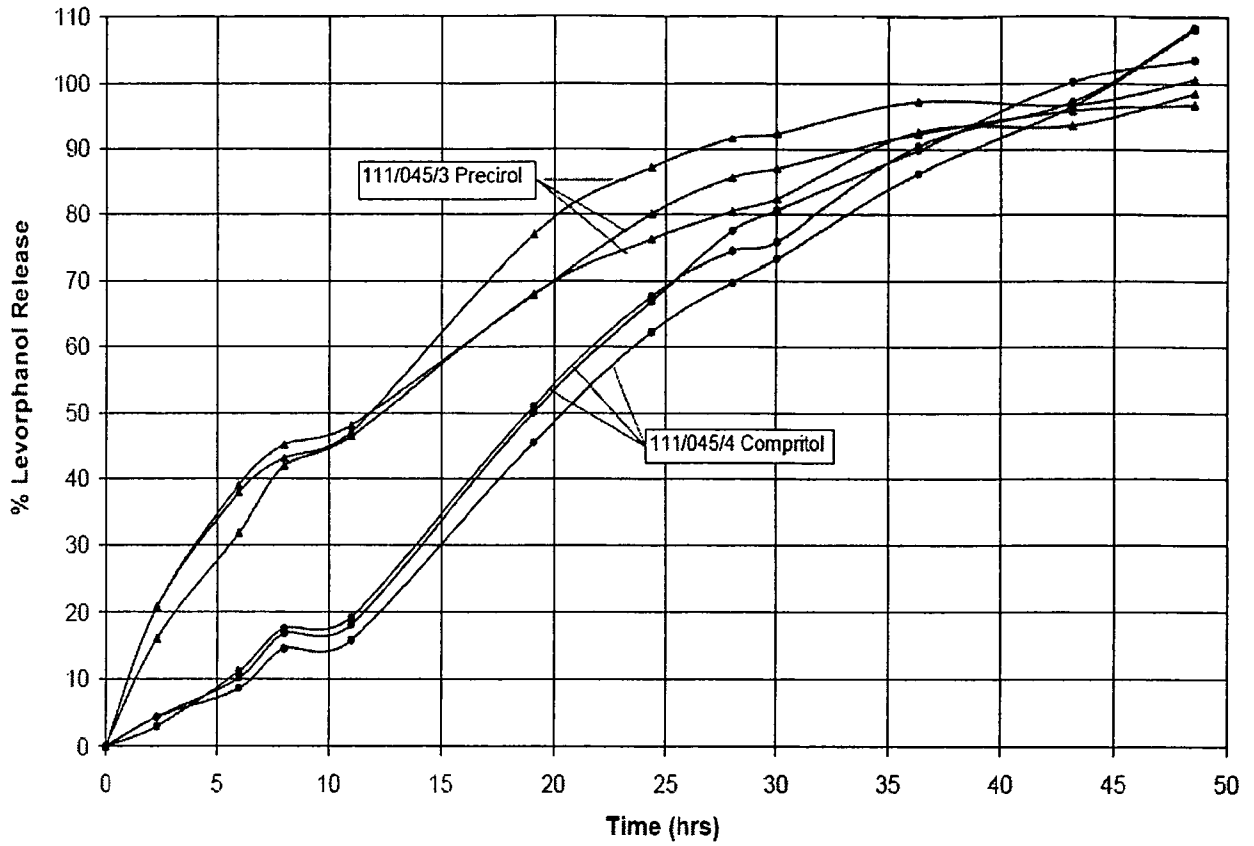


Figure 32
Mean percentage Levorphanol Release versus time from 111/045/3 (Precirol) & 111/045/4 (Compritol)

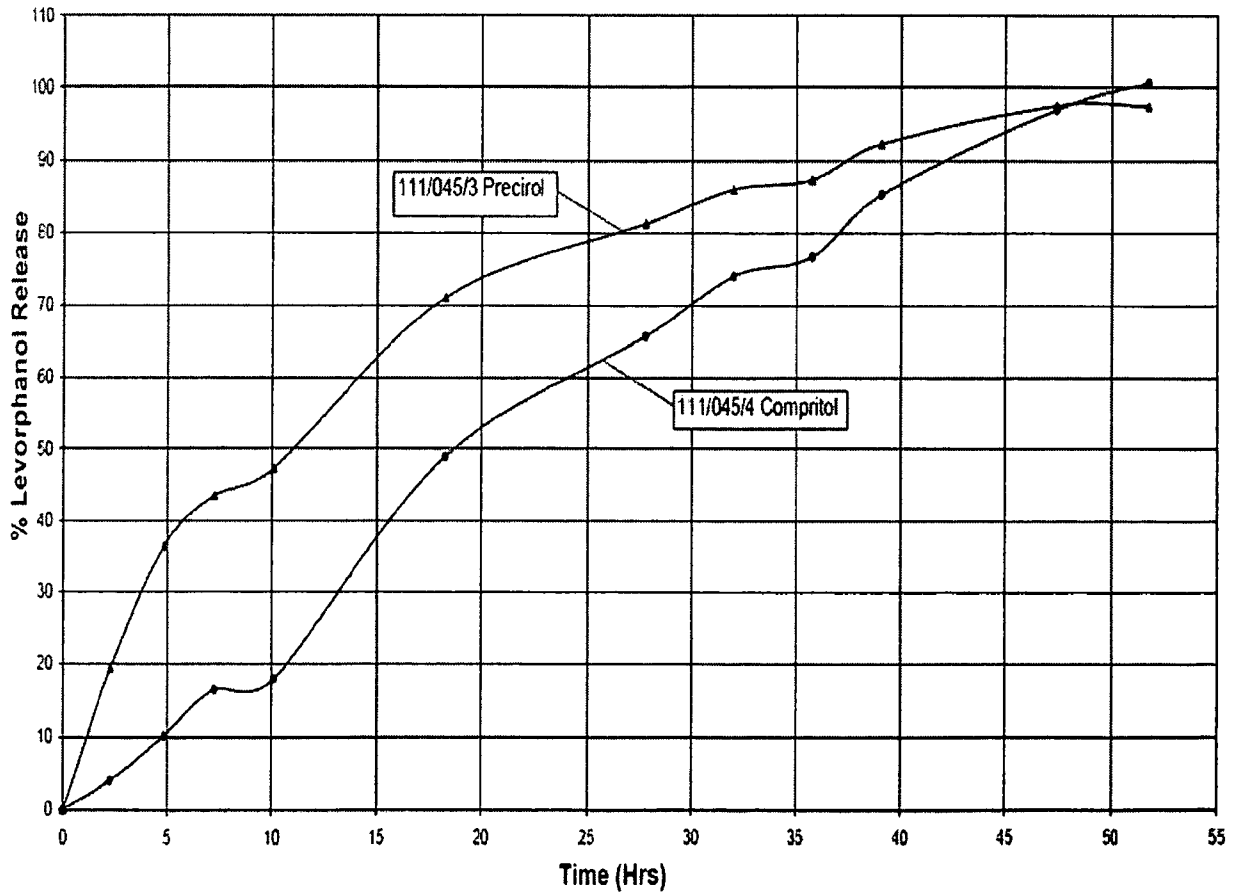


Figure 33

Abuse resistance; EtOH extraction, Test 1 (intact dosage unit) at T₃ month

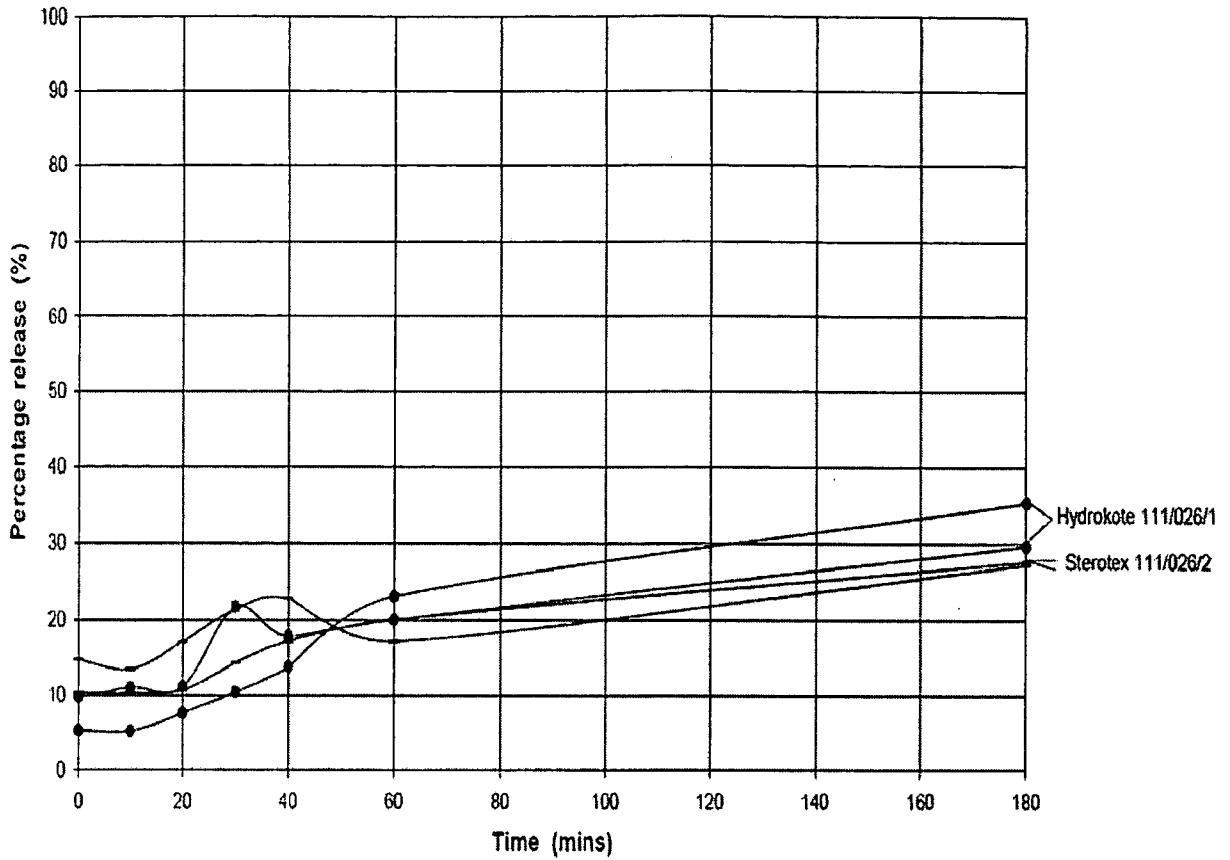


Figure 34

Percentage Levorphanol Release versus time from Hydrokote (faster) formulation 111/060/1

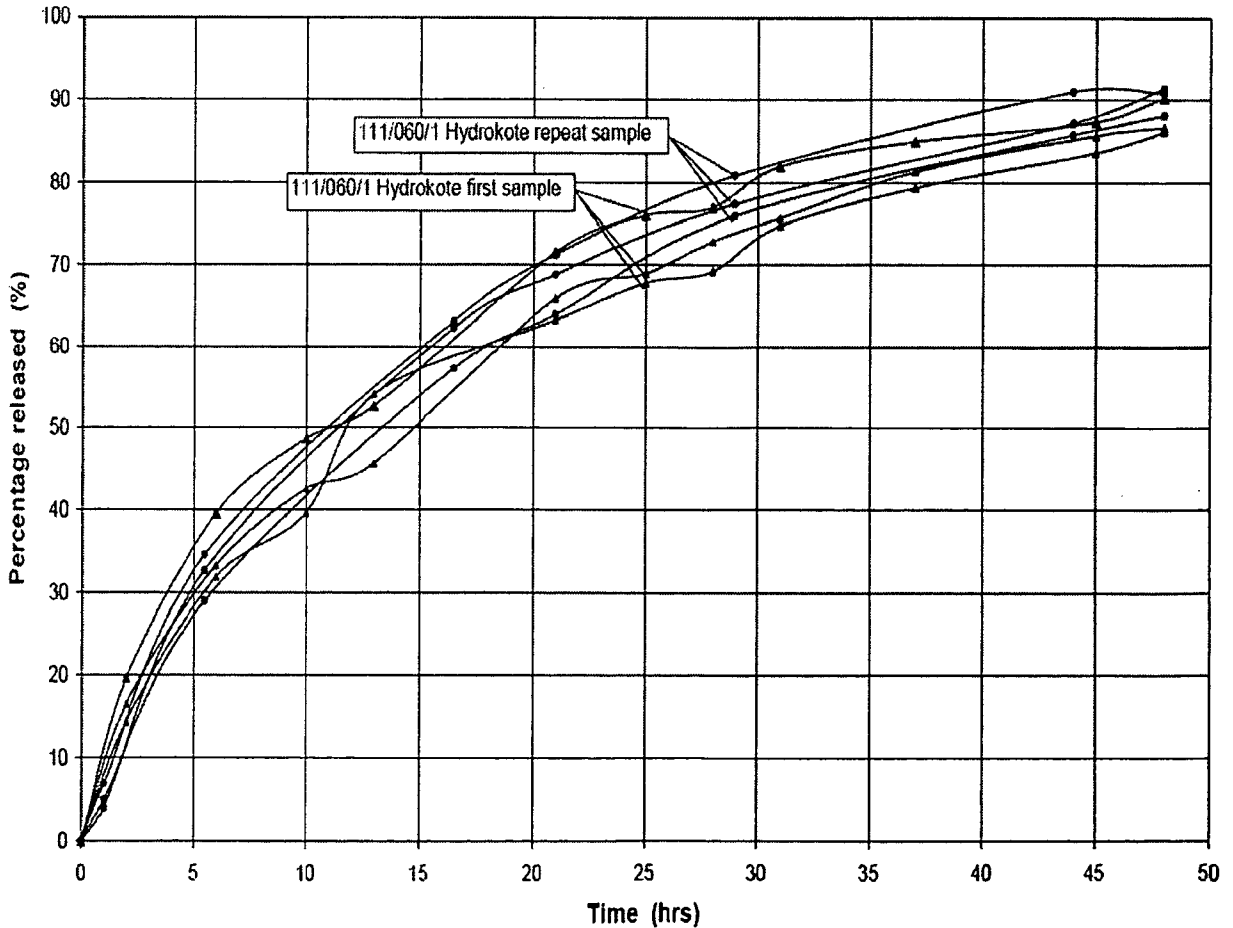


Figure 35
Percentage Levorphanol Release versus time from Sterotex (accelerated 'slow') formulation
111/059/2

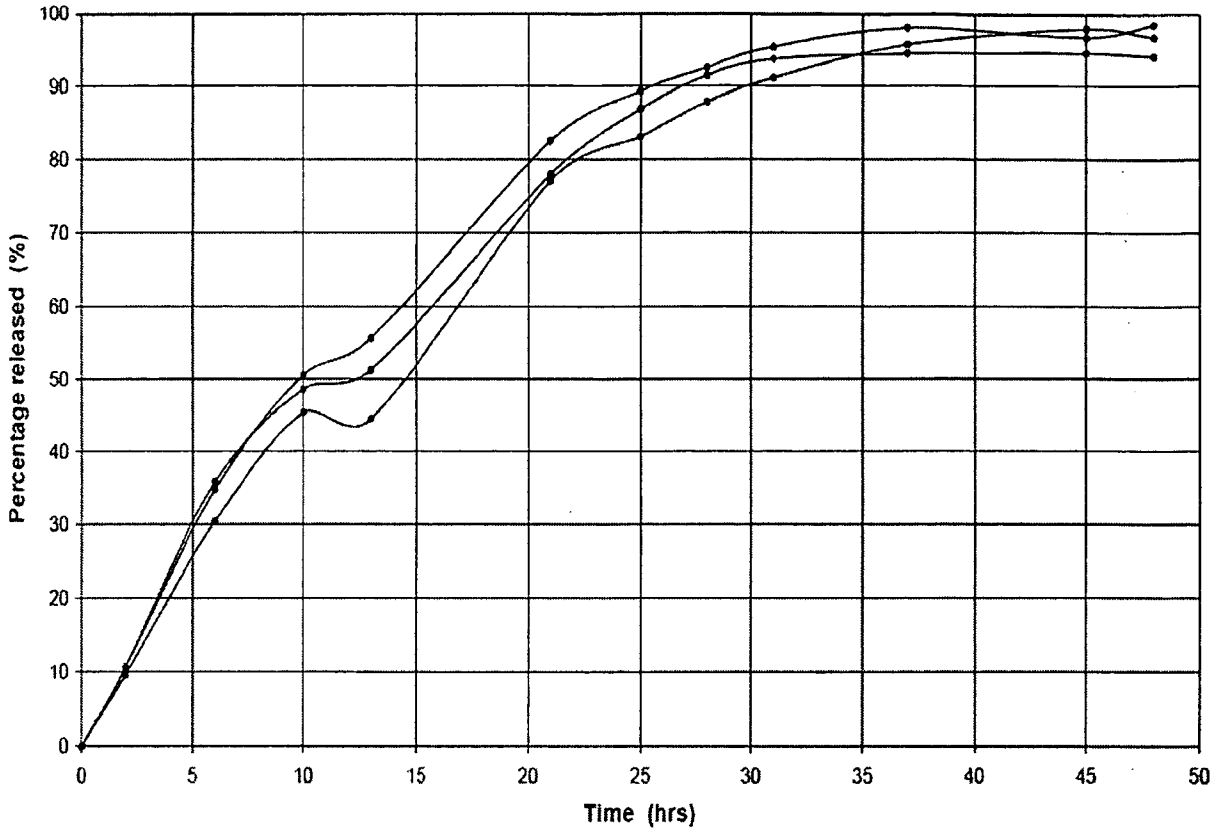


Figure 36
Percentage levorphanol release from 111/038/4, Compritol 888 ATO, versus time.
T_{1 month} sample at 25°C

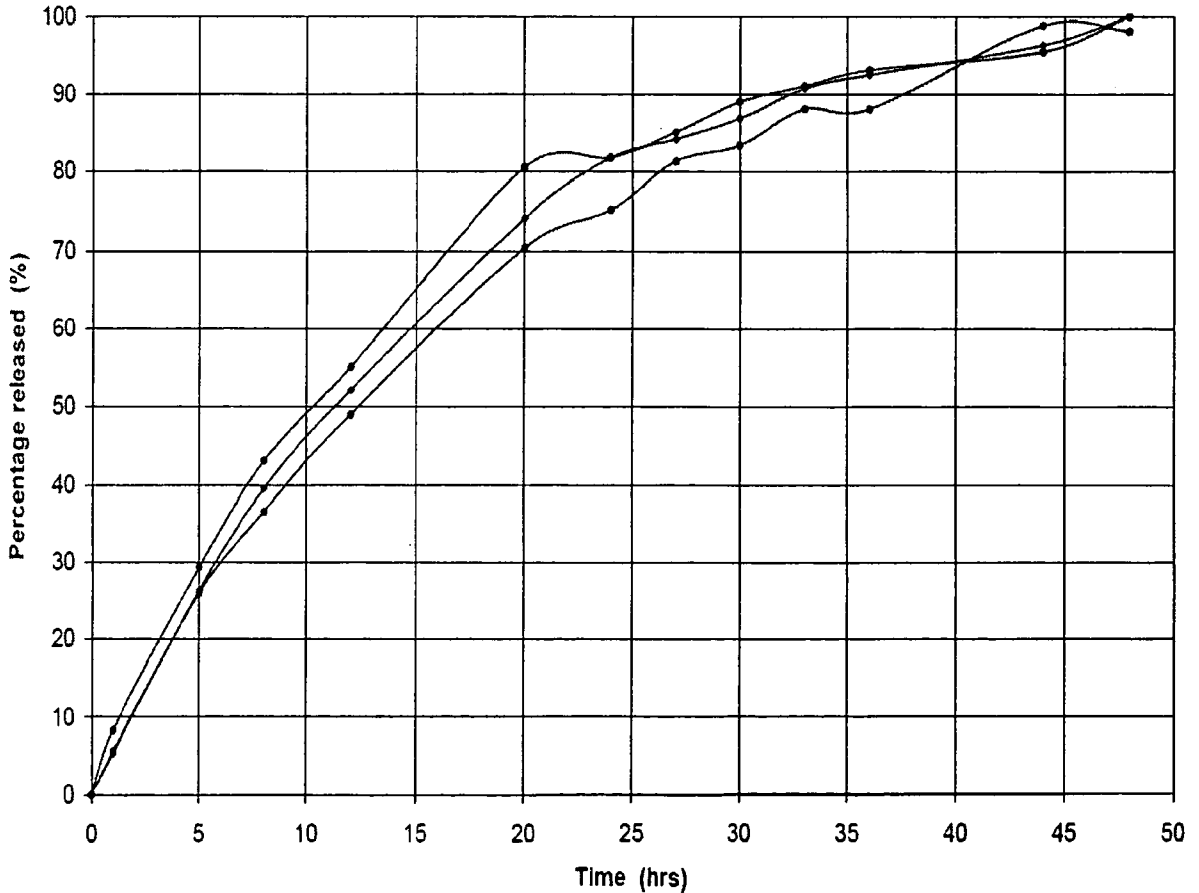


Figure 37
Percentage levorphanol release from Compritol (slow) dissolution vs time at 1 month 111/045/4

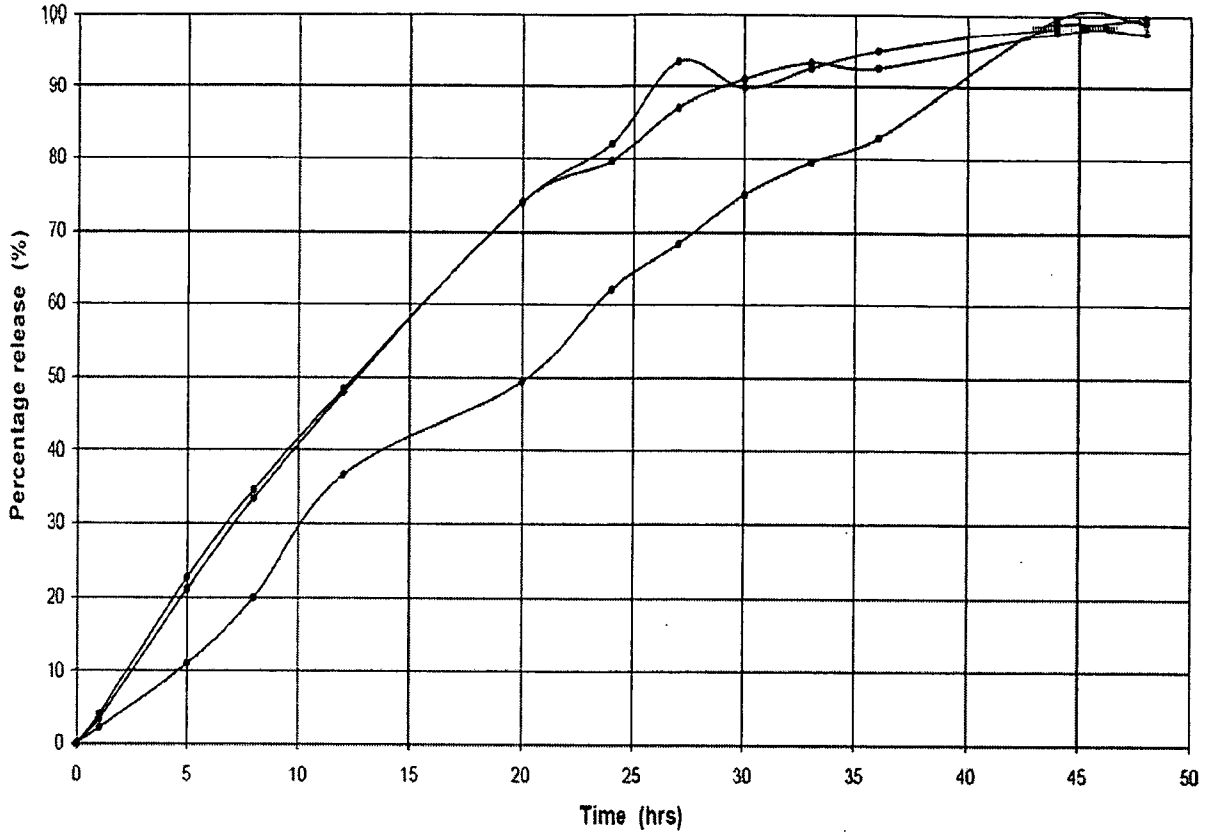


Figure 38
Average percentage release from 111/038/4, Compritol 888 ATO, versus time.
 T_0 and $T_{1 \text{ month}}$ samples at 25°C.

