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(54) Title: SUSTAINED RELEASE HYDROMORPHONE FORMULATIONS EXHIBITING BIMODAL CHARACTERISTICS (57) Abstract <p>The invention is related to a biphasic solid sustained release once-a-day oral dosage form comprising hydromorphone or a pharmaceutically acceptable salt thereof together with a sustained release carrier, and to the use thereof in the treatment of human patients. The dosage provides a rise in plasma concentration to an initial early peak concentration, followed by a second peak with plateau plasma concentrations (figure 2).</p>		

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**SUSTAINED RELEASE HYDROMORPHONE
FORMULATIONS EXHIBITING BIMODAL CHARACTERISTICS**

BACKGROUND OF THE INVENTION

During the past decade, physicians, pharmacists and epidemiologists have devoted increasing attention to the palliative treatment of patients who suffer from chronic pain. While the early interest in long-term analgesia arose from the worldwide problem of inadequate pain control among cancer patients, many researchers now recognize a substantial population of patients with non-malignant pain who do not receive satisfactory relief. Since the supervised use of opioid analgesics can provide effective and economical pain relief for nearly all patients suffering from chronic pain, inadequate pain management has been characterized as unnecessary and attributed to failure to apply available knowledge concerning analgesics

Although problems of inadequate pain treatment are global, the particular barriers to relief of pain vary across and within societies. In industrialized countries, where most patients have access to advanced and technically complex medical care, the systematic focus on disease-specific interventions by both providers and patients may divert attention from issues of pain relief and patient comfort. Other specific impediments to the use of opioids include overestimation by physicians and patients of the risk of addiction, confusion about the concepts of tolerance and physical dependence, local regulatory burdens that signal opioids as drugs of abuse, and the social stigmatization of opioids as drugs of hopelessness. These latter opioid-specific concerns are particularly important for morphine, but also interfere with appropriate medical prescribing of other strong opioids such as hydromorphone.

National and international medical authorities, increasingly attuned to issues of palliative care and quality of life, now regard the use of opioids, in particular oral opioids, as an essential element in the care of patients with cancer pain. The World Health Organization (WHO) and the U. S. government's Agency for Health Care Policy and Research (AHCPR) advocate a three-step

analgesic prescription strategy that employs non-opioids for patients with mild pain and advances to opioids, with or without supplemental non-opioids, for the treatment of moderate or severe. Preference is given to the oral route of administration whenever practical. Medication schedules should provide around-the-clock analgesia with additional medication available as needed for breakthrough or incident pain. The simplest dosing schedules and least invasive modalities should be used first.

Opioids are the agents of choice for the management of moderate to severe pain whether in acute settings such as surgery, accidental trauma, or sickle cell crises, or in persistent, chronic forms in patients with cancer or who have chronic non-malignant pain that is refractory to non-opioid. The use of opioids for moderate to severe acute pain and in patients with cancer pain now stands as unchallenged standard practice, while the use of opioids for selected patients with chronic non-malignant pain is gaining acceptance.

Currently available opioid medications can be classed as pure agonists such as morphine, oxycodone, and hydromorphone, and mixed agonist/antagonists, depending on the drug's activity at the opioid receptor site within the central nervous system, and the pharmacologic effects produced. In most situations, including all settings where chronic use is expected and increasingly severe pain can be anticipated, pure agonists are preferred because they do not exhibit a ceiling effect. With appropriate dose adjustment, the oral route of administration provides adequate analgesia in most situations and is the preferred route because it avoids the discomfort, inconvenience, and expense of injection. The use of controlled-release opioids affords the added advantages of less frequent dosing with its many benefits.

With all formulations available today, dosages can be achieved that will usually relieve the most severe pain. Clinically, however, dose levels that can be used safely and comfortably are limited by adverse reactions associated with opioid therapy. With hydromorphone, these limitations are compounded by the short elimination half-life of immediate-release formulations, which typically require dosing every 4 hours to maintain optimal levels of analgesia.

Immediate-release formulations of hydromorphone are available as tablets and solutions (Dilaudid®, Knoll Pharmaceutical Co. and others) providing a potent analgesic for treating moderate to severe pain. However, the rapid metabolism and elimination of hydromorphone from the body necessitates that the conventional immediate-release oral formulations of hydromorphone be administered every 4 hours around the clock to maintain adequate analgesia to manage moderate levels of persistent pain. Many difficulties can result for patients from having to remember and take several timed daily doses of medication. In order to address these problems which are associated with immediate release hydromorphone, there exists a need to formulate a controlled release hydromorphone formulation which can be taken once daily to provide effective pain management for about 24 hours or longer. Advantageously, once daily dosing formulations provides both increased convenience and compliance.