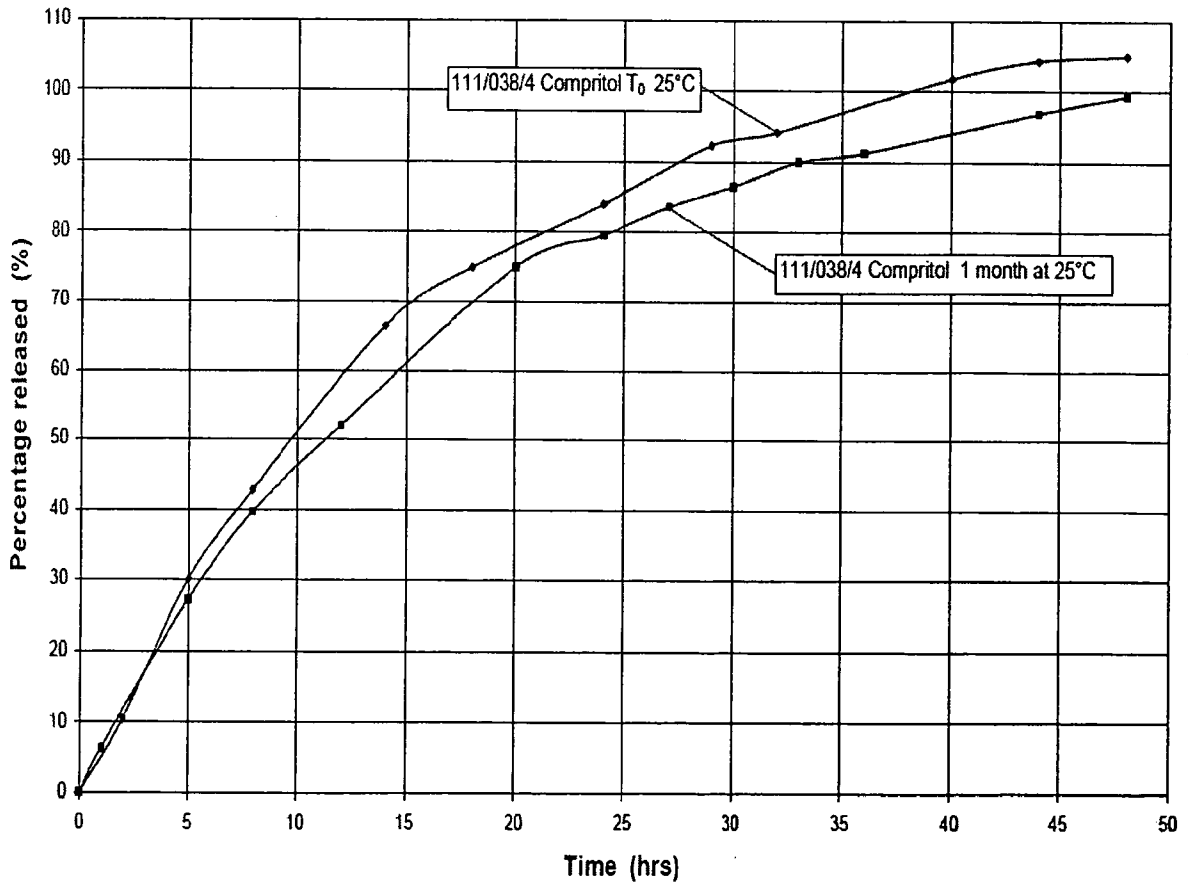


Figure 39
Average percentage release from Compritol (slow) at T_0 and $T_{1\text{month}}$ at 25°C 111/045/4

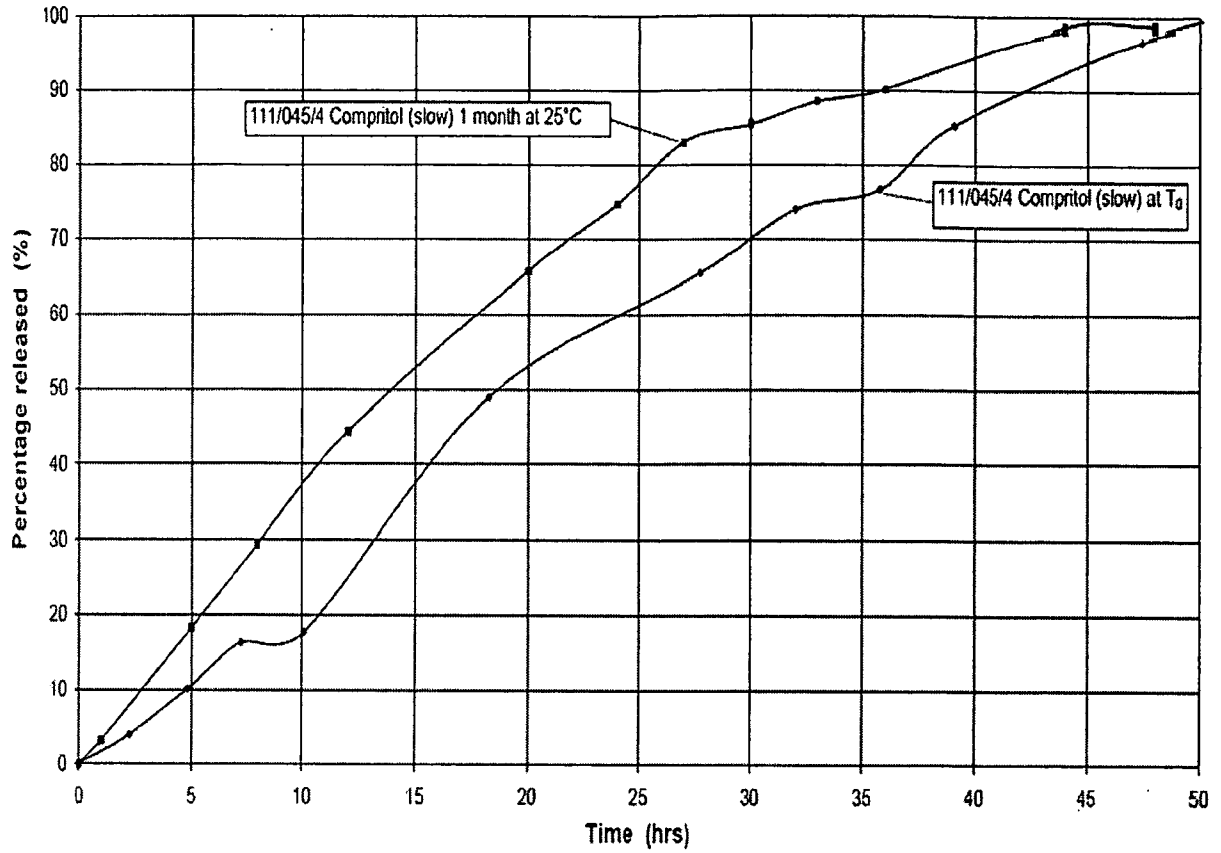


Figure 40
Percentage levorphanol release from 111/068/2, 57% Sterotex versus time. T₀ sample at 25°C

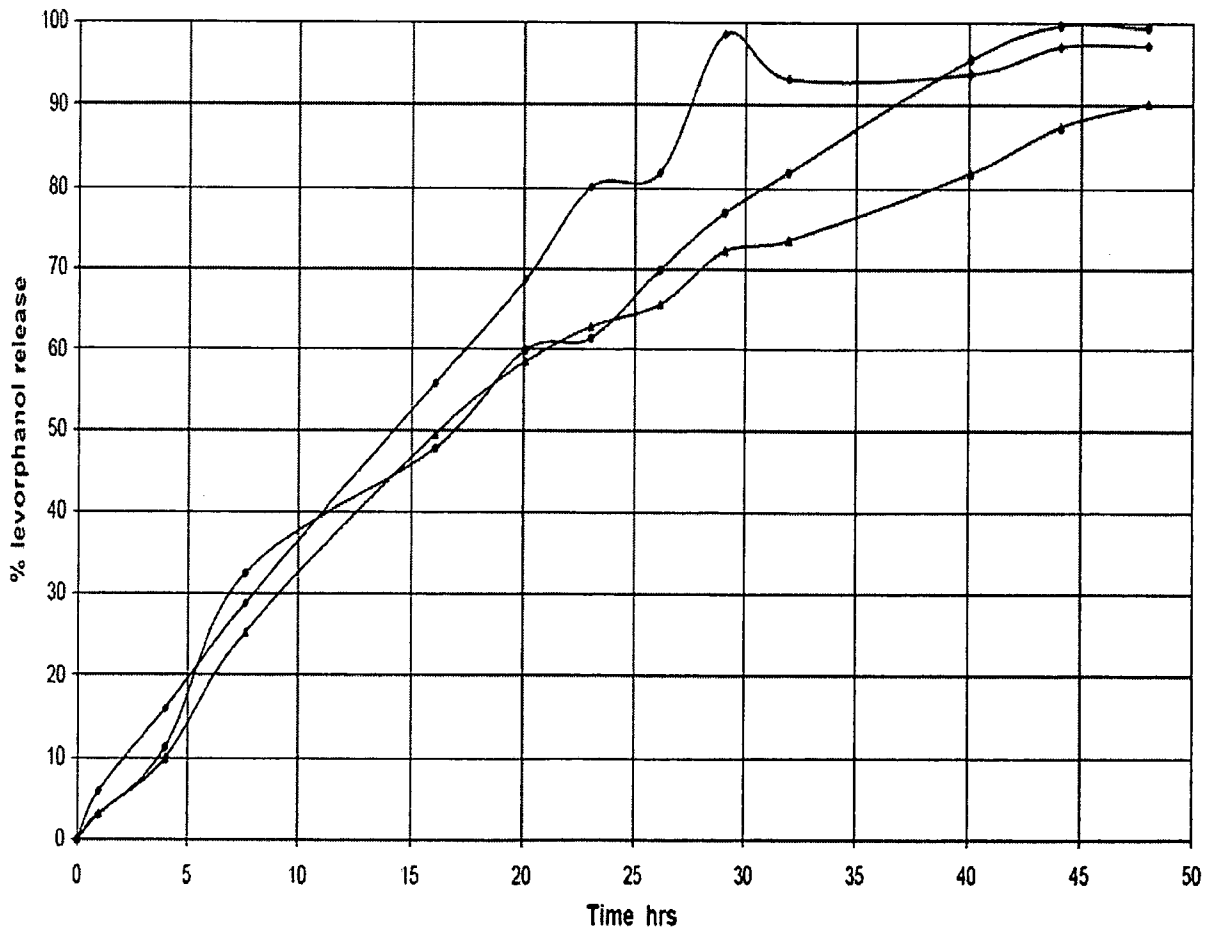


Figure 41

Percentage levorphanol release from 111/069/2 55% Sterotex versus time. T₀ sample at 25°C

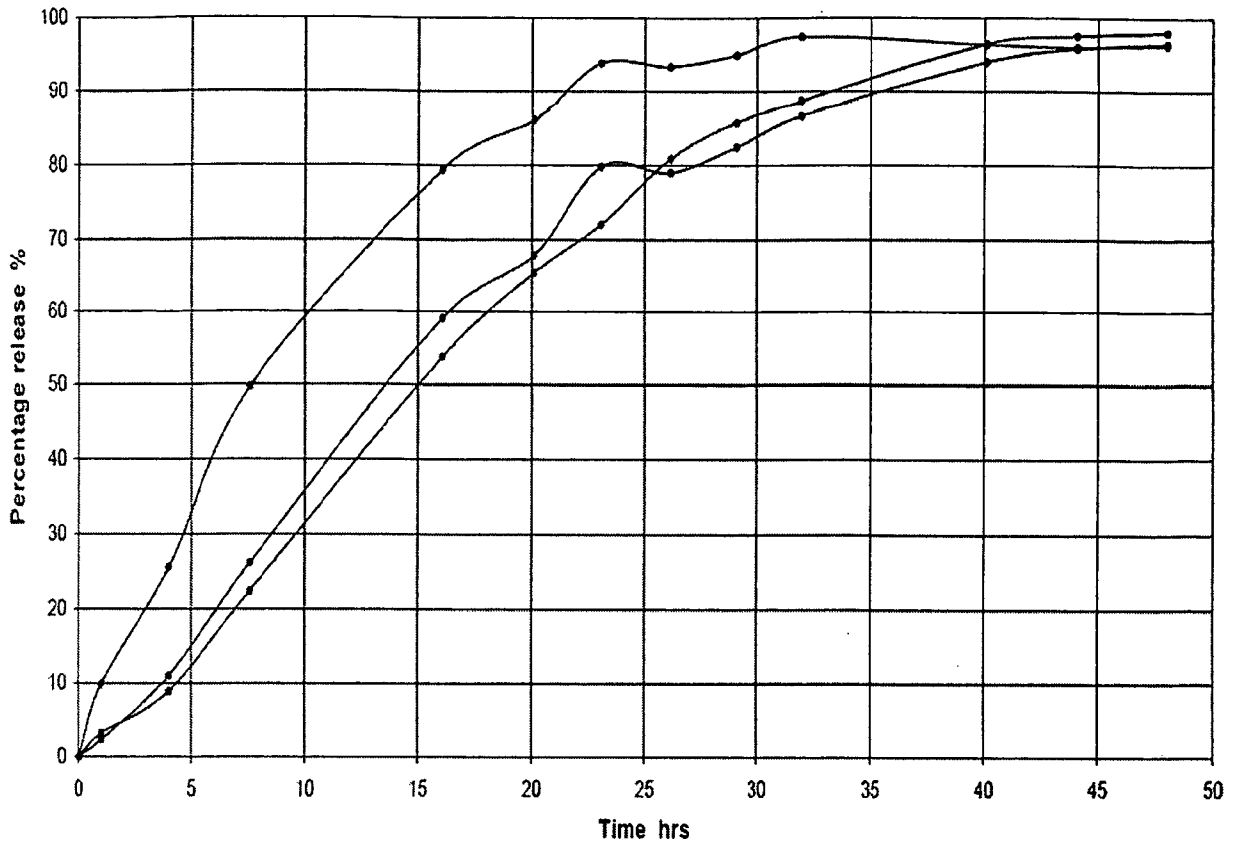


Figure 42

Average levorphanol release from in Sterotex 111/068/2 (57% Sterotex, 11.5% Methocel) and 111/069/2 (55% Sterotex, 13.5% Methocel)

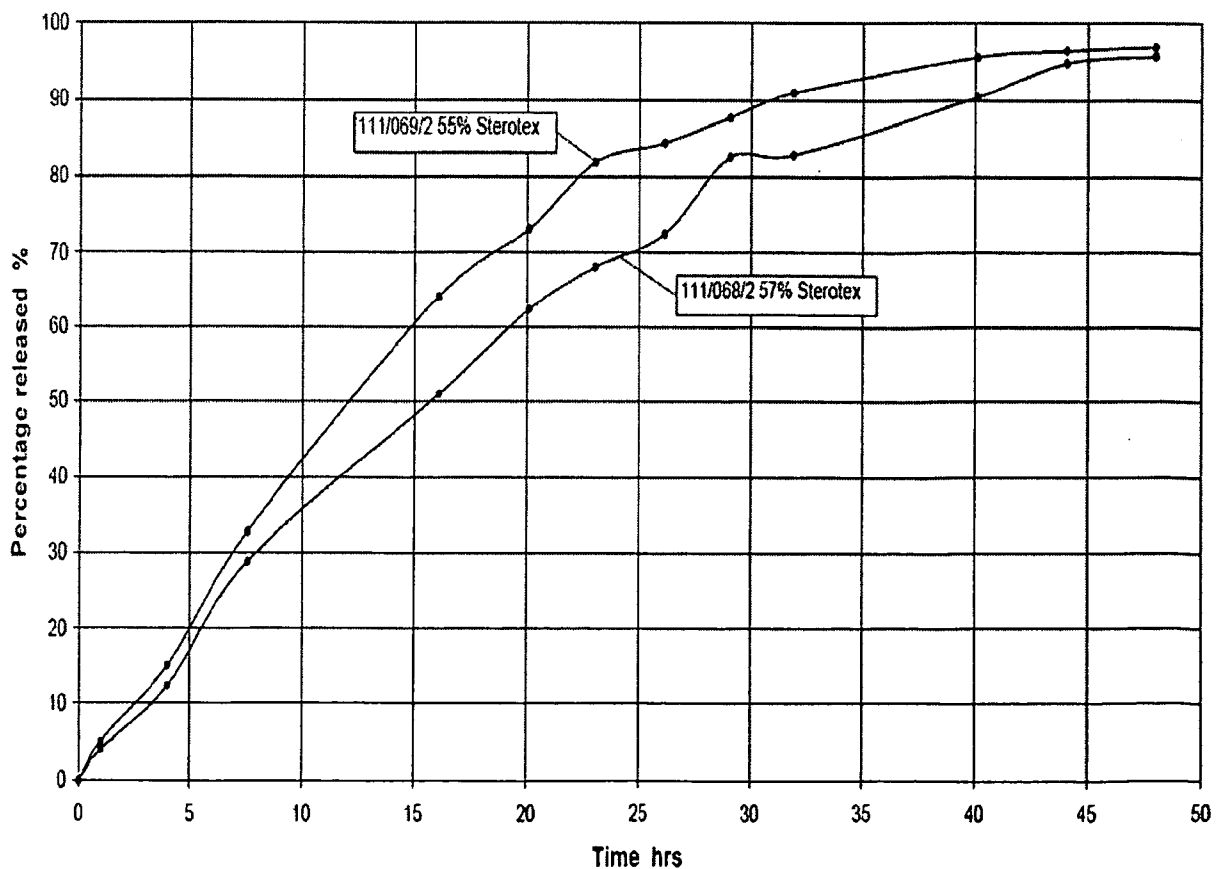


Figure 43
Relative dissolution rates for R&D formulations 111/026/1, 111/026/2, 111/038/4 and 111/068/2

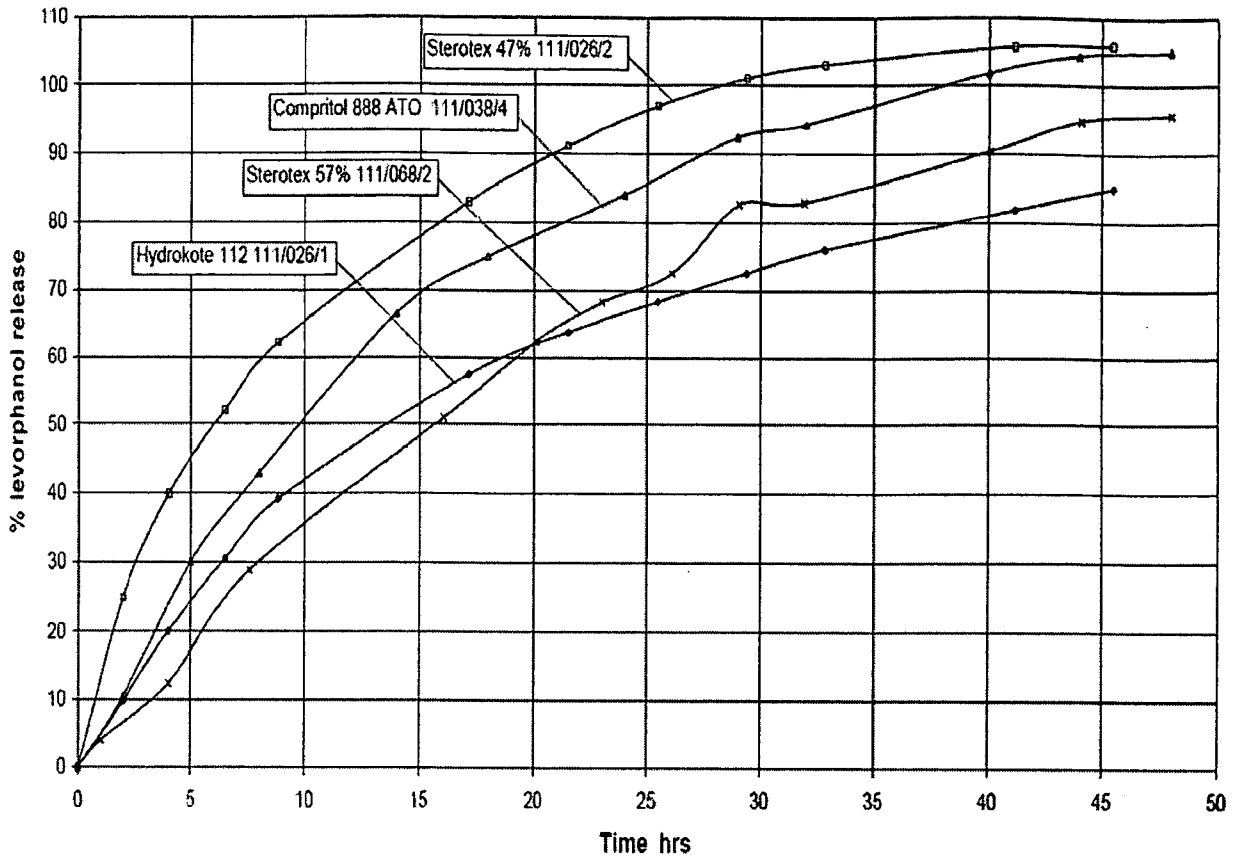


Figure 44

Abuse resistance testing on Levorphanol batches VE2470, VE2471, VE2472 & VE2473:
EtOH extraction, Test 1 (Intact dosage units)