It is known in the pharmaceutical art to prepare compositions which provide for sustained release of pharmacologically active substances contained in the compositions after oral administration to humans and animals. Sustained release formulations known in the art include specially coated pellets, coated tablets and capsules wherein the slow release of the active medicament is brought about through selective breakdown of the coating of the preparation or through compounding with a special matrix to affect the release of a drug. Some sustained release formulations provide for related sequential release of a single dose of an active compound at predetermined periods after administration.

It is the intent of all sustained release formulations to provide a longer period of pharmacologic action after administration than is ordinarily obtained after administration of immediate-release dosage forms. Sustained release compositions may be used to delay absorption of a medicament until it has reached certain portions of the alimentary tract, and maintain a desired concentration of said medicament in the blood stream for a longer duration than would occur if conventional immediate release dosage forms are administered. Such longer periods of response provide for many therapeutic benefits that are not achieved with corresponding short acting, immediate release preparations. Thus, therapy may be continued

without interrupting the sleep of the patient, which is of special importance, for example, when treating a patient for moderate to severe pain (e.g., a post-surgery patient, a cancer patient, etc.), or for those patients who experience migraine headaches on awakening, as well as for the debilitated patient for whom sleep is essential. A further general advantage of longer acting drug preparations is improved patient compliance resulting from the avoidance of missed doses through patient forgetfulness.

Unless conventional immediate acting drug therapy is carefully administered at frequent intervals to maintain effective steady state blood levels of the drug, peaks and valleys in the blood level of the active drug occurs because of the rapid absorption, systemic excretion of the compound and through metabolic inactivation, thereby producing special problems in maintenance therapy of the patient.

Due to the difficulties presented by the pharmacotherapy of pain, particularly chronic pain, opioid analgesics are ideal drugs to be administered as controlled release formulations. Certain sustained-release opioid analgesic formulations are commercially available. For example, morphine, which is considered to be the prototypic opioid analgesic, has been formulated into 12 hour controlled-release formulations (i.e., MS Contin® tablets, commercially available from Purdue Frederick Company). More recently, oxycodone has been formulated into 12 hour controlled-release formulation (i.e., OxyContin® tablets, commercially available in the U.S. from Purdue Pharma).

Various techniques have been used to prepare controlled release dosage forms. Specially coated pellets, tablets and capsules wherein the slow release of the active medicament is brought about through selective breakdown of the coating of the preparation or through compounding with a special matrix to affect the release of a drug are known in the art. Certain controlled release formulations provide for related sequential release of a single dose of an active compound at predetermined periods after administration.

U.S. Patent Nos. 4,990,341 and 4,844,909 (Goldie, et al.), both assigned to the assignee of the present invention and incorporated herein by reference, describe hydromorphone

compositions wherein the dissolution rate in-vitro of the dosage form, when measured by the USP Paddle or Basket Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37E C, is between 12.5 and 42.5% (by wt) hydromorphone released after 1 hour, between 25 and 55% (by wt) released after 2 hours, between 45 and 75% (by wt) released after 4 hours and between 55 and 85% (by wt) released after 6 hours, the in-vitro release rate being independent of pH between pH 1.6 and 7.2 and chosen such that the peak plasma level of hydromorphone obtained in-vivo occurs between 2 and 4 hours after administration of the dosage form. At least 12 hours of pain relief is obtained with these hydromorphone formulations.

A method of effectively treating pain in humans is described in U.S. Patent Nos. 5,478,577 and 5,672,360 (Sackler, et al., both assigned to Purdue Pharma and incorporated by reference), which comprises administering an oral sustained release dosage form which upon administration provides a time to maximum plasma concentration in about 2 to about, e.g., 8-10 hours, and which provides a maximum plasma concentration of the opioid which is more than twice the plasma concentration after about 24 hours.

U.S. Patent No. 5,913,131 (Ayer, et al.) describes a hydromorphone dosage form which is said to comprise a drug layer, a delivery layer and a semipermeable wall including a passageway in a delivery dose pattern of 0-20% released by 4 hours after administration, 20-50% released by 8 hours after administration, 55-85% released by 14 hours after administration, and 80-100% released by 24 hours after administration.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide bioavailable hydromorphone formulations which provides analgesia with a less frequent dosing requirement than is currently available.

It is a further object of the present invention to provide an orally administered pharmaceutical dosage form of hydromorphone that is suitable for once-a-day administration.