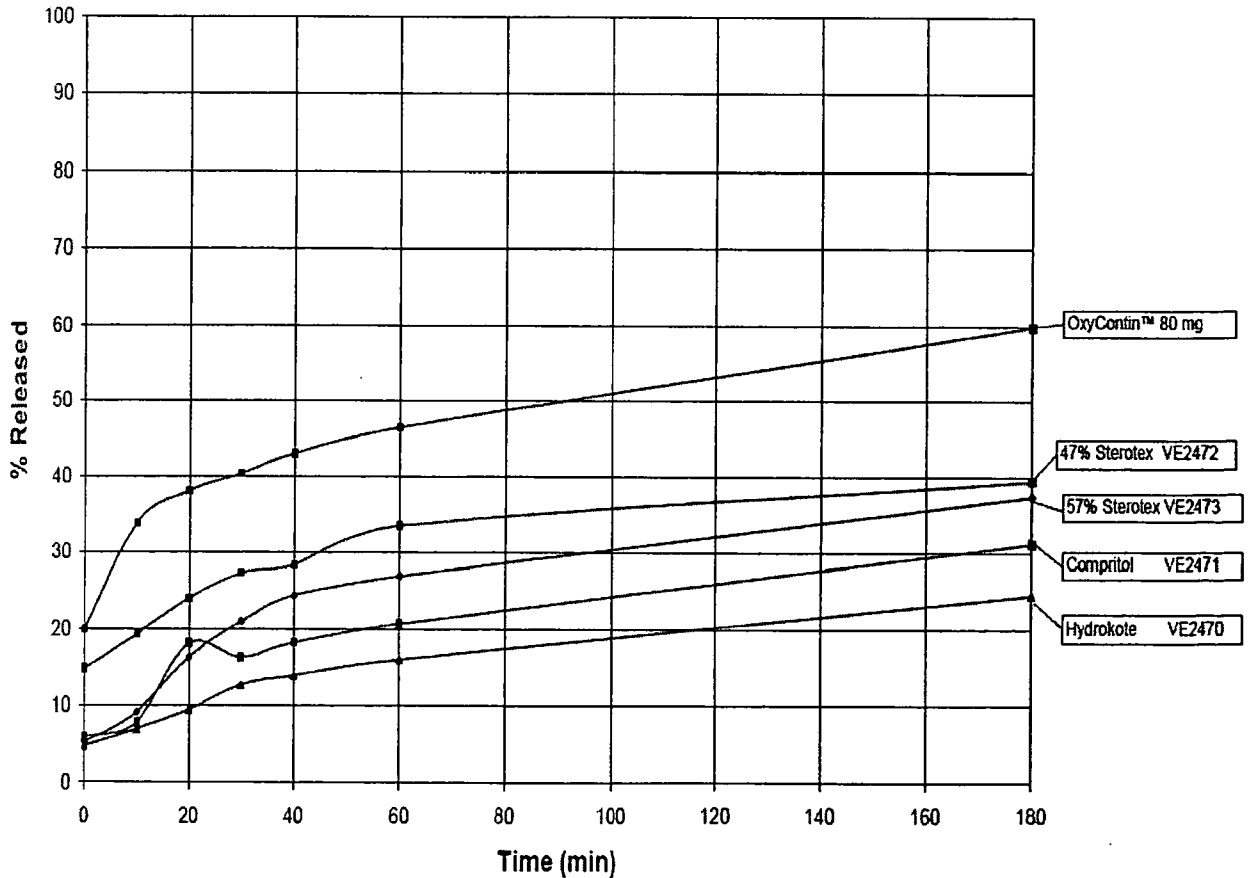


Figure 45
Abuse resistance testing on Levorphanol batches VE2470, VE2471, VE2472 & VE2473:
Test 1a. (Cut in half or single crush of dosage units)

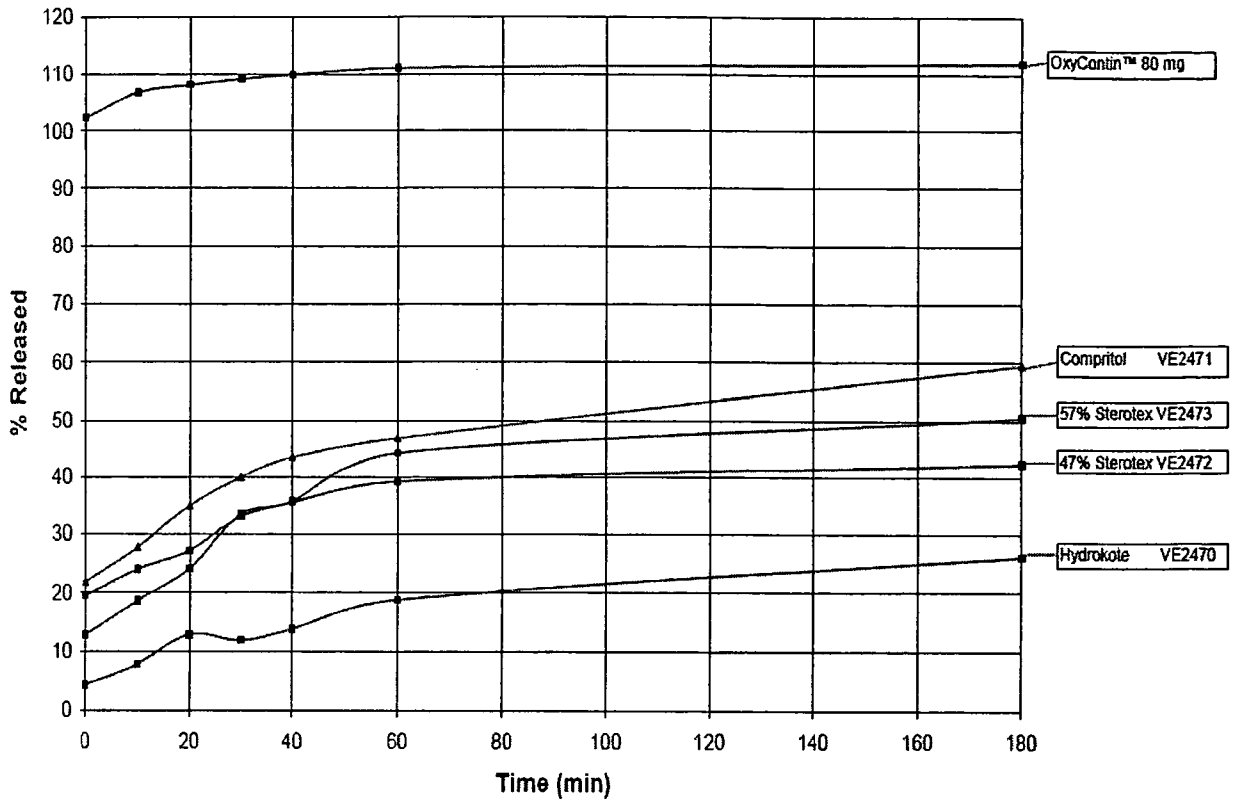


Figure 46

Percentage release of levorphanol from Hydrokote VE2470 at T₀ 25°C

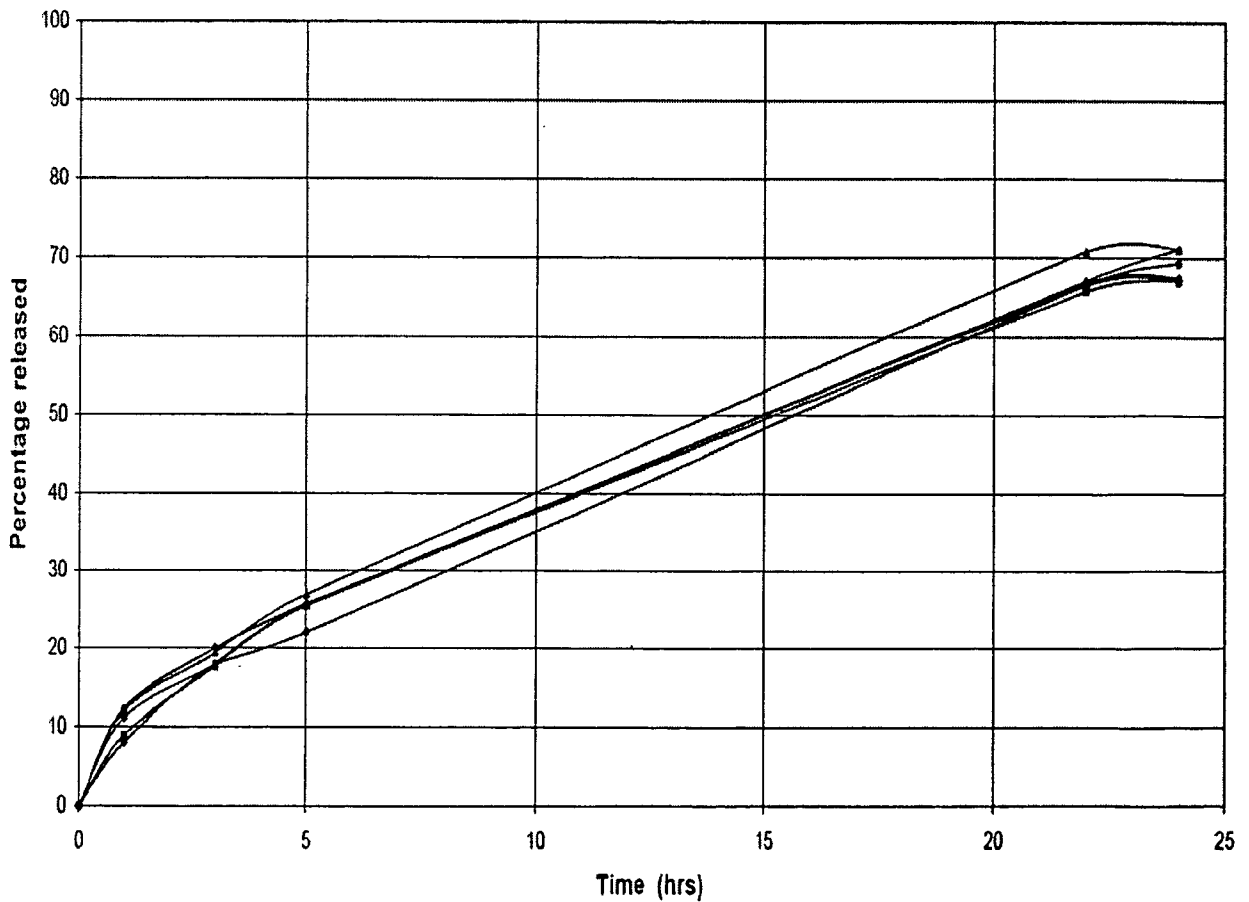


Figure 47
Average release of levorphanol from Hydrokote VE2470 at T_0 , $T_{1\text{ month}}$ & $T_{2\text{ month}}$ at 25°C

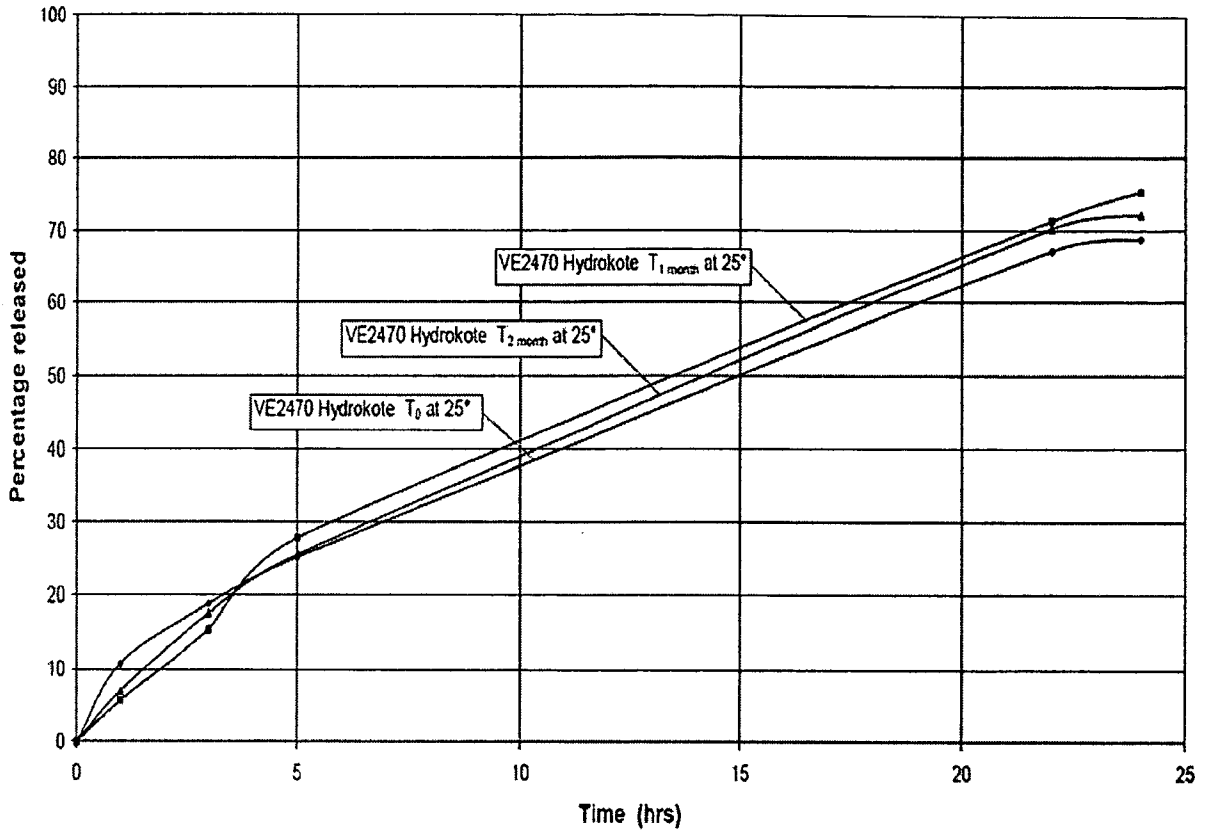


Figure 48
Percentage release of levorphanol from Compritol VE2471 at T_0 25°C

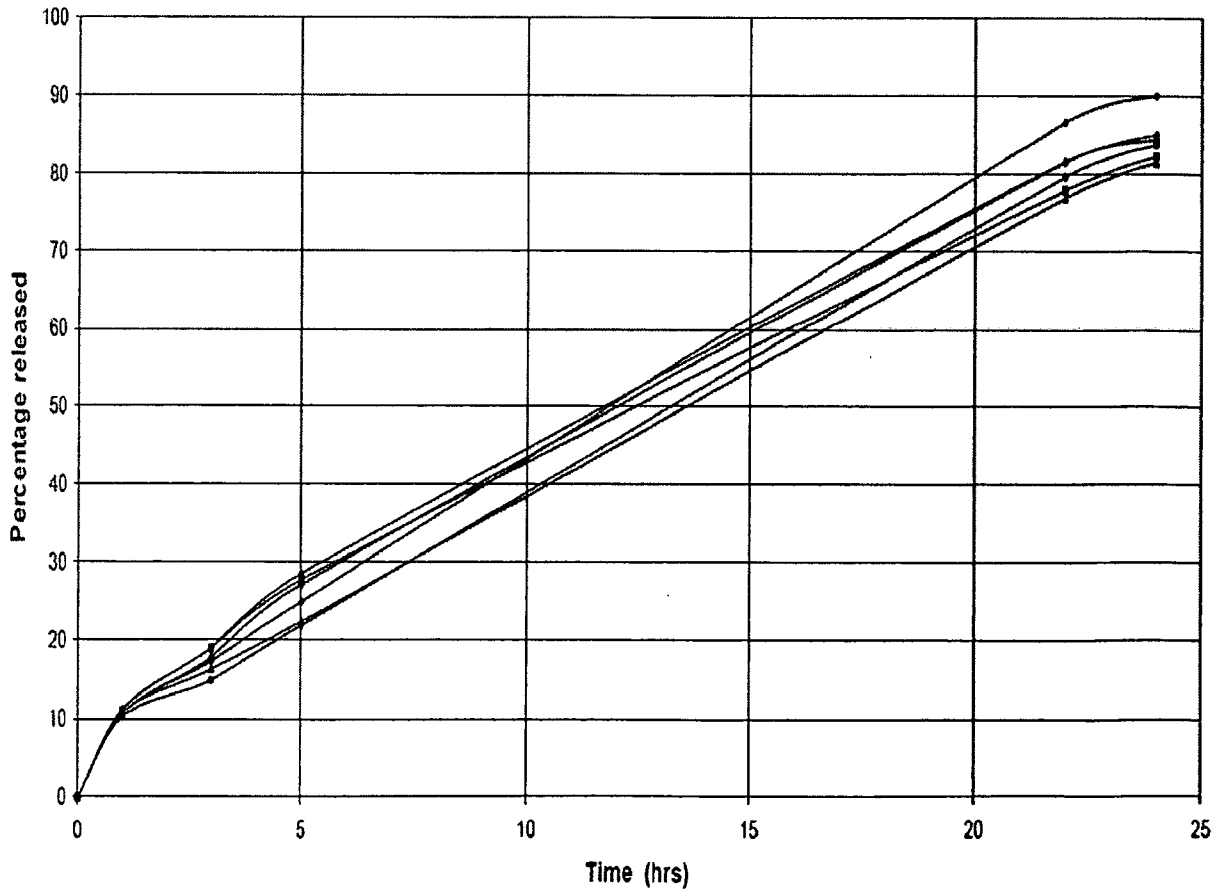


Figure 49
Average release of levorphanol from Compritol VE2471 at T_0 , $T_{1\text{ month}}$ & $T_{2\text{ month}}$ at 25°C

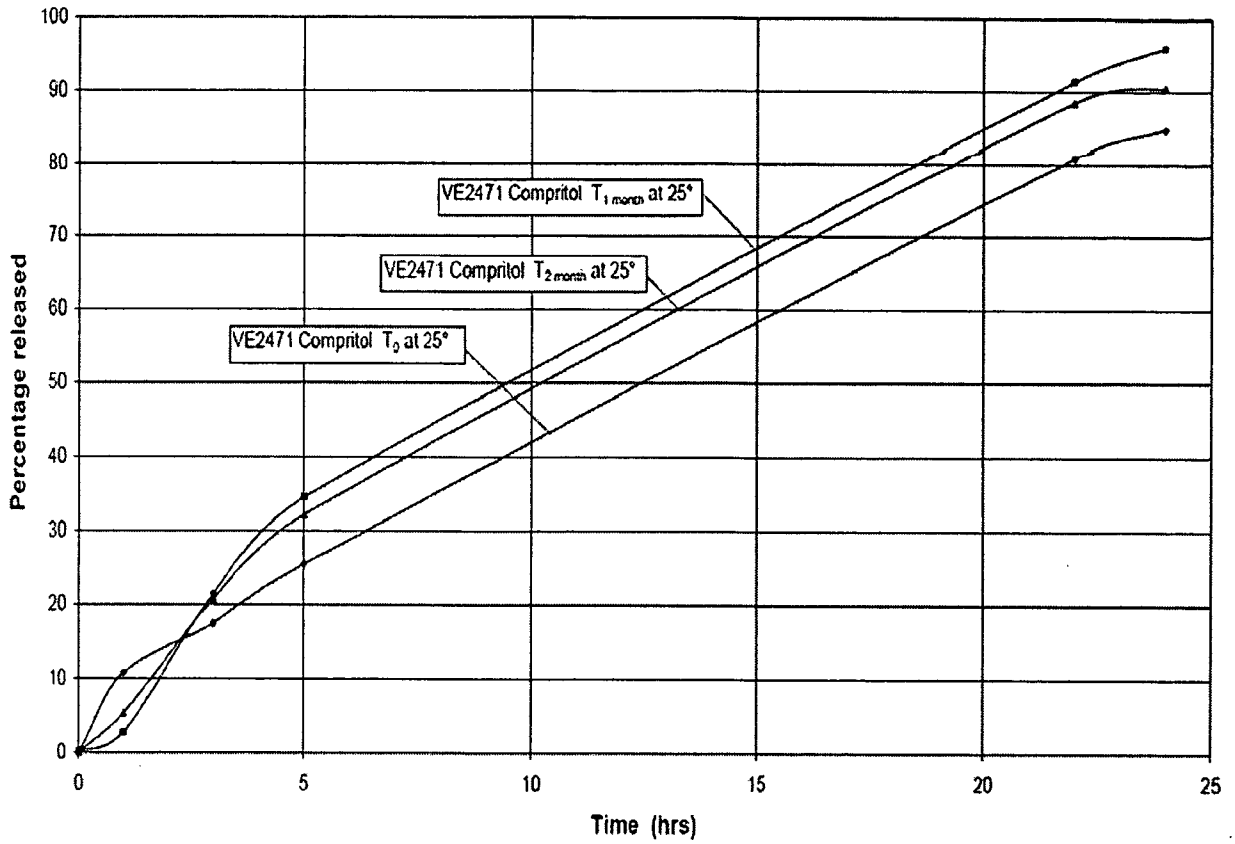


Figure 50
Percentage release of levorphanol from Sterotex 47% VE2472 at T_0 25°C

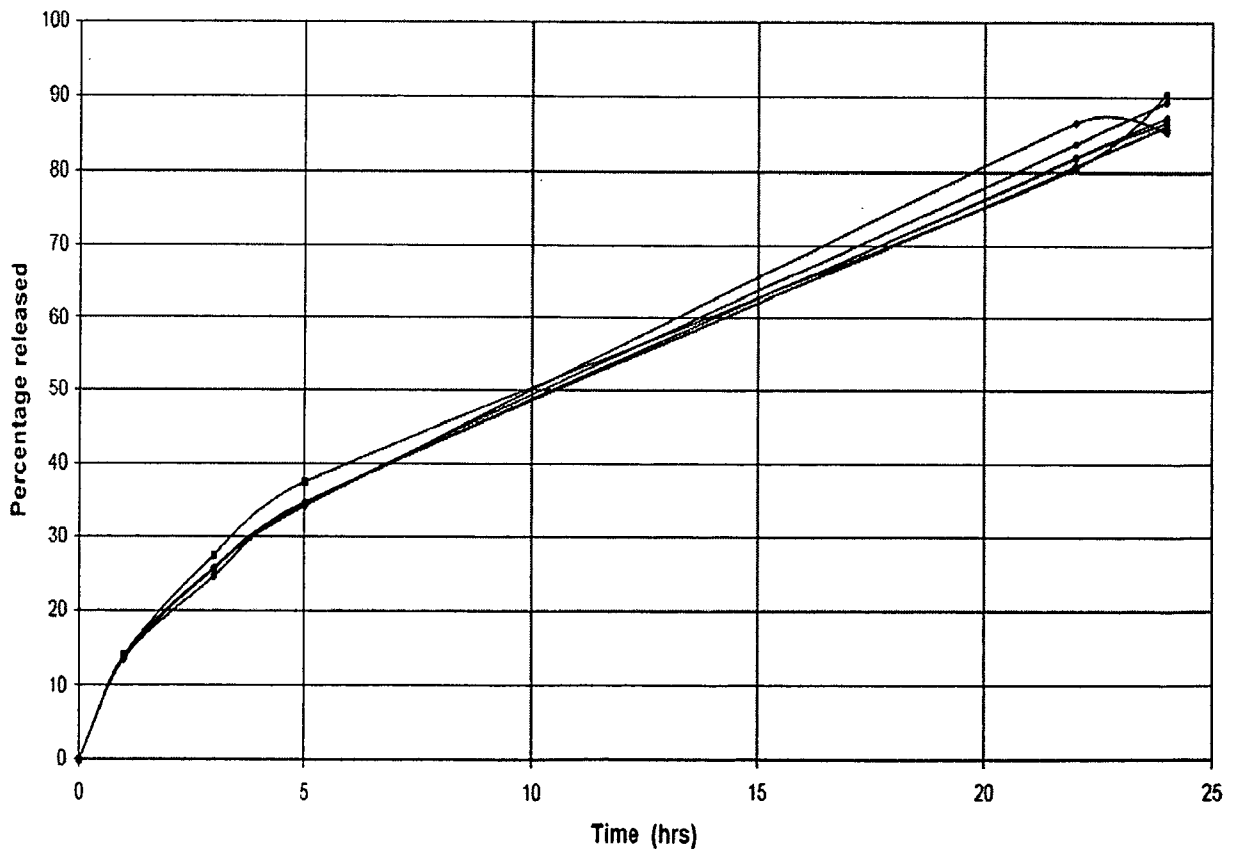


Figure 51

Average release of levorphanol from Sterotex 47% VE2472 at T_0 , $T_{1\text{ month}}$ & $T_{2\text{ month}}$ at 25°C

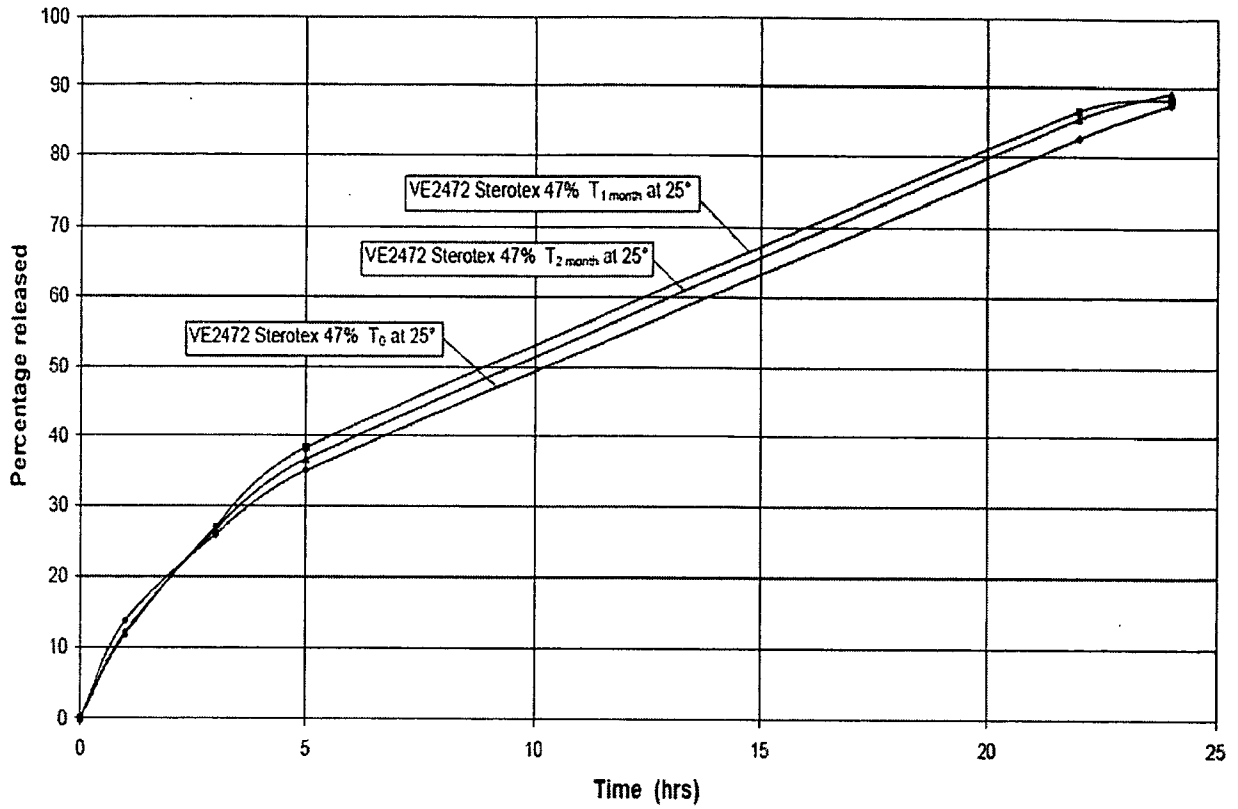


Figure 52

Percentage release of levorphanol from Sterotex 57% VE2473 at T_0 25°C

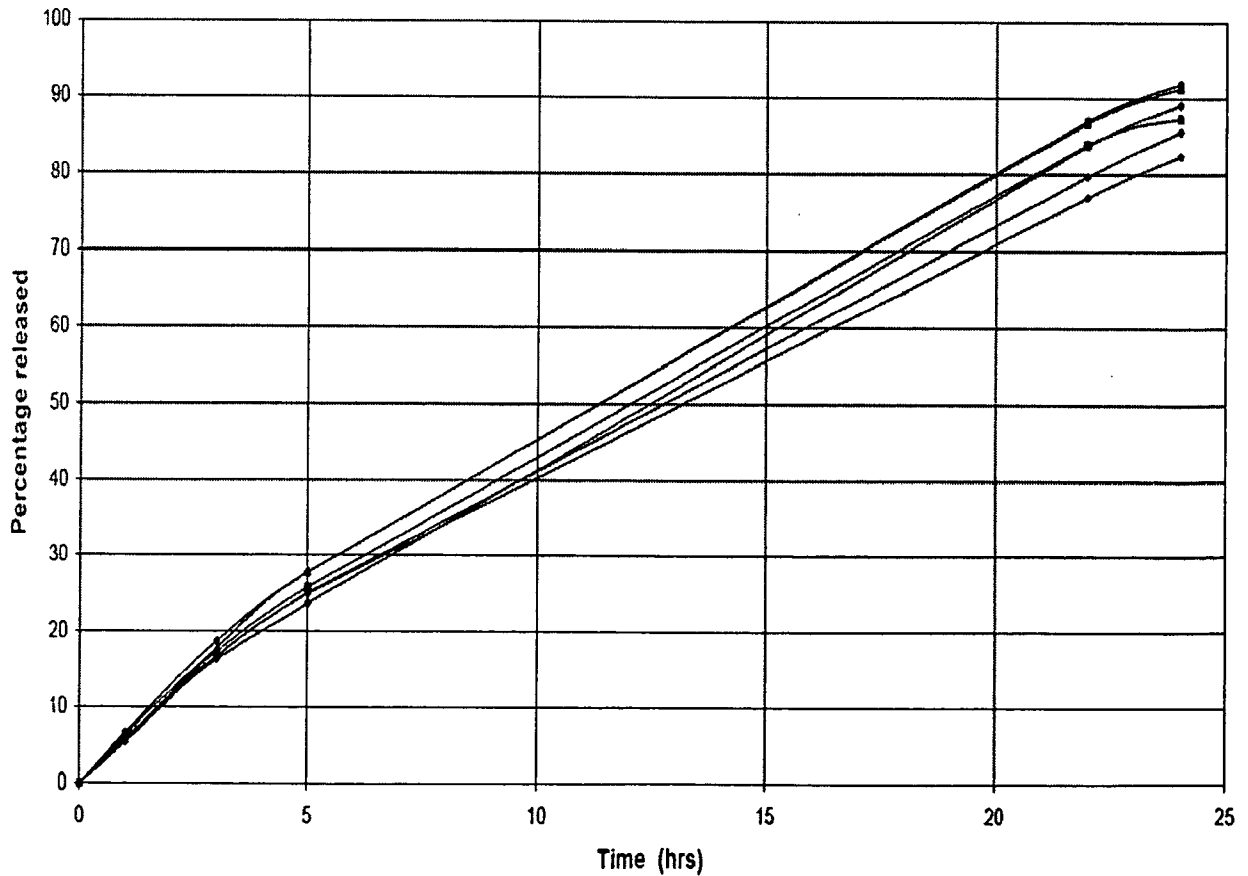


Figure 53
Average release of levorphanol from Sterotex 57% VE2473 at T_0 , $T_{1\text{ month}}$ & $T_{2\text{ month}}$ at 25°C

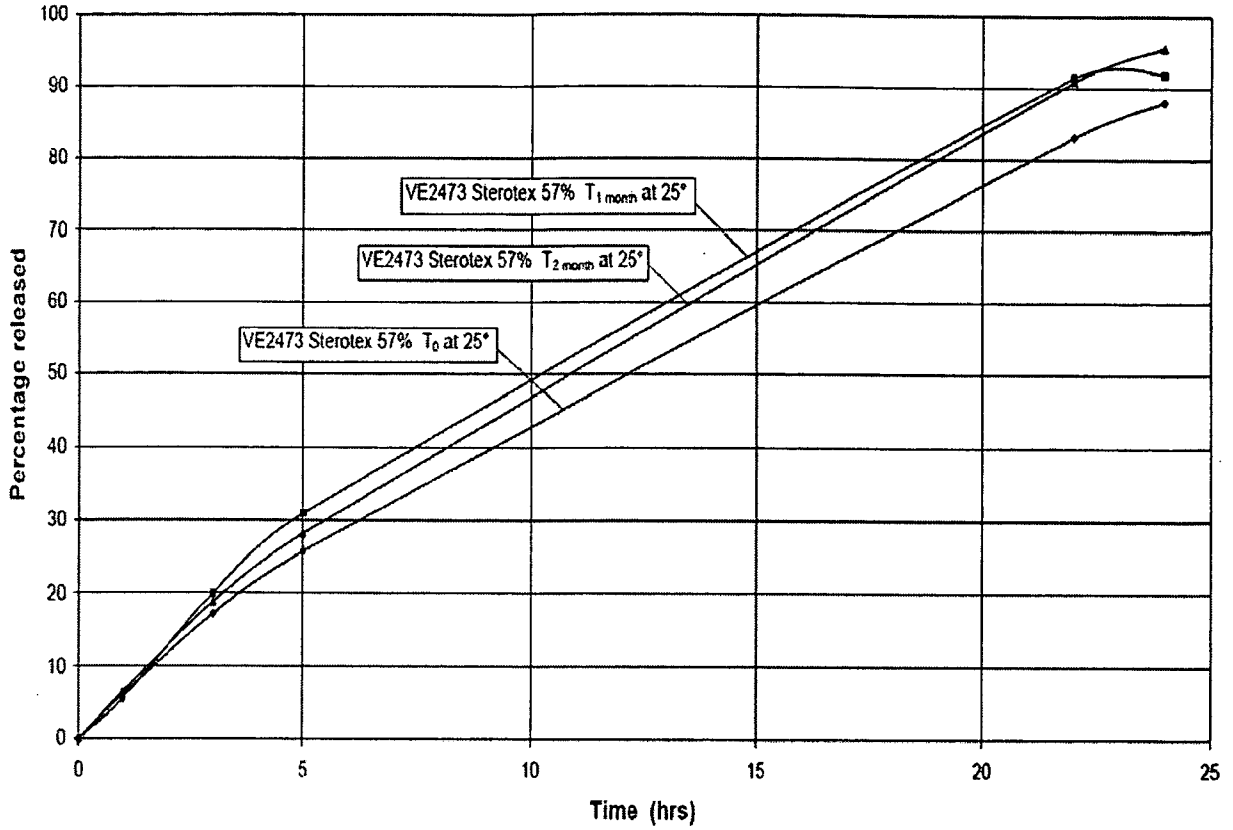
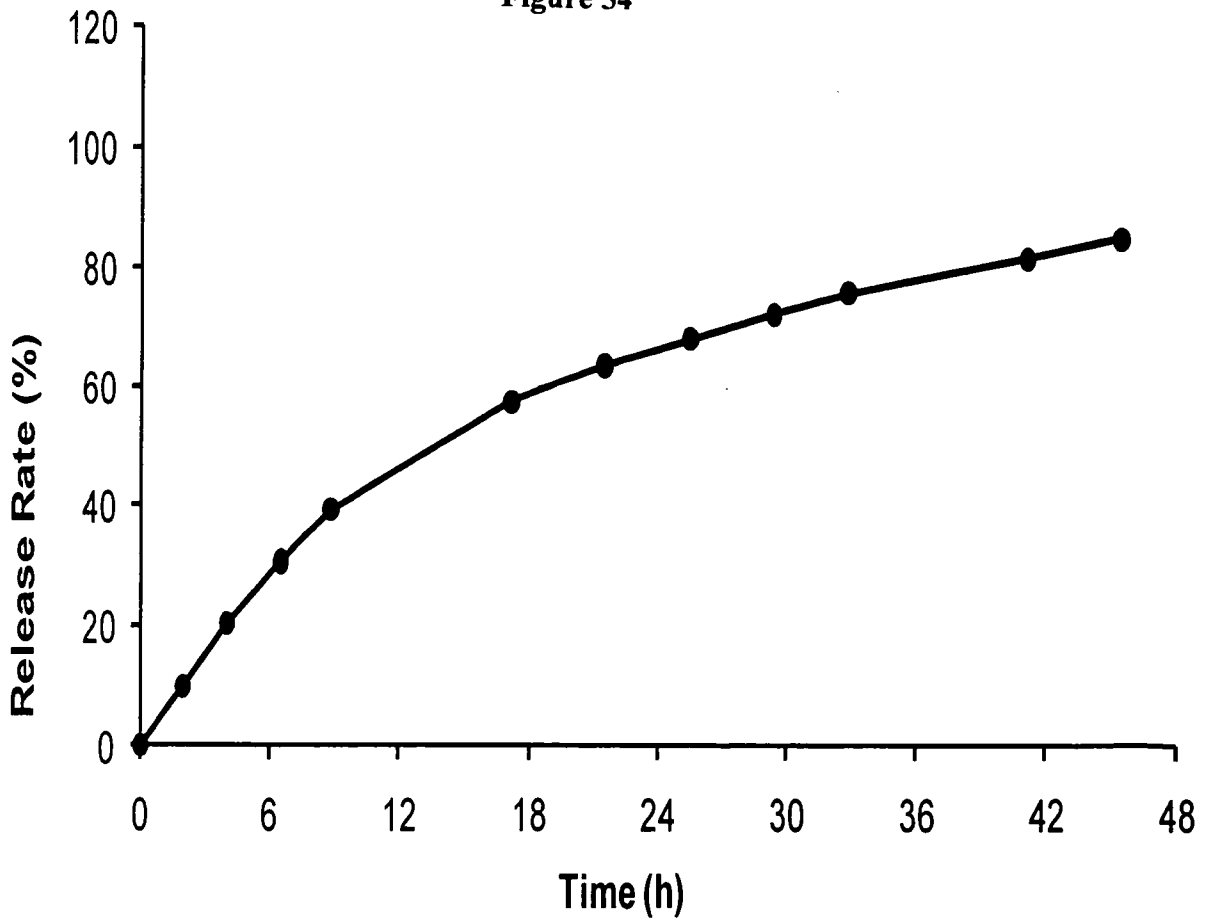
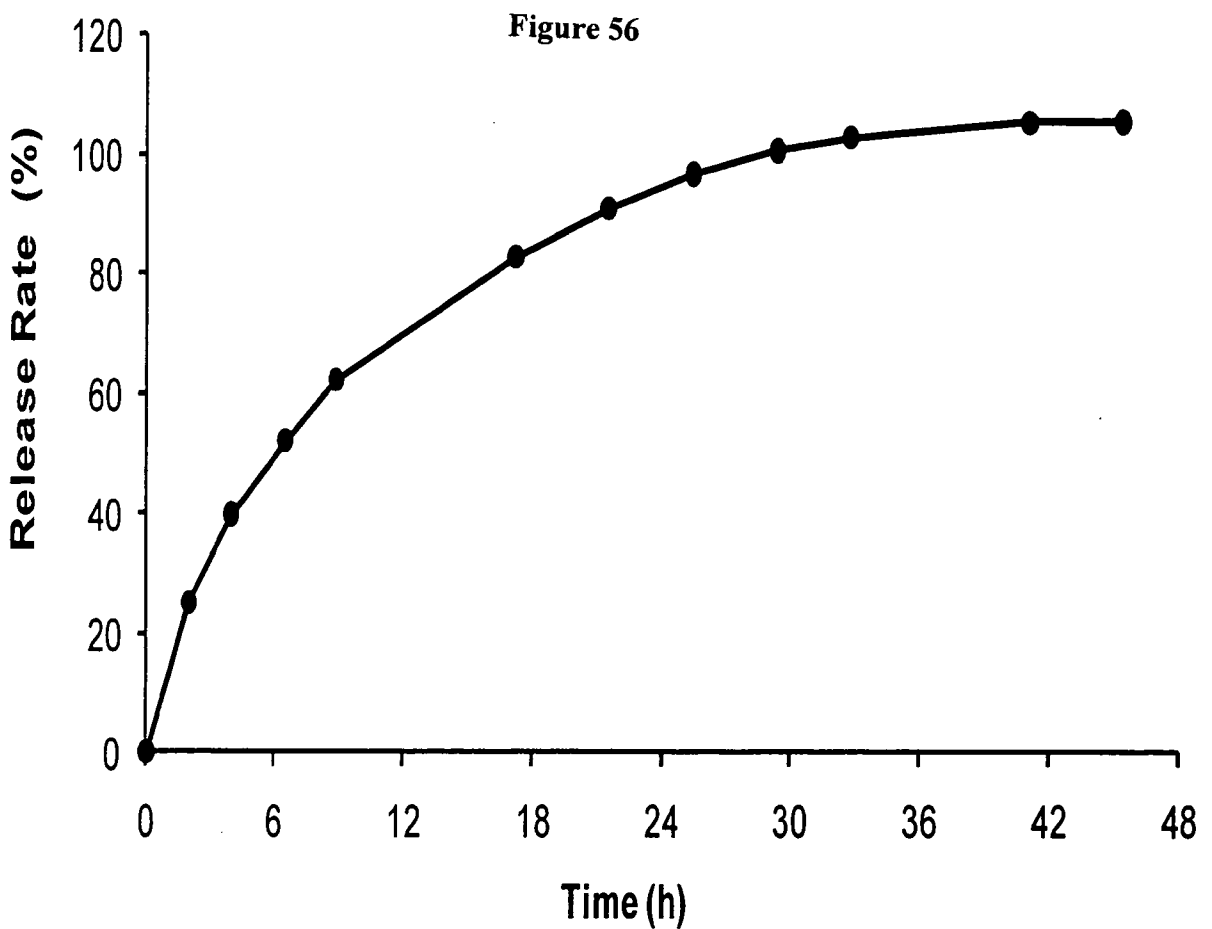
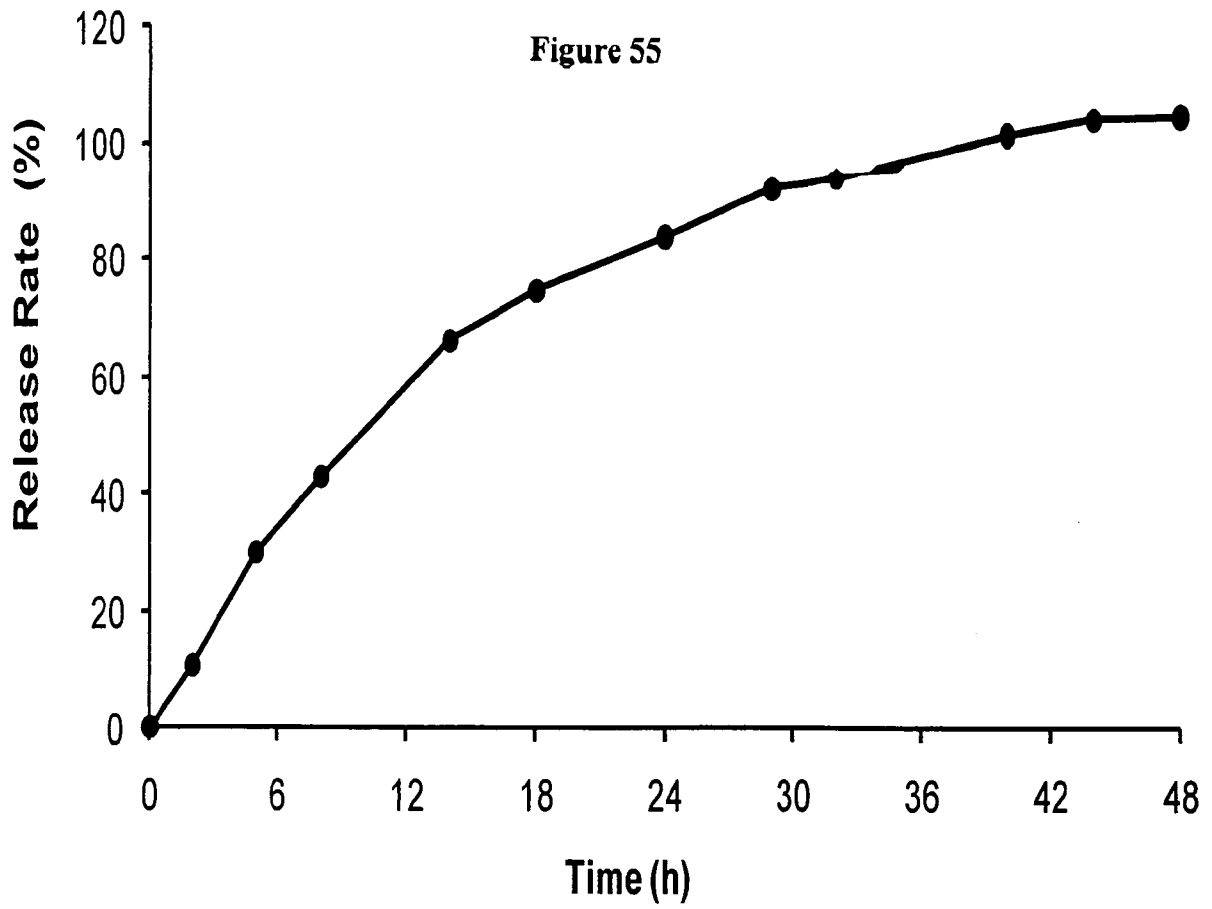
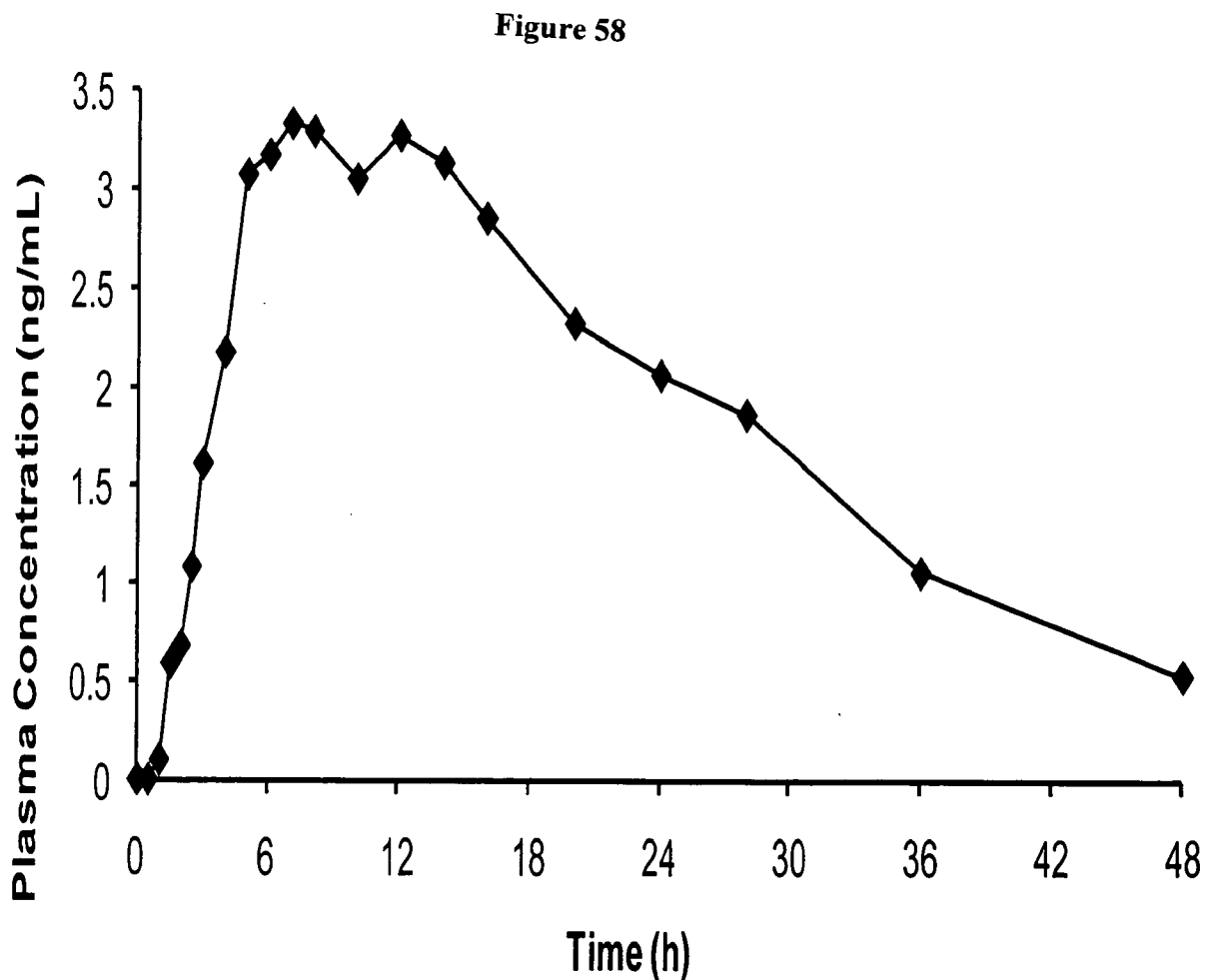
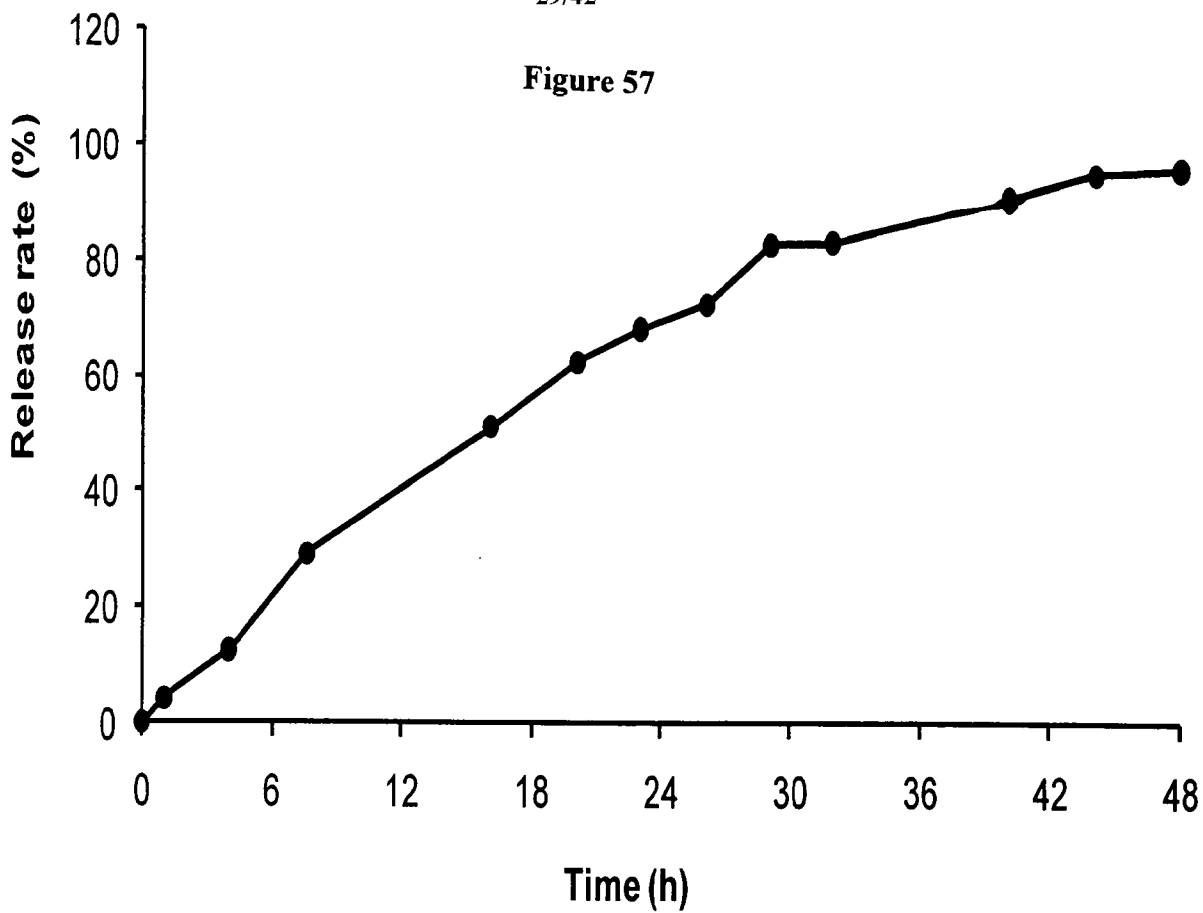
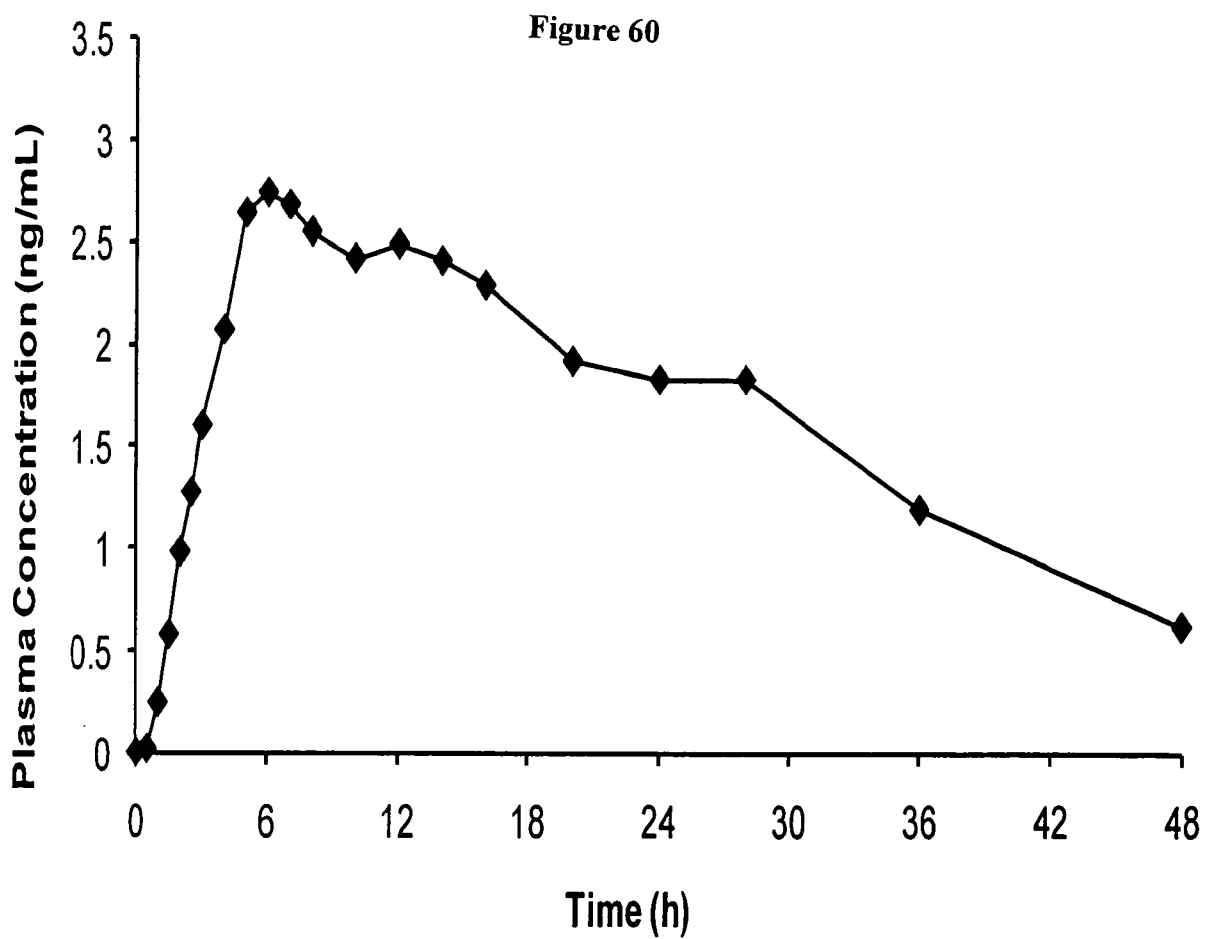
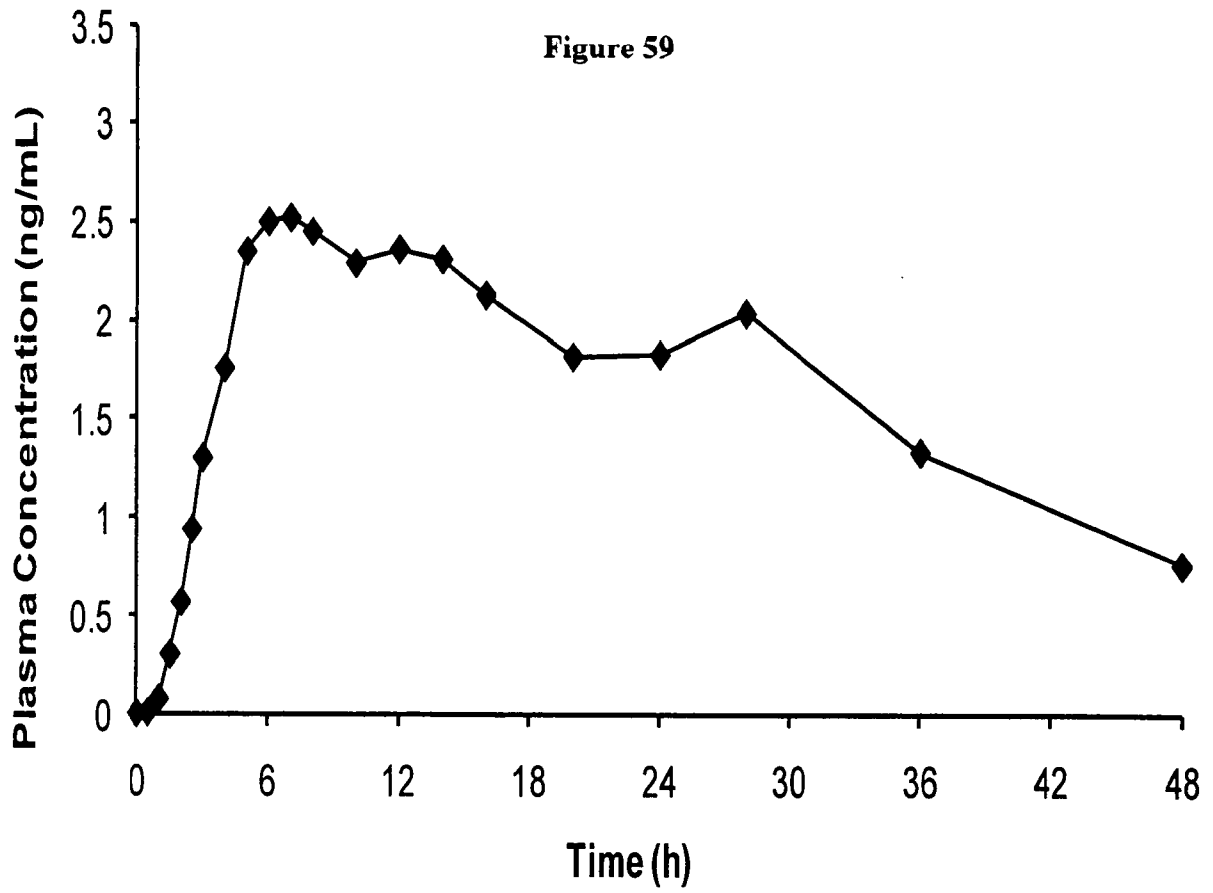