It is a further object of the present invention to provide oral dosage forms of hydromorphone or a pharmaceutically acceptable salt thereof which are administrable on a once-a-day basis and which provide effective treatment of pain in mammals, particularly humans.

It is a further object of the invention to control moderate to severe pain in patients who require around-the-clock opioid medications for more than a few days by administering a hydromorphone formulation having pharmacokinetic characteristics suitable for around-the-clock pain relief.

It is a further object of the invention to provide patients the reliable and safe analgesia associated with hydromorphone with the convenience of once-a-day dosing.

It is a further object of the invention to provide once-daily dosing of an analgesic dosage form in order to reduce the risk of missed doses, thereby decreasing the frequency and severity of episodic breakthrough pain and minimizing a source of patient anxiety and providing an improved quality of life.

It is a further object of the invention to provide patients with a treatment for their pain which provides a reduction in their pain intensity within about 1 to about 2 hours after administration, and which treatment further provides sufficient plasma levels of the drug to provide pain relief at a later time in during the dosage interval at which it may be expected that the patients may experience breakthrough pain.

It is a further object of the invention to provide a once-a-day controlled release dosage form exhibiting a biphasic absorption pattern which provides a relatively rapid, initial absorption of hydromorphone as evidenced by reductions in pain intensity within 1 to 2 hours after

administration) followed by a prolonged phase of absorption providing a maintained therapeutic concentration, in order to provide pain relief both early and throughout the 24-hour dosing period.

It is a further object of the invention to accomplish the above objects utilizing a controlled release hydromorphone formulation which when administered every 24 hours, is equivalent, in terms of extent of absorption, to the same dose of immediate-release hydromorphone given in divided doses every 6 hours.

It is a further object of the invention to provide a sustained release hydromorphone formulation which, when administered every 24 hours, provides a lower maximum and higher minimum plasma hydromorphone concentrations (e.g., a peak to trough fluctuation) than those from the same total dose of immediate-release hydromorphone administered every 6 hours, preferably while also accomplishing the objects set forth above.

It is a further object of the invention to provide a sustained release hydromorphone dosage form which does not alter the profile of hydromorphone metabolism in a human patient as compared to an equal dose of immediate release hydromorphone.

In view of the above objects and others, the present invention in certain embodiments is directed to a solid sustained release once-a-day oral dosage form of hydromorphone which provides a biphasic absorption of hydromorphone when administered to a patient. Preferably, the biphasic administration results in a first peak concentration which occurs early in the dosage interval, such that the patient experiences a reduced pain intensity within about 1 to about 2 hours after administration, and which treatment further provides sufficient plasma levels of the drug to provide pain relief at a later time in during the dosage interval at which it may be expected that the patients may experience breakthrough pain.

In certain preferred embodiments, the sustained release hydromorphone formulations of the invention provides a first peak plasma concentration of the hydromorphone in about 0.3 to

about 5 hours after oral administration of the dosage form to the patient (T_{max} #1). In other preferred embodiments, the first peak plasma concentration occurs in about 0.3 to about 4 hours after oral administration. In still other preferred embodiments, the first peak plasma concentration occurs in about 1 to about 3 hours after oral administration.

In other preferred embodiments of the invention, the sustained release hydromorphone formulations provide a second peak plasma concentration which occurs in about 10 to about 24 hours after oral administration of the dosage form to the patient (T_{max} #2). In other preferred embodiments, the second peak plasma concentration occurs in about 12.5 to about 24 hours after oral administration of the dosage form to the patient. In other preferred embodiments, the second peak plasma concentration occurs in about 12.5 to about 16 hours after oral administration of the dosage form to the patient.

In certain preferred embodiments, C_{max} #1 is from about 1 to about 3 ng/ml, per administration of a 12 mg dosage of hydromorphone hydrochloride. In other preferred embodiments, C_{max} #1 is from about 0.4 to about 2.5 ng/ml, per administration of a 12 mg dosage of hydromorphone hydrochloride. In certain preferred embodiments, the second peak plasma concentration (C_{max} #2) is from about 1.0 to about 3.6 ng/ml, per 12 mg hydromorphone administered over the 24 hour period. In other preferred embodiments, the second peak plasma concentration is from about 0.5 to about 3.0 ng/ml, per 12 mg hydromorphone administered over the 24 hour period. Because the dosage of hydromorphone in the sustained release oral formulations of the invention is preferably dose-proportional, one can easily determine the maximum plasma concentrations for C_{max} #1 and/or C_{max} #2 for different dosages of hydromorphone over a 24 hour period.