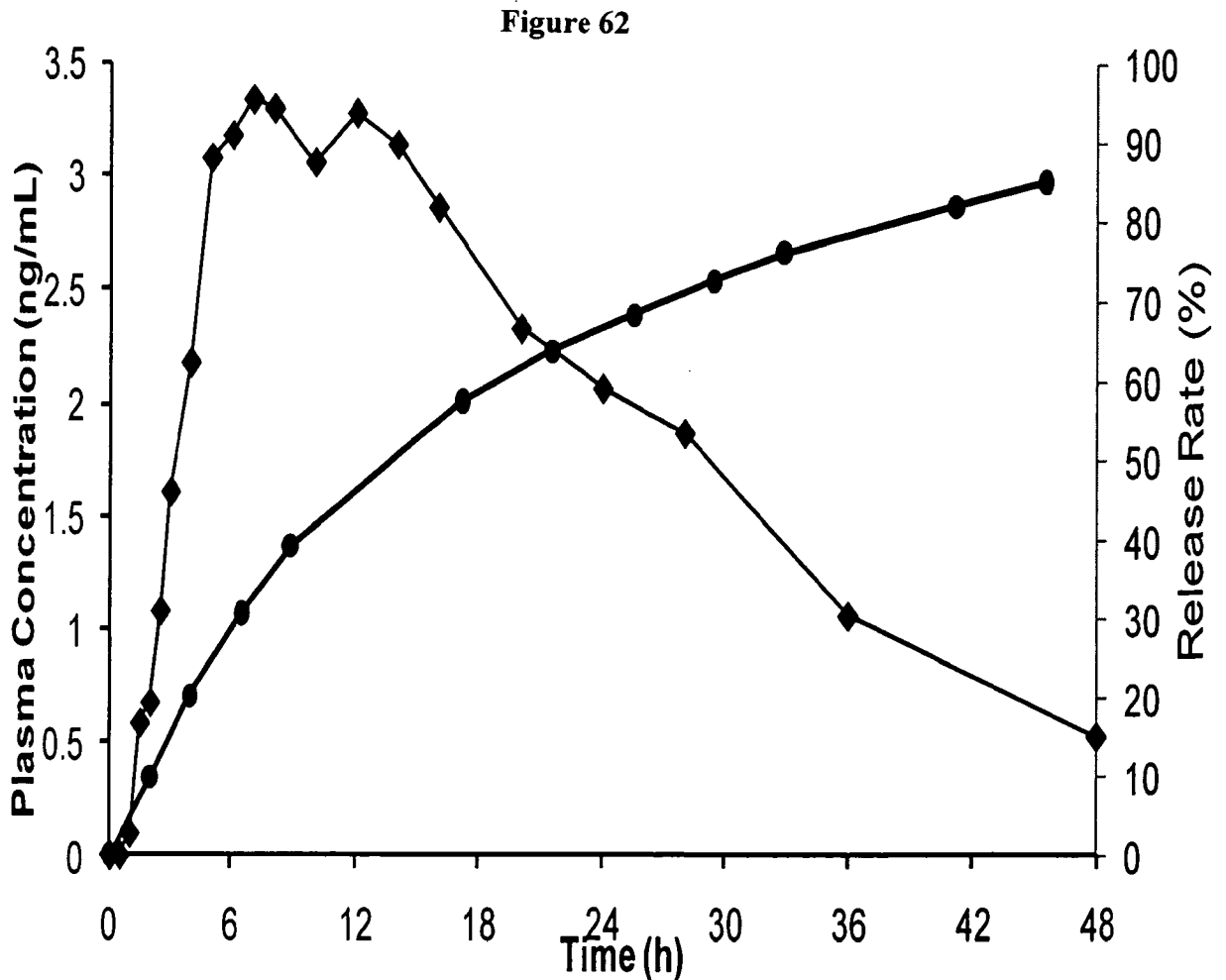
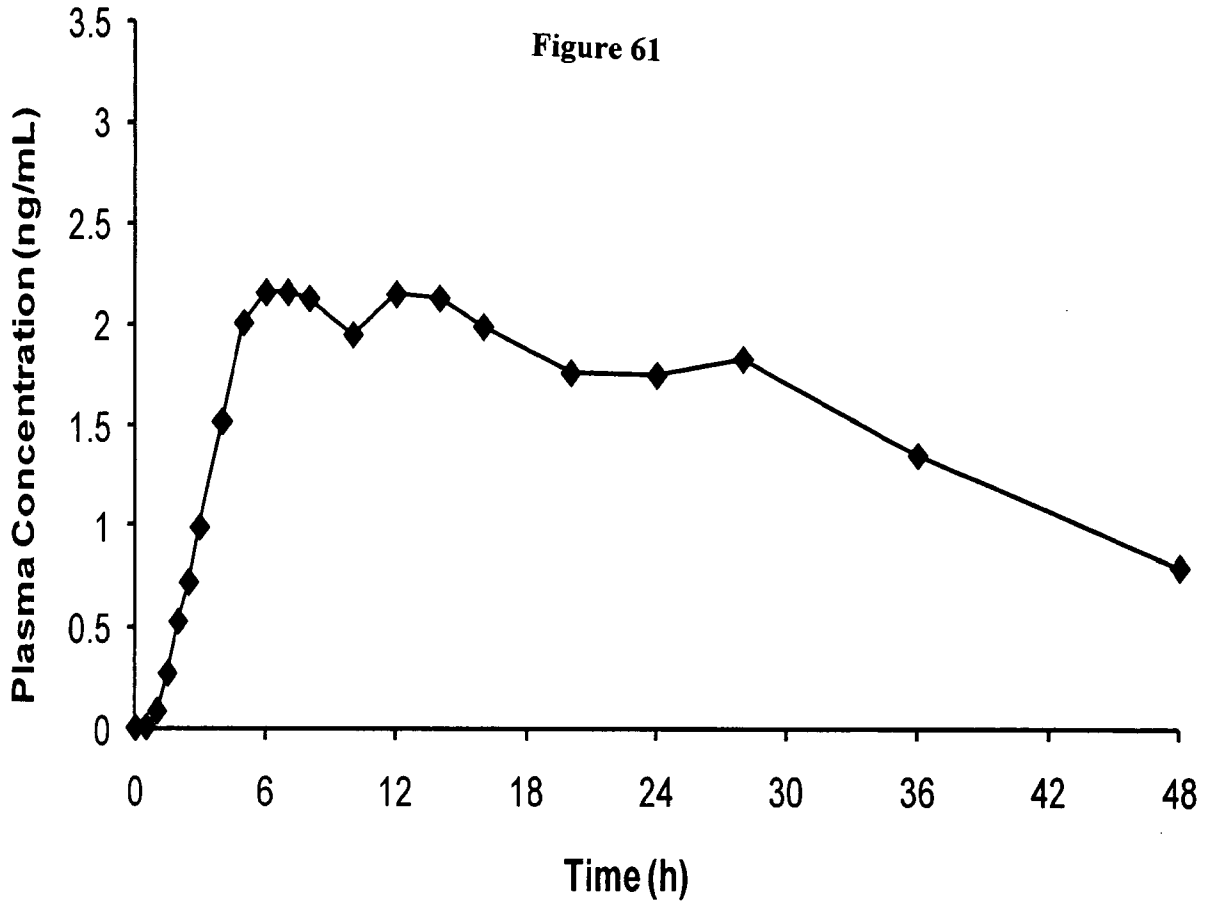
Figure 54

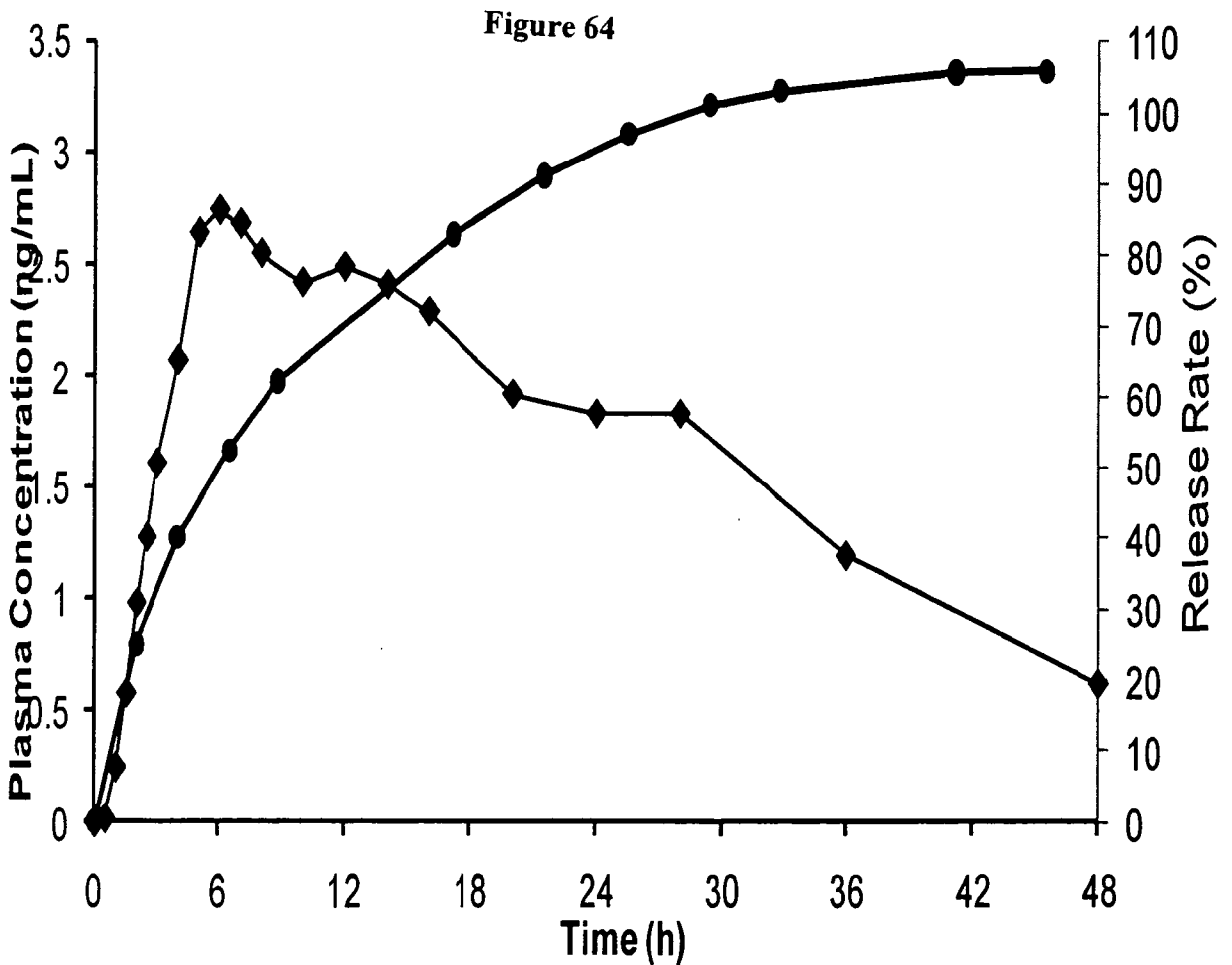
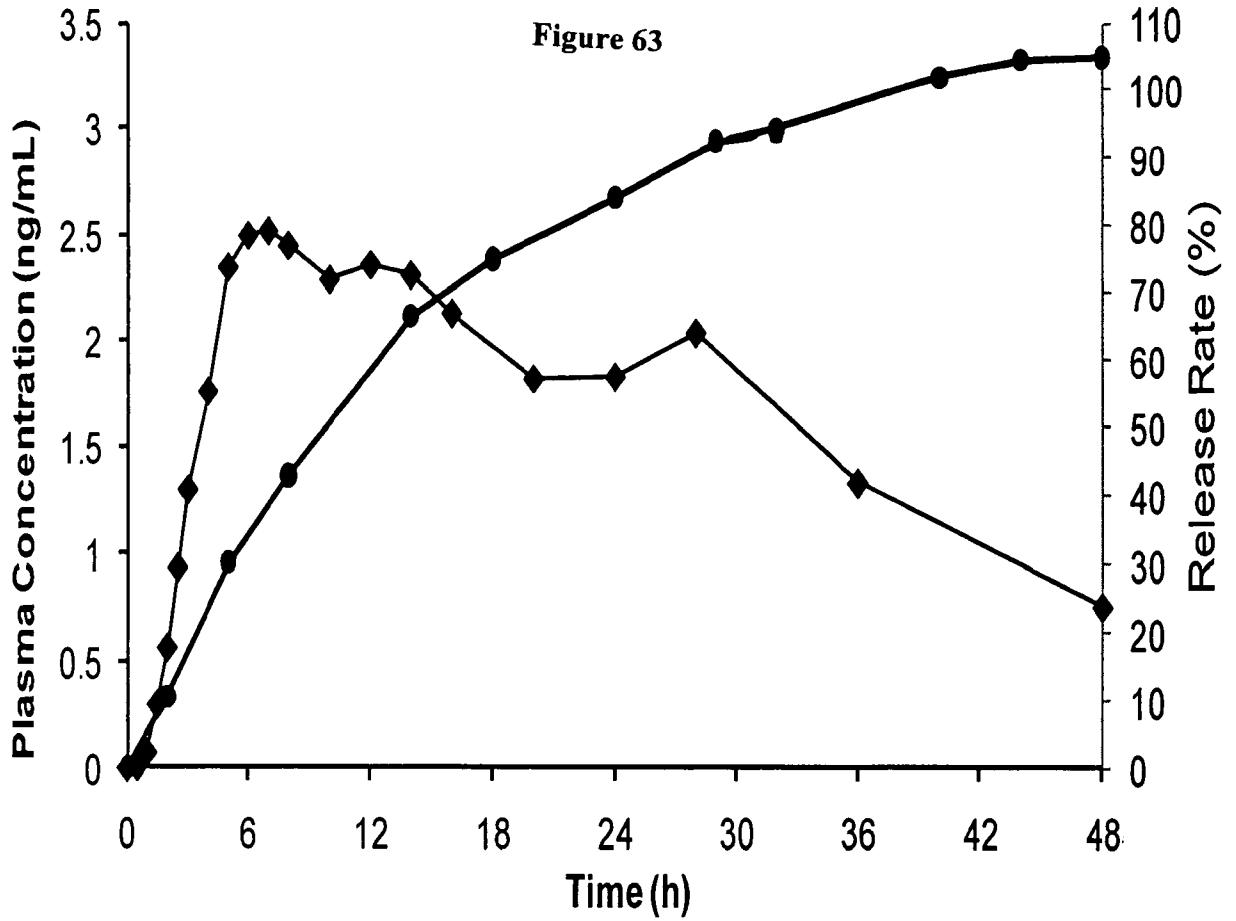


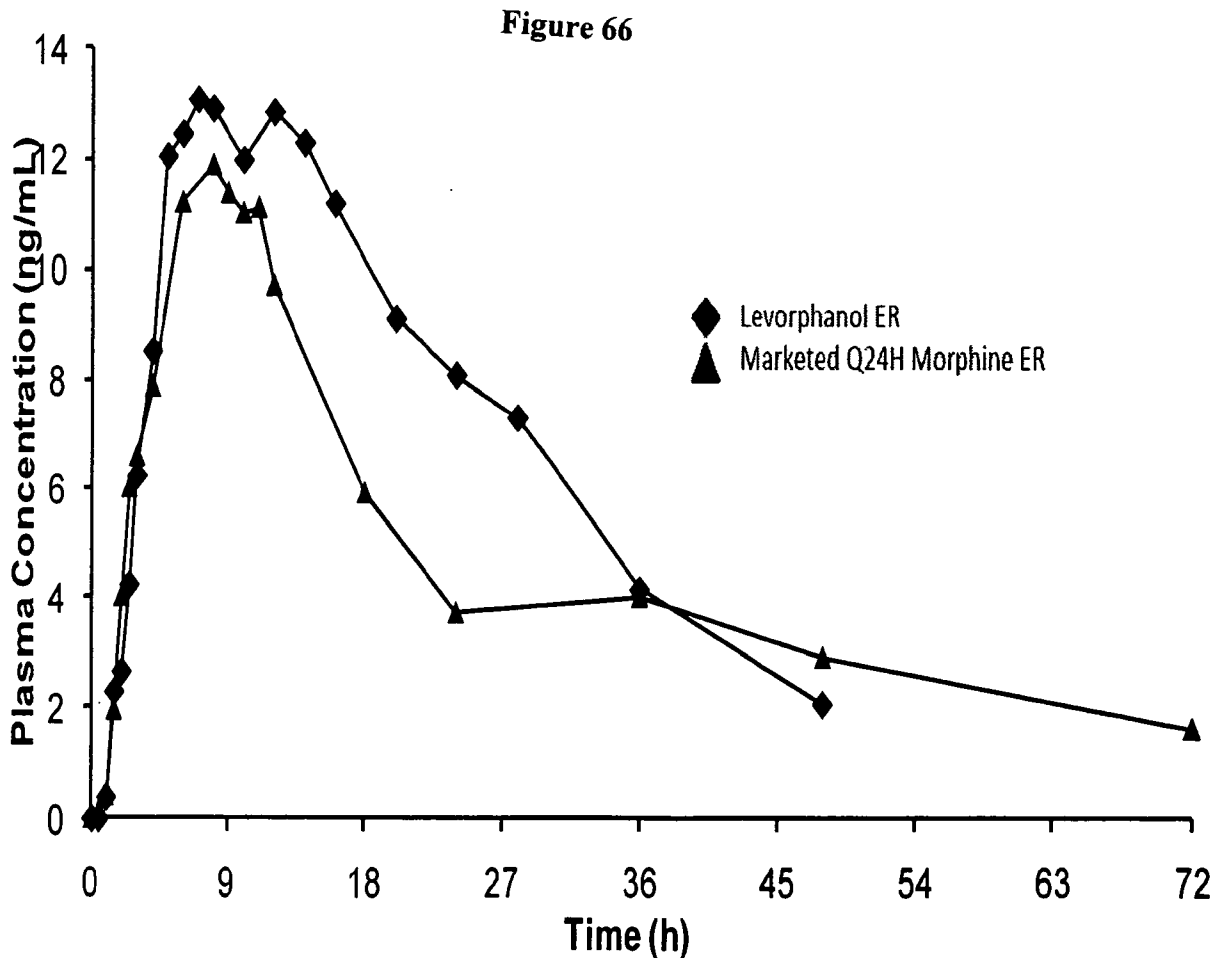
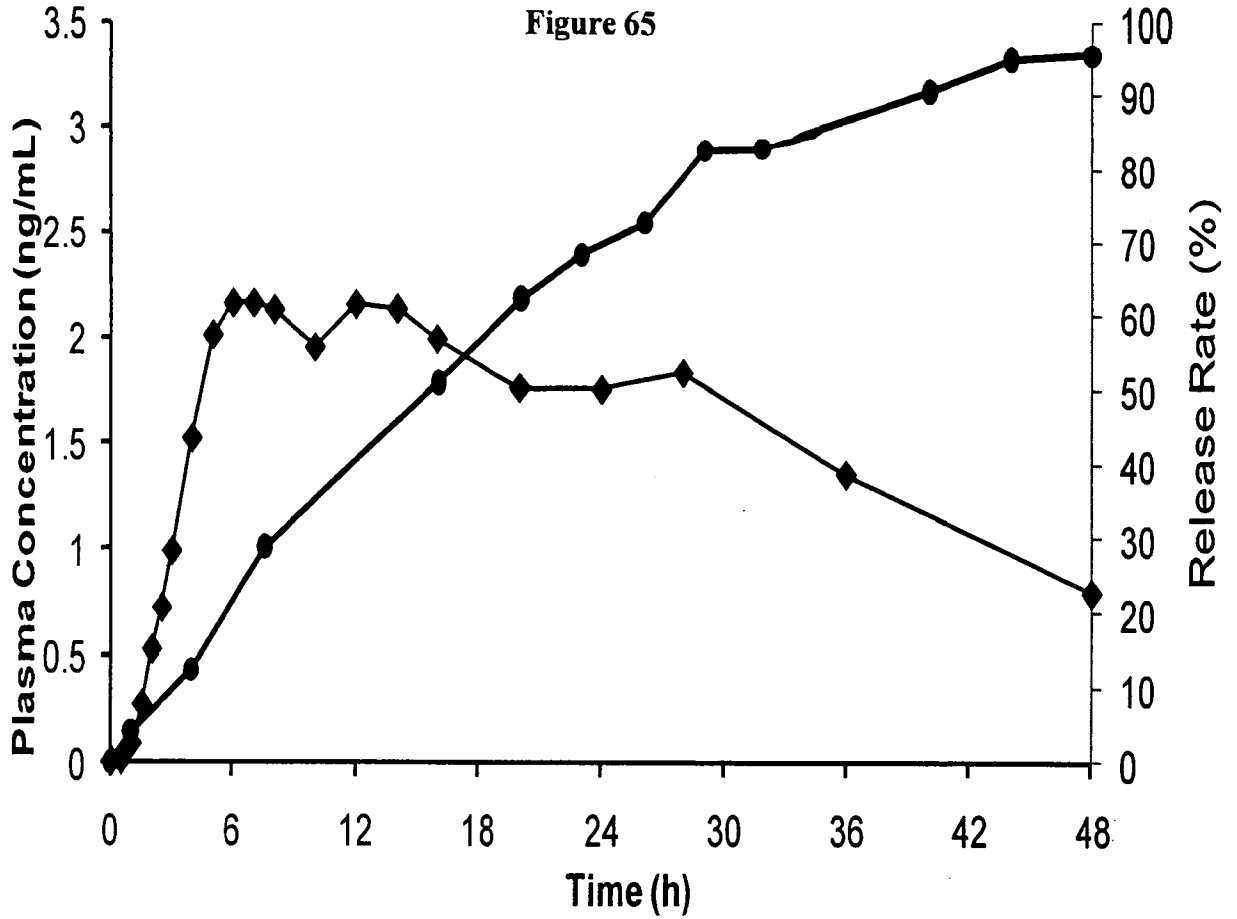


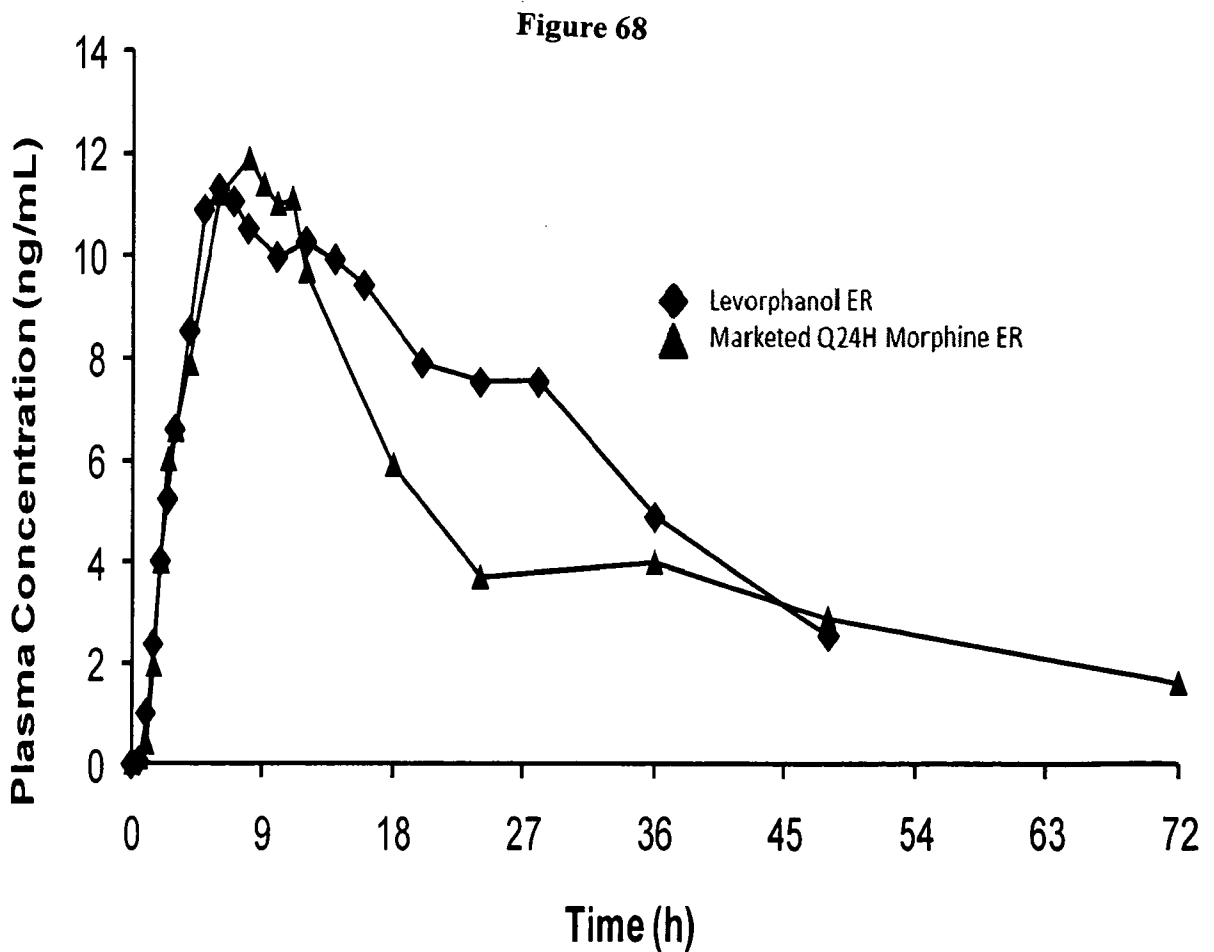
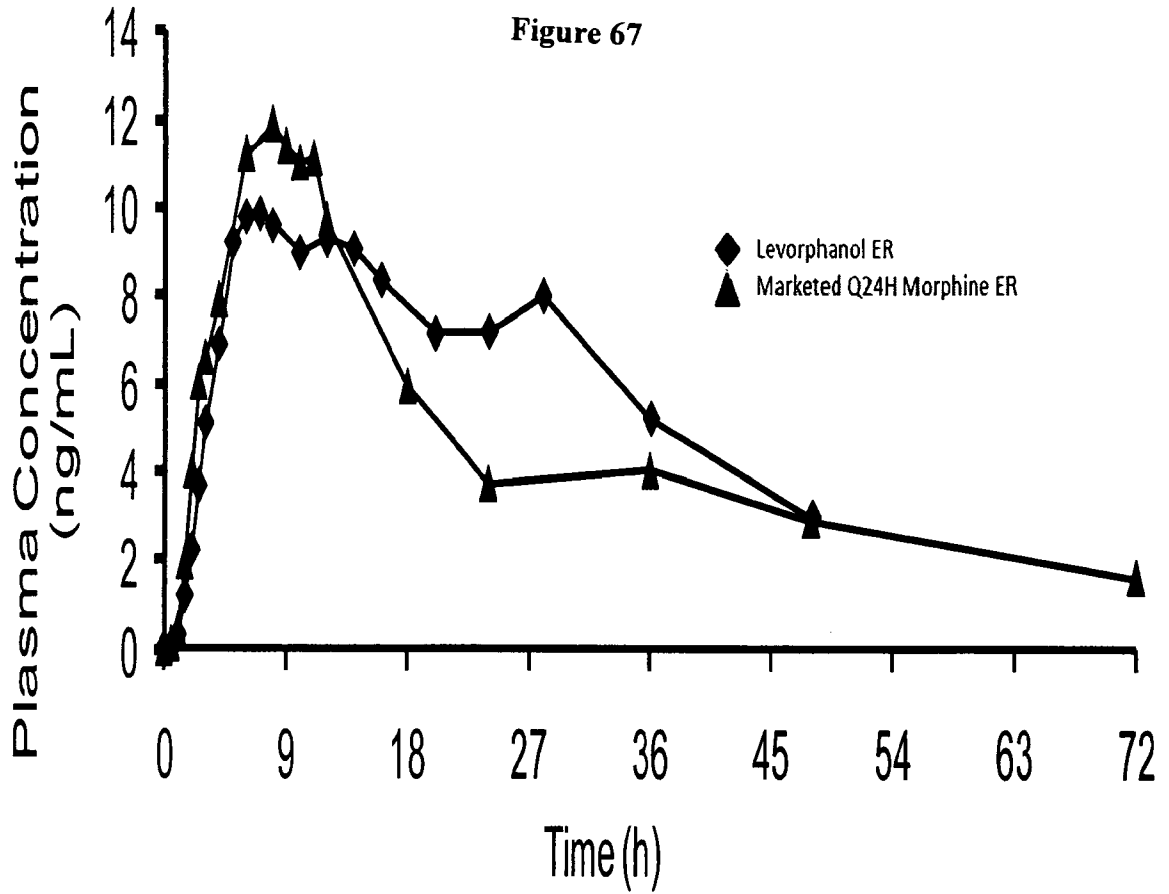












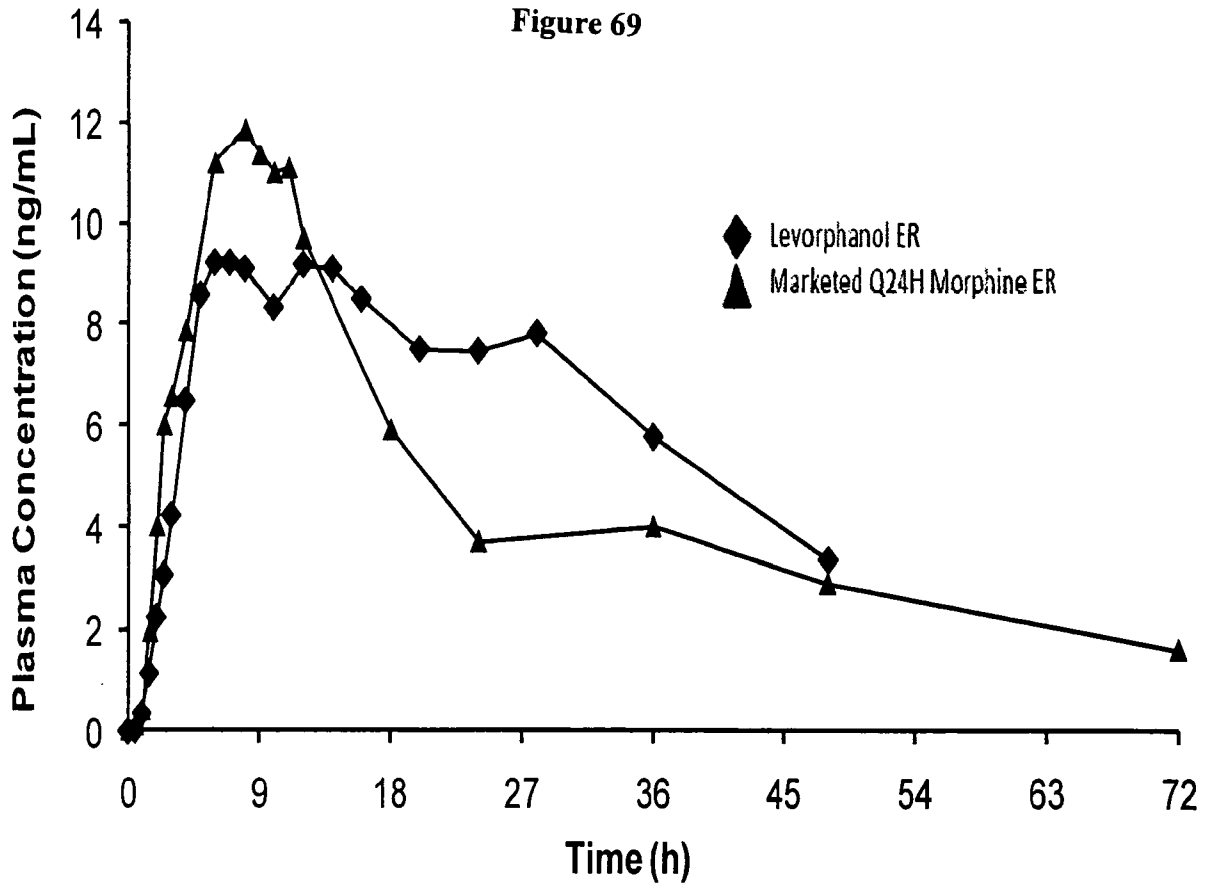


Figure 70
Abuse resistance testing on Levorphanol batches VE2470, VE2471, VE2472 & VE2473:
EtOH extraction, Test 1 (Intact dosage units)

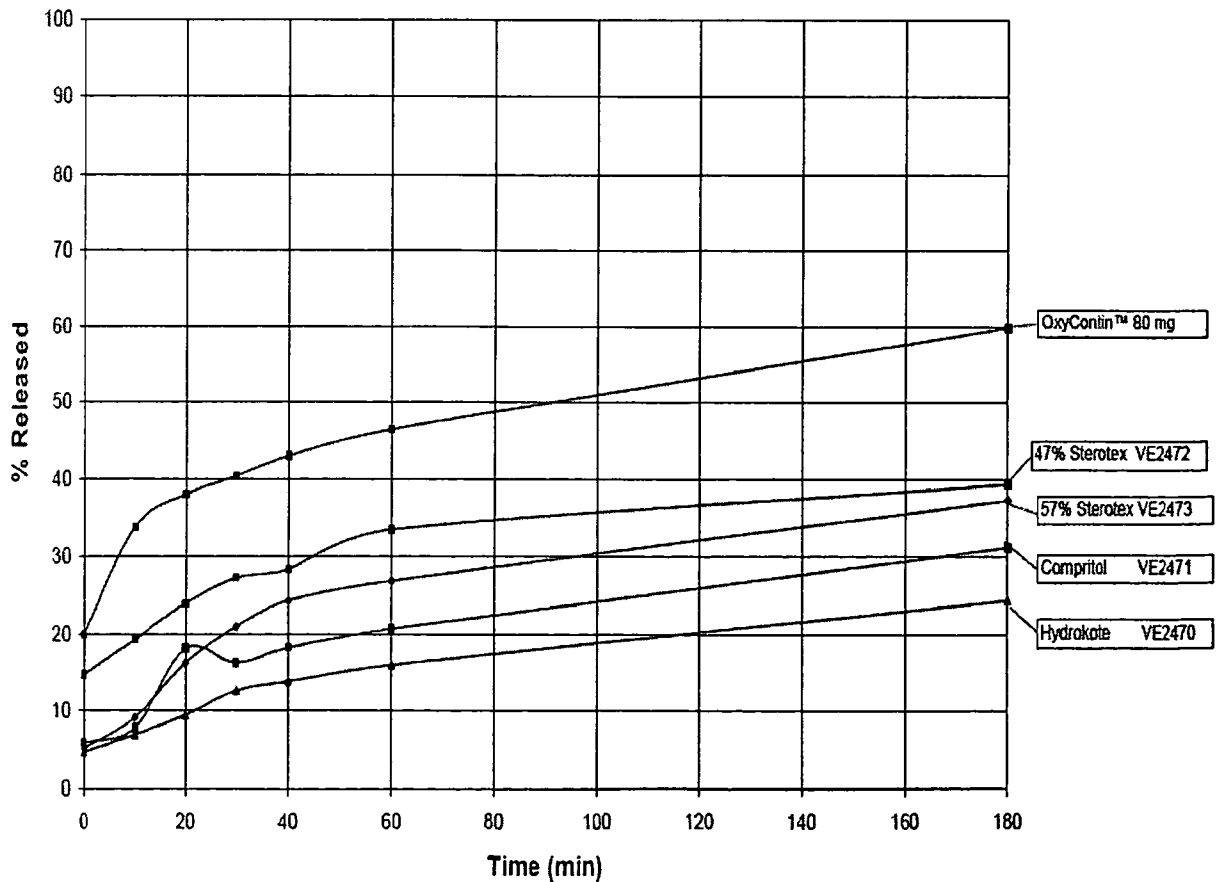


Figure 71
Abuse resistance testing on Levorphanol batches VE2470, VE2471, VE2472 & VE2473:
Test 1a. (Cut in half or single crush of dosage units)