In certain preferred embodiments, the width of the plasma concentration curve at 50% of the height (W_{50}) of C_{max} #1, the height of C_{max} #1 being based on the trough (minimum plasma concentration) which occurs between C_{max} #1 and C_{max} #2, is preferably from about 1.5 to about 4.5 hours, and preferably from about 2.5 to about 3.5 hours in certain preferred embodiments. In certain preferred embodiments, the width of the plasma concentration curve at

50% of the height (W50) of Cmax #2, the height of Cmax #2 being based on the trough (minimum plasma concentration) which occurs between Cmax #1 and Cmax #2, is preferably from about 6 to about 20 hours, and most preferably from about 6.5 to about 10 hours in certain embodiments. In other preferred embodiments, the W50 of Cmax #2 is from about 4.5 to about 9 hours, and preferably from about 5.5 to about 7 hours.

In certain preferred embodiments, the sustained release hydromorphone formulations of the invention provides a Cmax which is less than twice the plasma level of hydromorphone at about 24 hours after administration of the dosage form.

In certain further preferred embodiments, the sustained release hydromorphone formulations of the invention provide a Cmax which is less than twice the plasma level of hydromorphone at the Cmin which occurs between Cmax #1 and Cmax #2.

In preferred embodiments of the invention, the sustained release hydromorphone formulation provides a mean resonance time (MRT, the average time a drug molecule spends in the body) of hydromorphone from about 15 to about 35 hours, more preferably from about 25 to about 30 hours.

In preferred embodiments of the invention, the sustained release hydromorphone formulation provides a percent fluctuation (of plasma hydromorphone concentration) from about 20% to about 220%, preferably from about 60% to about 180% and most preferably about 125%.

In preferred embodiments of the invention, the sustained release hydromorphone formulation provides a percent fluctuation which is about 30% to about 50% of the percent fluctuation exhibited by an equivalent dose of a (reference standard) immediate release hydromorphone administered every 6 hours.

In certain further preferred embodiments, the sustained release hydromorphone formulations of the invention may be characterized by other pharmacokinetic values which are set forth in the data provided in the appended examples, which data can be readily gleaned by one of ordinary skill in the art reviewing the appended Tables and Figures. Such pharmacokinetic values may be derived in part based on parameters such as C_{ss,max} (ng/ml);

$C_{ss,min}$ (ng/ml); $C_{t,min}$ (ng/ml); $t_{ss,max}$ (hr); fluctuation (%) (expressed as the difference between $C_{ss,max}$ and $C_{ss,min}$ expressed as a percentage of $C_{ss,min}$); T_{ss} (days), and any combination thereof.

In certain preferred embodiments, the sustained release hydromorphone formulations of the invention provide an in-vitro dissolution of from about 5% to about 25% hydromorphone released after 1 hour; from about 40% to about 75% hydromorphone released after 8 hours; and not less than about 80% hydromorphone released after 18 hours. In additional preferred embodiments, the sustained release hydromorphone formulations of the invention provide an in-vitro dissolution of from about 10% to about 30% hydromorphone released after 2 hours; from about 40% to about 70% hydromorphone released after 8 hours; and at least about 80% hydromorphone released after 22 hours. The in-vitro dissolution method may be one of those set forth in the appended examples. Alternatively, the in-vitro dissolution method may be, e.g., the USP Paddle or Basket Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C.

In certain preferred embodiments, the once-a-day sustained release oral dosage forms of hydromorphone of the present invention are prepared using ingredients and methods set forth in detail herein with respect to the discussion concerning melt extrusion techniques.

The once-a-day sustained release oral dosage forms of hydromorphone of the present invention may be pH independent, e.g., the in-vitro release rate being independent of pH between pH about 1.7 and about 7.5. Alternatively, the once-a-day sustained release oral dosage forms of hydromorphone of the present invention may be pH dependent.

It has been surprisingly discovered that the hydromorphone sustained release dosage forms of the present invention can be used to provide novel clinical advantages to human patients which have not been achieved heretofore. By virtue of the present invention, the disclosed hydromorphone formulations which exhibit bimodal release can be administered to a human patient in a manner to provide the C_{max} #1, e.g., during waking hours (when the patient experiences pain due to everyday activity e.g. physical or mental effort); and to provide the

C_{max} #2, e.g., at bedtime of the patient (to alleviate pain and to allow the patient to obtain a restful sleep). Alternatively, the hydromorphone dosage form can be administered in a manner to provide the C_{max} #1 at the bedtime of the patient and the C_{max} #2 during waking hours.