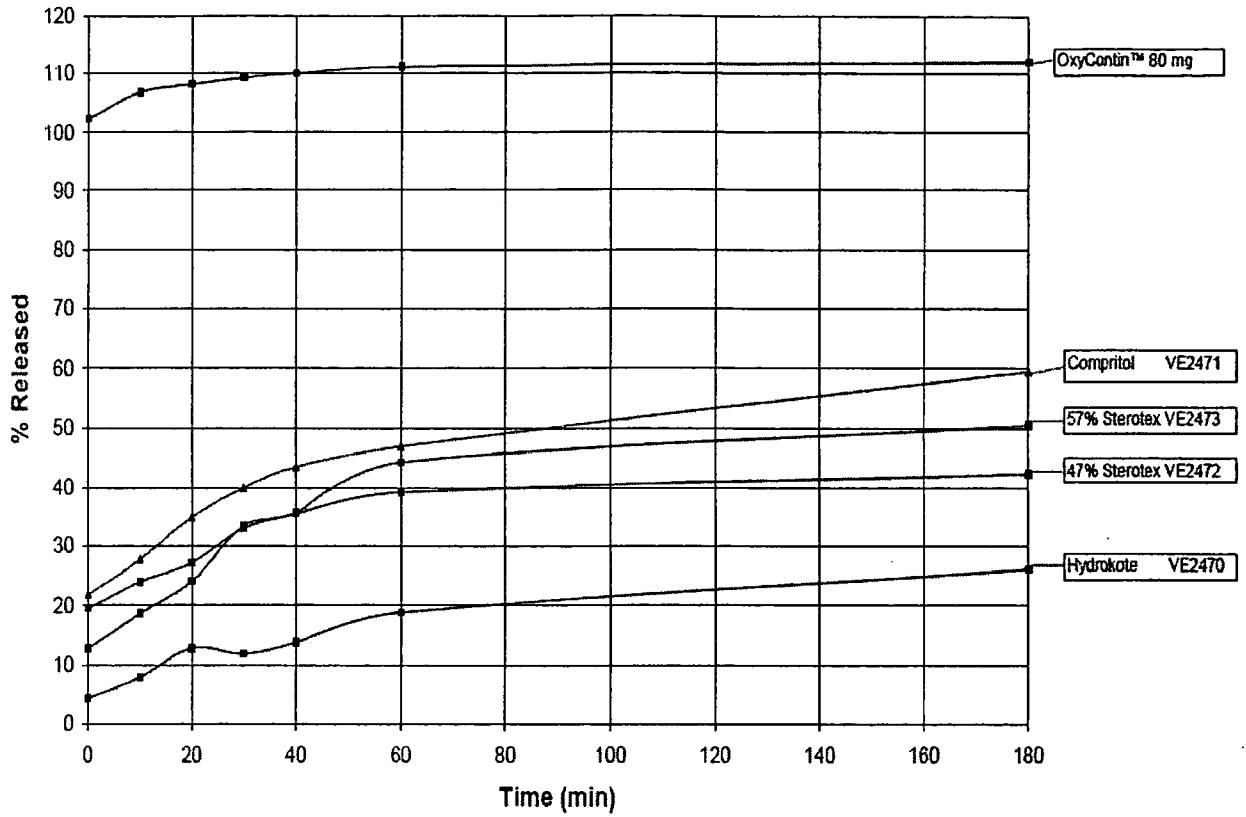


Figure 72

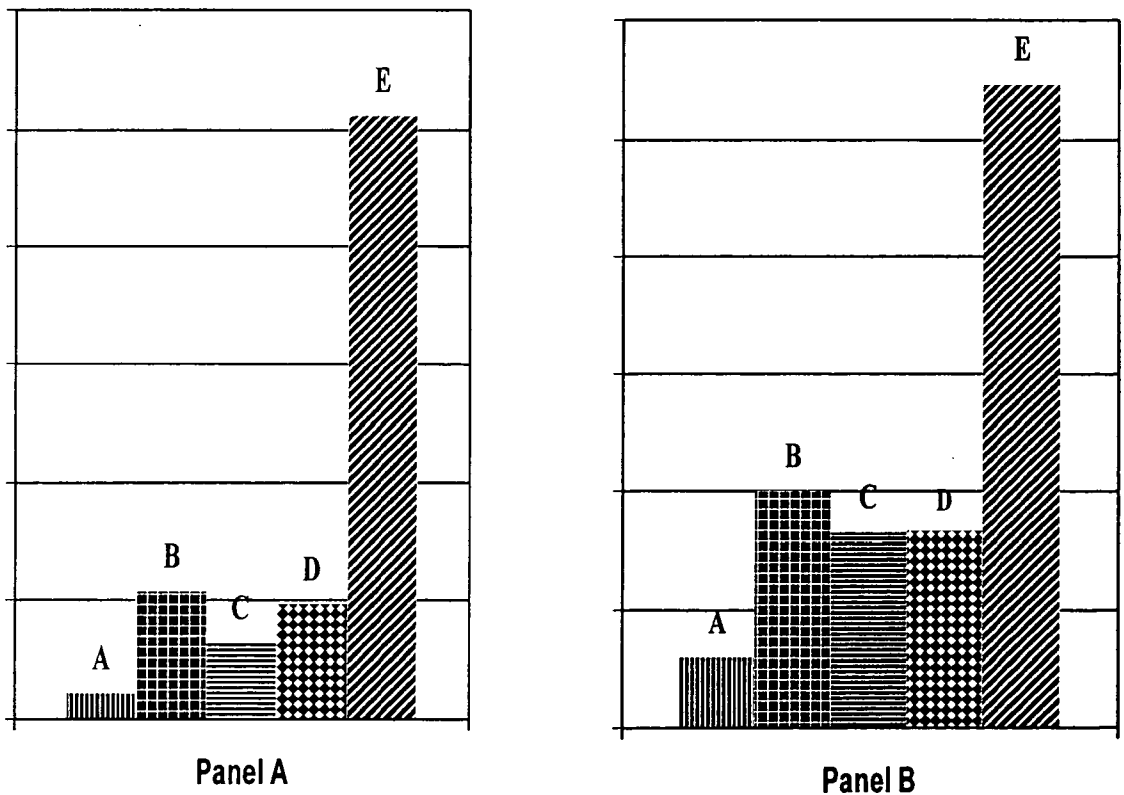


Figure 73

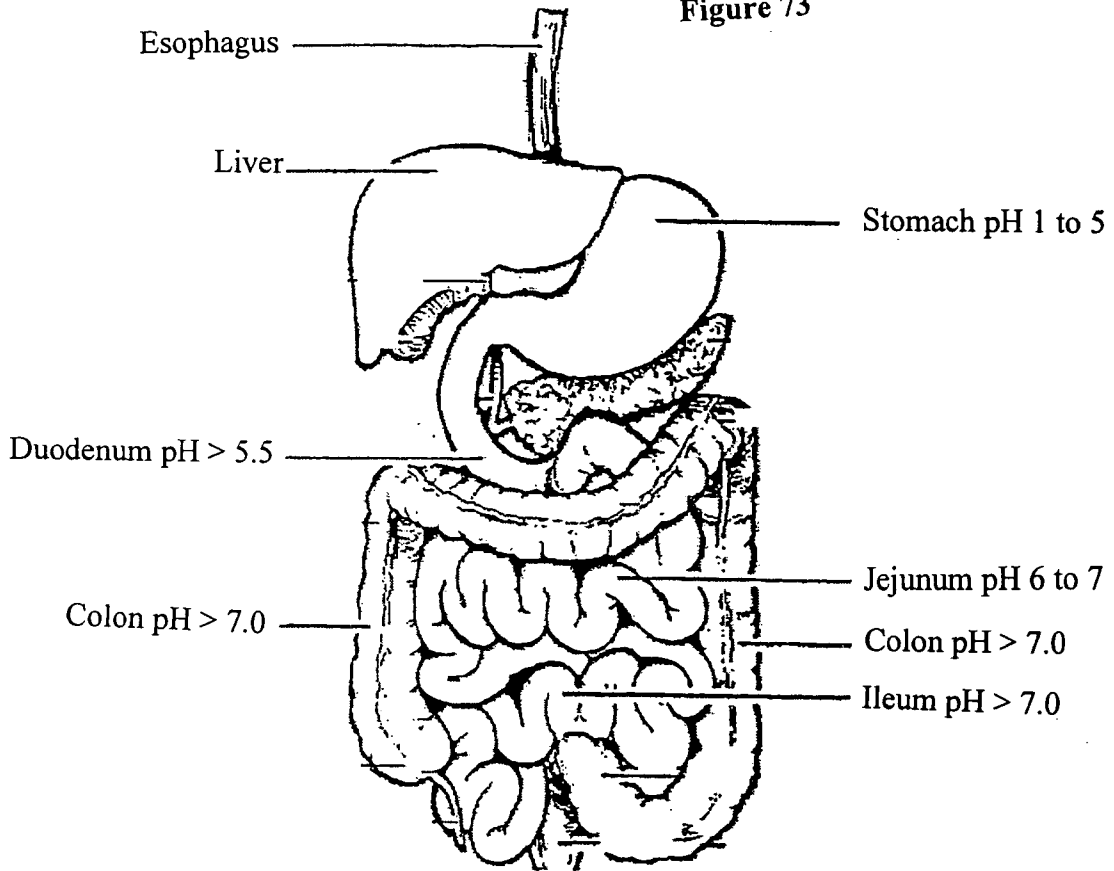


Figure 74

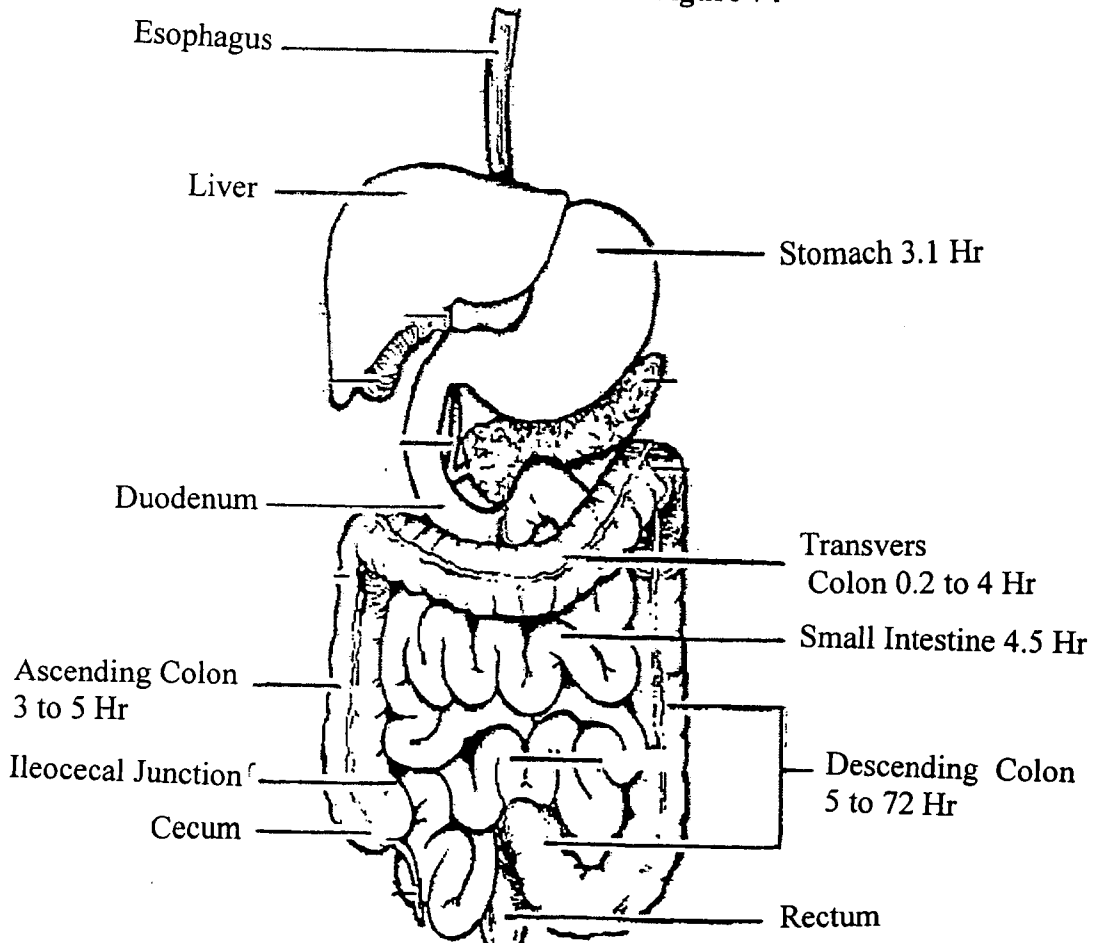


Figure 75

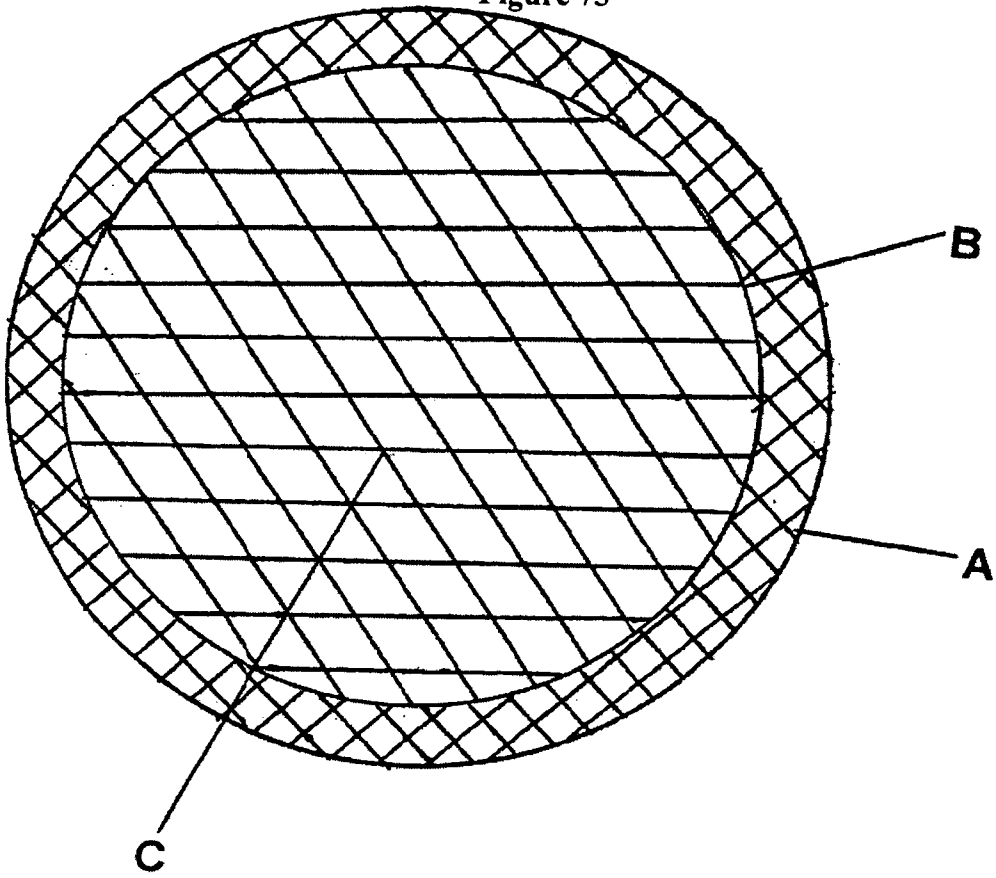


Figure 76

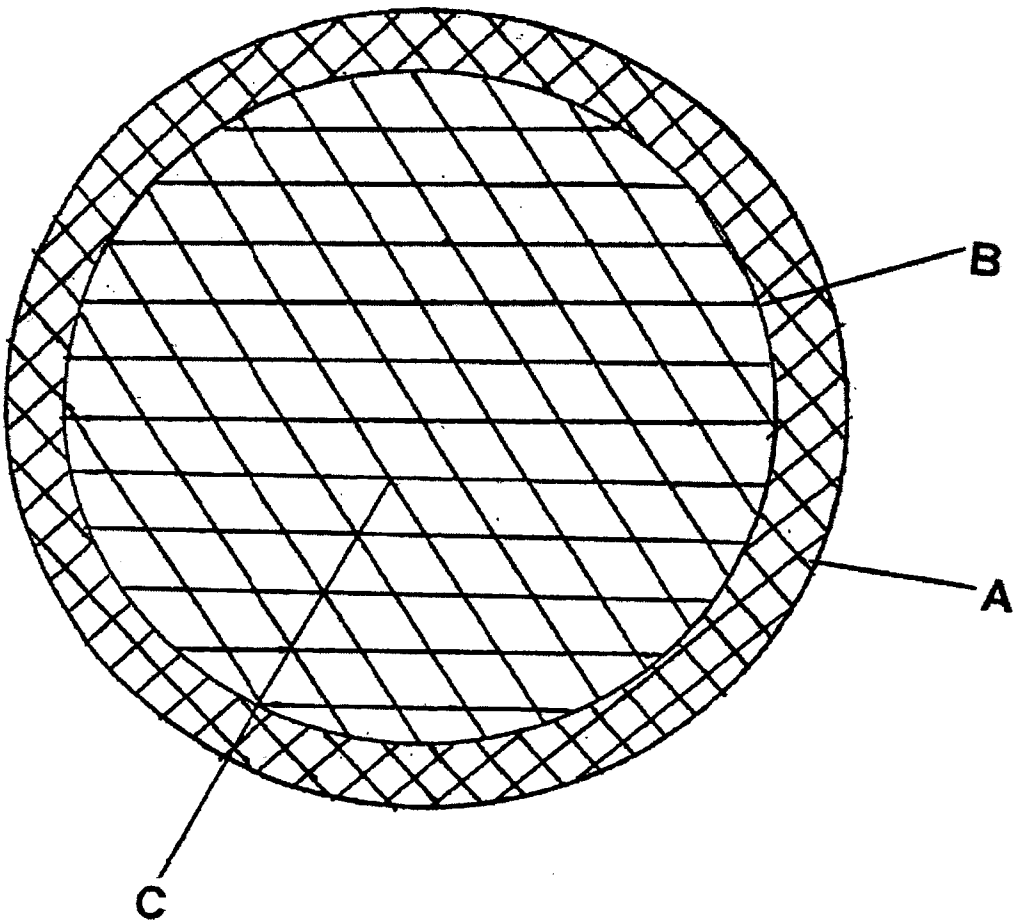


Figure 77

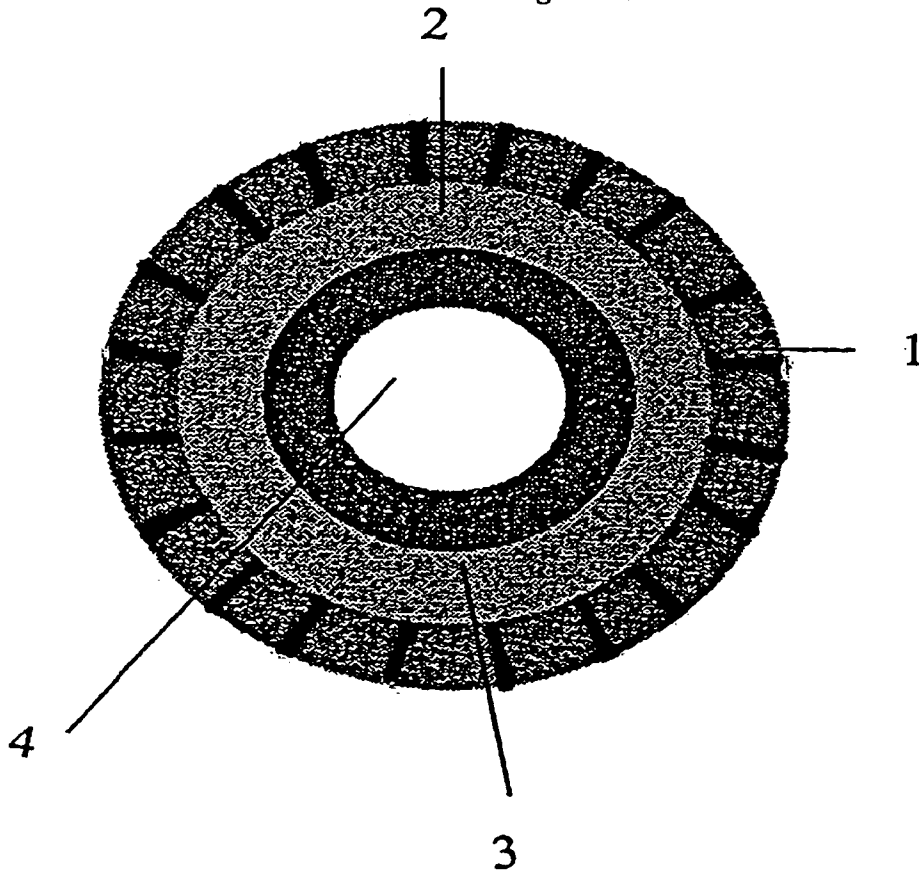
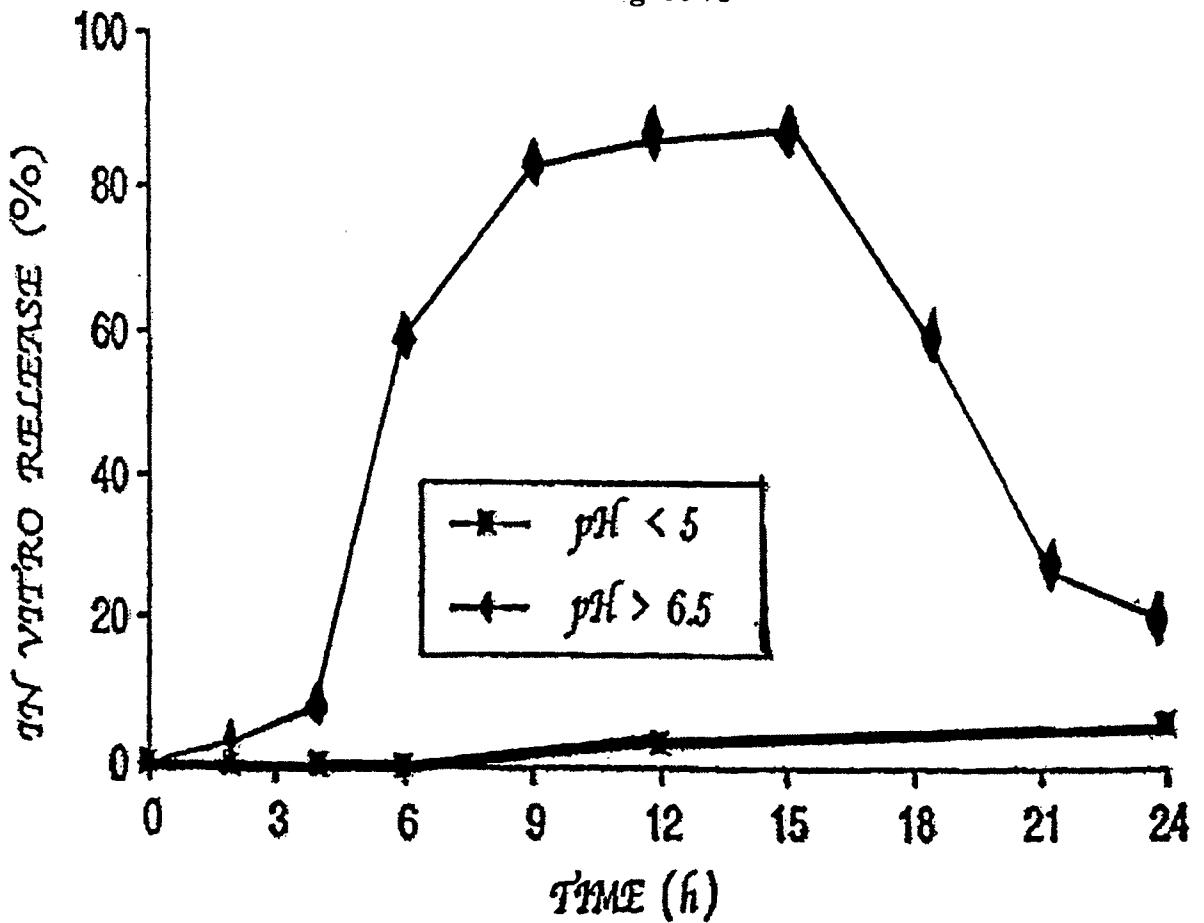


Figure 78



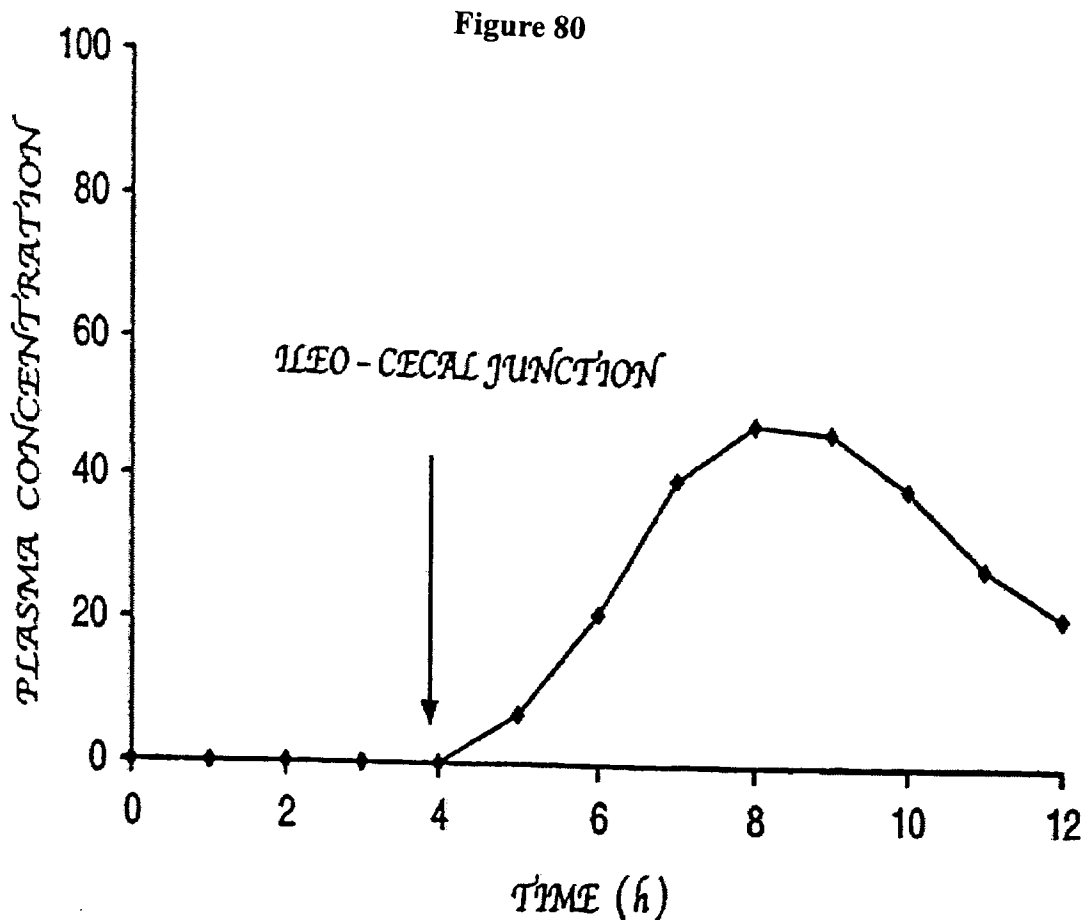
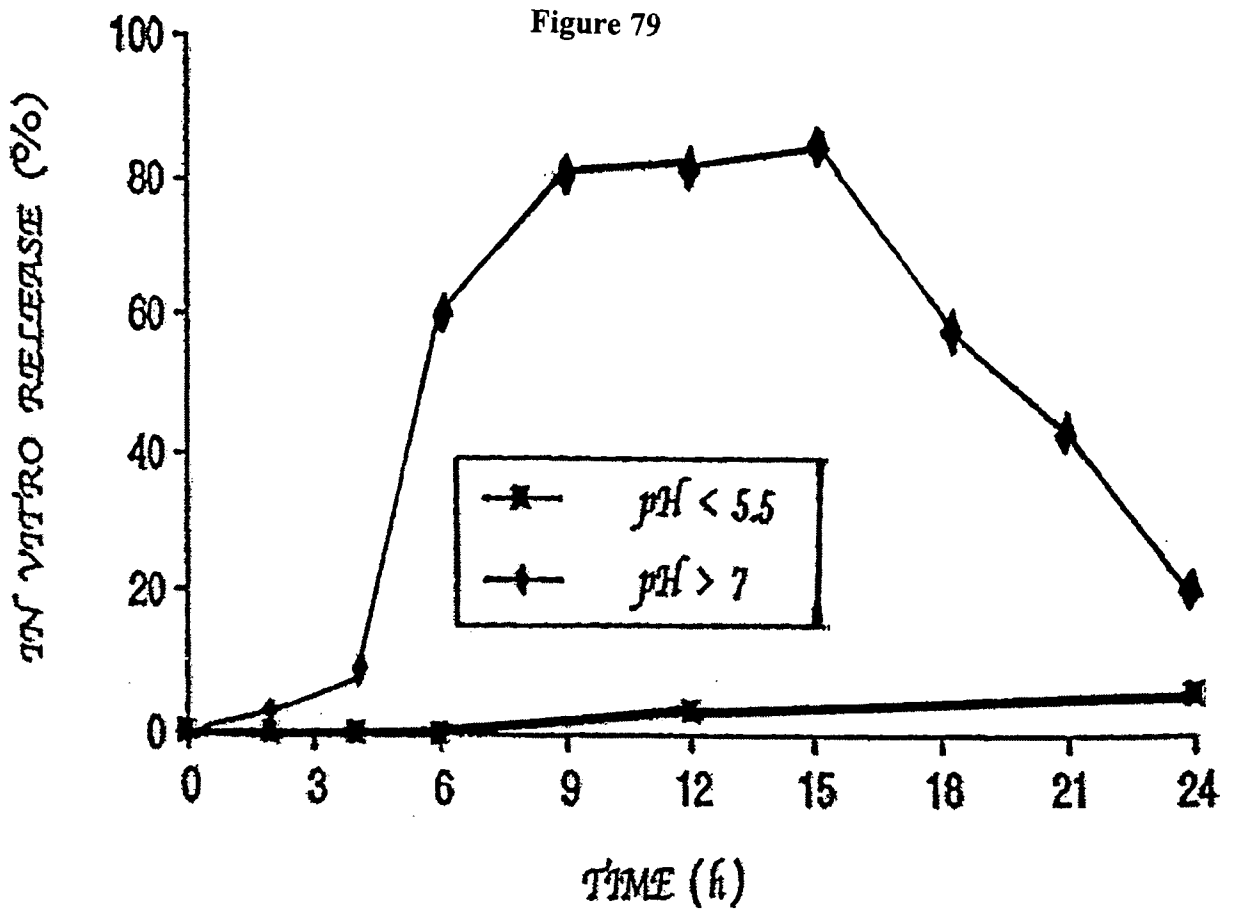


Figure 81

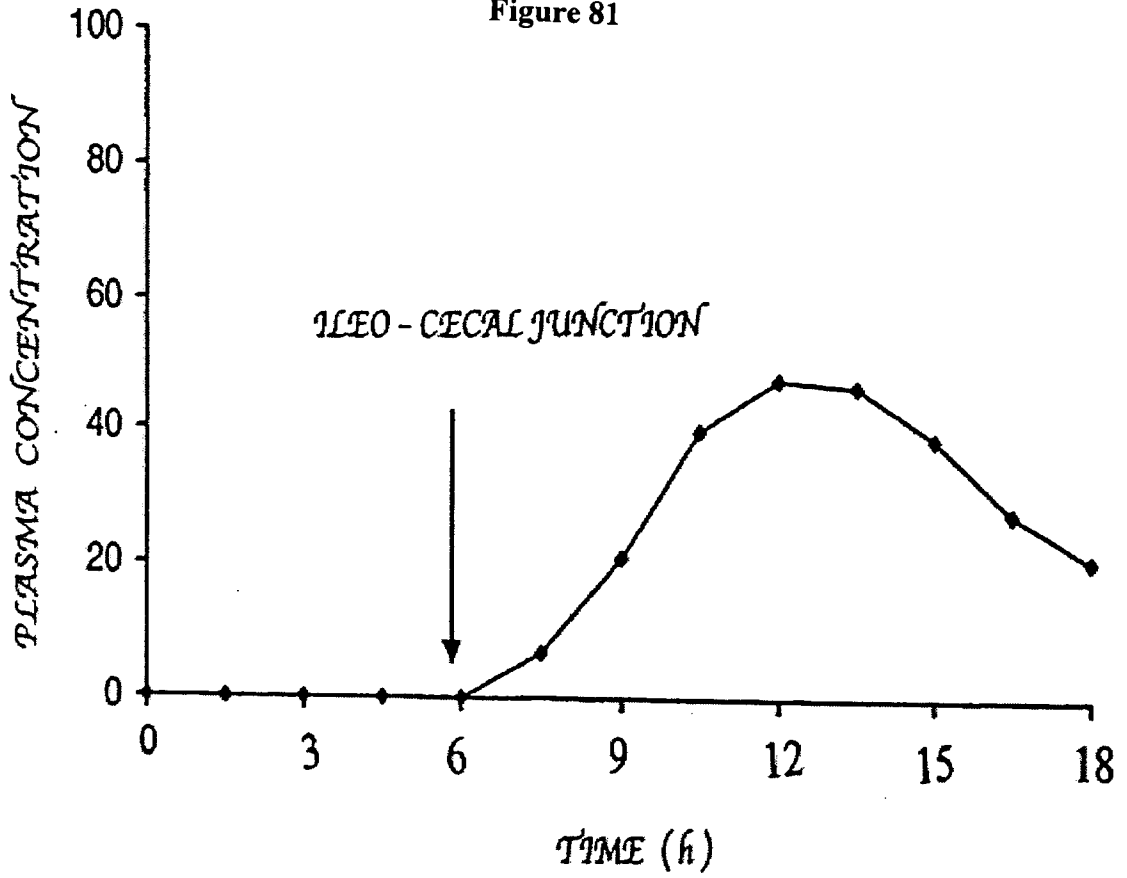


Figure 82

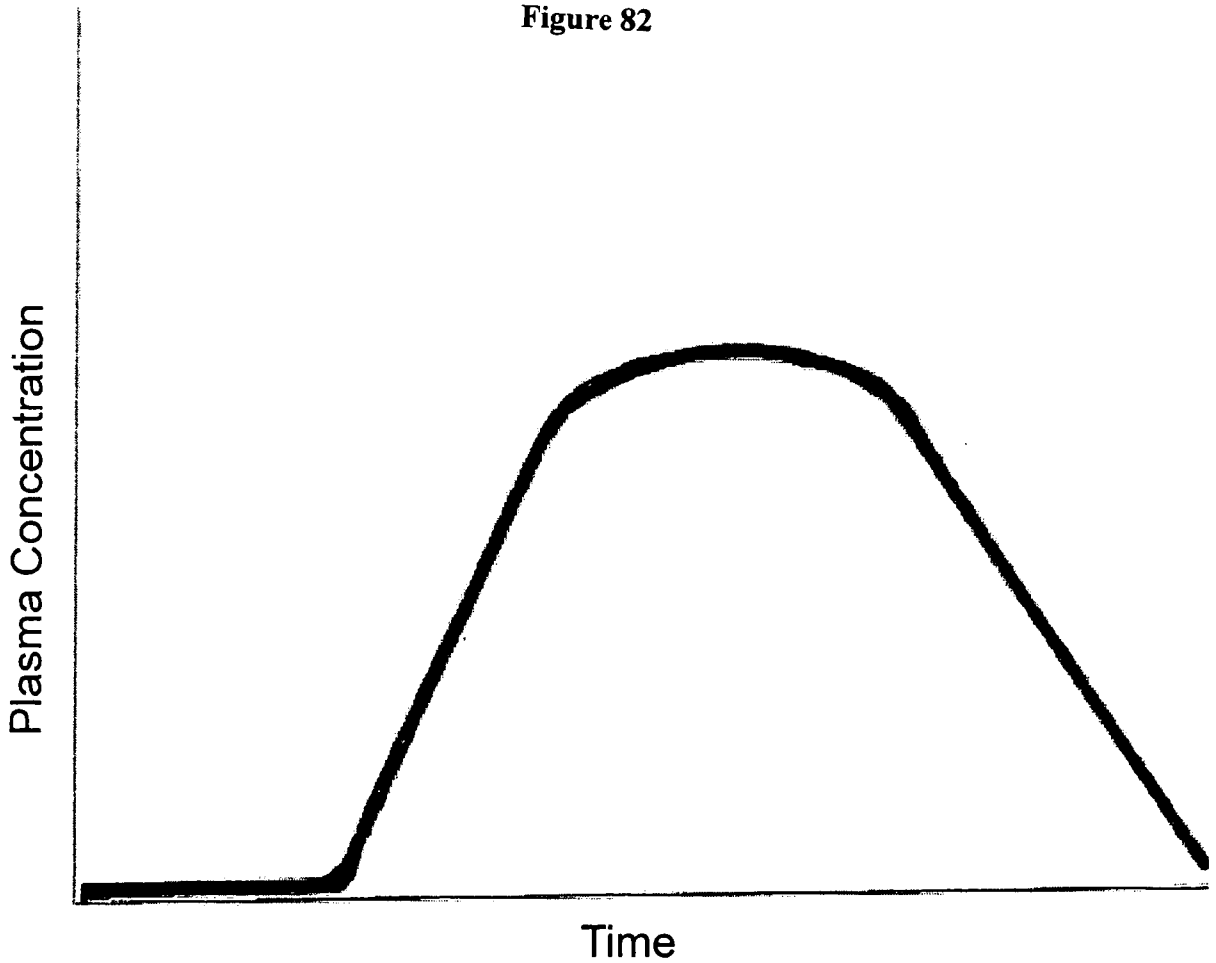


Figure 83

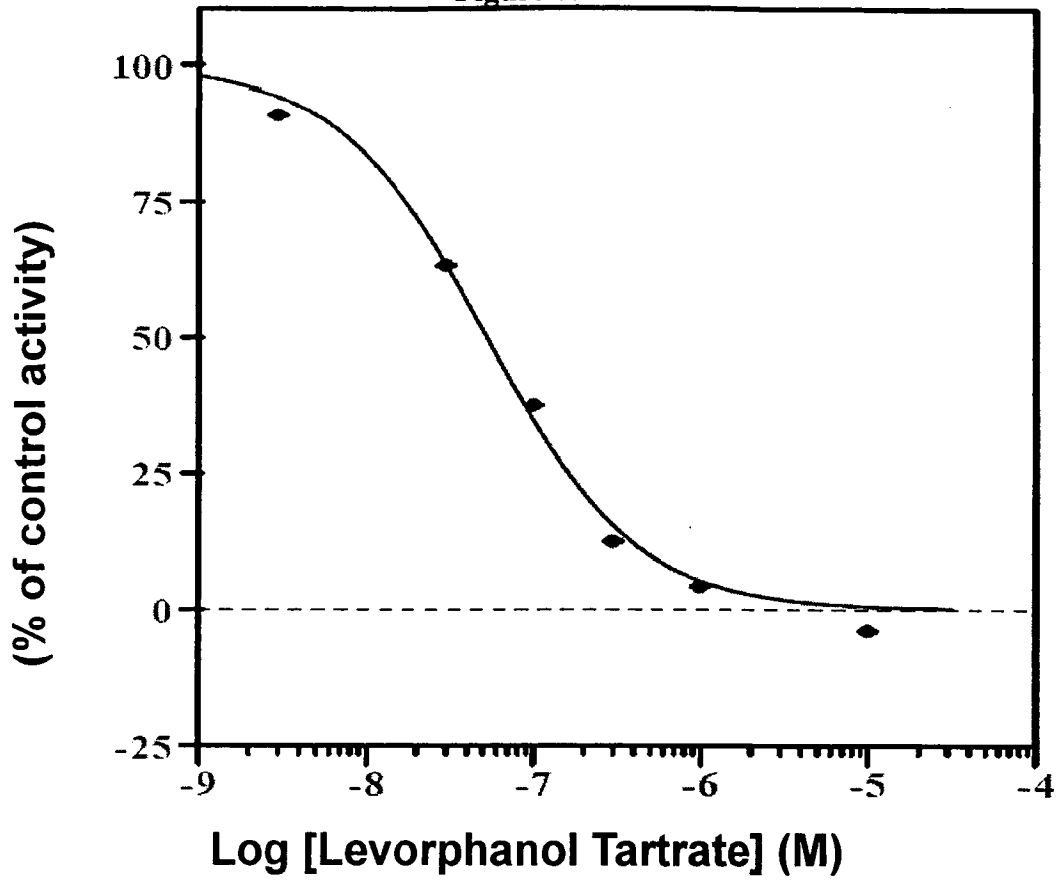
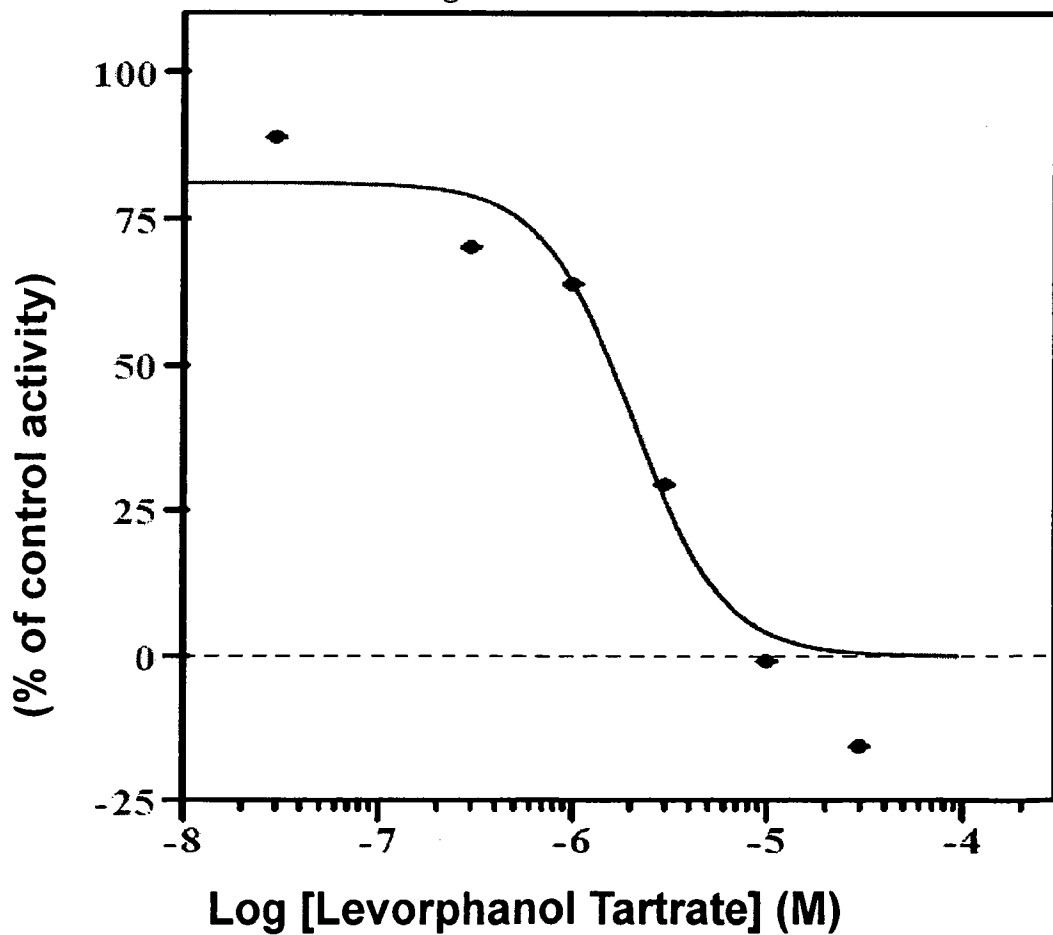


Figure 84



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/25694

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A01N 43/42; A61K 31/44 (2010.01) USPC - 514/282 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) USPC: 514/282		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: 424/731; 424/738; 514/57; 514/317; 546/74 (see search terms below)		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Electronic Database Searched: PubWest (PGPB,USPT,USOC,EPAB,JPAB), Google. Search Terms Used: 3-hydroxy-N-methylmorphinan, 17-methylmorphinan-3-ol, levorphanol, plasma concentration curve, paddle or basket, oral dosage		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/0018934 A1 (Vaya et al.) 26 January 2006 (26.02.2006) entire document, especially para [0021], [0025]-[0027], [0044], [0061], [0072], [0080], [0088], [0188]	19-34 and 45-48
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Y		1-18, 35-44 and 49-52
Y	US 4,703,761 A (Rathbone et al.) 03 November 1987 (03.11.1987) especially abstract; col 2, ln 27-41	1-3 and 17-18
Y	US 6,103,261 A (Chasin et al.) 15 August 2000 (15.08.2000) especially col 2, ln 23-35, ln 48-67	4-16, 35, 37-44 and 49-50
Y	US 2003/0068392 A1 (Sackler) 10 April 2003 (10.04.2003) especially para [0018]-[0020], [0079]	36 and 51-52
A	US 6,716,446 B2 (Edelstam) 06 April 2004 (06.04.2004) entire document	1-52
A	US 2007/0142421 A1 (Mayo-Alvarez et al.) 21 June 2007 (21.06.2007) entire document	1-52
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 29 April 2010 (29.04.2010)		Date of mailing of the international search report 11 MAY 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774