The present invention is also directed to the discovery that hydromorphone sustained release dosage forms as disclosed herein, do not alter the profile of hydromorphone metabolism in human patients as compared to immediate release formulations. This discovery was surprising because hydromorphone is metabolized by several competitive pathways. Due to the metabolic pathway of hydromorphone, it was expected that the slow rate of delivery of hydromorphone to the liver from the sustained release dosage form would result in the utilization of different metabolic pathways and generate major differences in metabolic profiles as compared to the immediate release product. Thus, in preferred embodiments of the invention, the total amount of hydromorphone and its active or inactive metabolites (hydromorphone-3-glucuronide, dihydromorphine-6-glucuronide, hydromorphone-3-glucoside, dihydromorphine-6-glucoside, dihydromorphine and dihydro-iso-morphine) generated, or the type of metabolites being generated or observed, during the dosage interval (e.g., about 24 hours) is no more than about 30-40% different than the total amount of hydromorphone and its active or inactive metabolites generated during the same time period using immediate release preparations, and in certain preferred embodiments, the total amount (or type) generated is not significantly different.

The term "hydromorphone" is defined for purposes of the present invention as any pharmaceutically acceptable form of the drug, preferably in the form of the hydrochloride salt, but alternatively in the form of molar equivalent amounts of other hydromorphone salts, the hydromorphone base, or complexes of hydromorphone.

The term "sustained release" is defined for purposes of the present invention as the release of the drug (opioid analgesic) from the formulation at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range (above the minimum effective analgesic concentration or "MEAC") but below toxic levels over a period of time of about 24 hours or longer.

The term "minimum effective analgesic concentration" is defined for purposes of this invention as the minimum effective therapeutic plasma level of the drug at which at least some pain relief is achieved in a given patient. It will be well understood by those skilled in the medical art that pain measurement is highly subjective and great individual variations may occur among patients.

USP Paddle or Basket Method is the Paddle and Basket Method described, e.g., in U.S. Pharmacopoeia XXII (1990), herein incorporated by reference.

The term "Tmax #1" is defined for purposes of the invention as the time period which elapses after administration of the dosage form at which the plasma concentration of hydromorphone attains the first of two highest peak plasma concentrations during the dosage interval, i.e., about 24 hours.

The term "Cmax #1" is defined for purposes of the invention as the plasma concentration of hydromorphone at Tmax #1.

The term "Tmax #2" is defined for purposes of the invention as the time period which elapses after administration of the dosage form at which the plasma concentration of hydromorphone attains the second of two highest peak plasma concentrations during the dosage interval (i.e., about 24 hours).

The term "Cmax #2" is defined for purposes of the invention as the plasma concentration of hydromorphone at Tmax #2.

For purposes of the invention, the term "Cmax" (without a designated numerical indicia) is the highest plasma concentration of hydromorphone attained within the dosing interval, i.e., about 24 hours. Thus, the term "Cmax" (without designated numerical indicia) reflects the greater of either Cmax #1 or Cmax #2.

For purposes of the invention, the term "Cmin#1" is the lowest plasma concentration of hydromorphone attained between Cmax#1 and Cmax#2.

For purposes of the invention, the term "Cmin#2" is the lowest plasma concentration of hydromorphone attained within the dosing interval (i.e., about 24 hours) after Cmax#2 (for single

dose administration), or between $C_{max\#2}$ and the $C_{max\#1}$ of the next dosage interval (for steady-state administration).

For purposes of the invention, the term "T_{max}" (without a designated numerical indicia) is the time period which elapses after administration of the dosage form at which the plasma concentration of hydromorphone attains the highest plasma concentration of hydromorphone attained within the dosing interval (i.e., about 24 hours). Thus, the term "T_{max}" (without designated numerical indicia) is indicative of the greater of either $C_{max\#1}$ or $C_{max\#2}$.

For purposes of the invention, the term percent fluctuation is defined as the $(C_{max} - C_{min})/C_{min} \times 100$ (for an individual patient). The percent fluctuation for a patient population is defined as $(\text{the mean } C_{max} - \text{the mean } C_{min})/\text{the mean } C_{min} \times 100$.

The term "pH-dependent" for purposes of the invention is defined as having characteristics (e.g. dissolution) which vary according to environmental pH (e.g., due to changes in the in-vitro dissolution media, or due to passage of the dosage form through the gastrointestinal tract).

The term "pH-independent" for purposes of the invention is defined as having characteristics (e.g., dissolution) which are substantially unaffected by pH, in that a difference, at any given time, between an amount of opioid released at one pH and an amount released at any other pH, when measured in-vitro using the USP Paddle Method of U.S. Pharmacopeia XXII (1990) at 100 rpm in 900 ml aqueous buffer, is no greater than 10%.

The term "mean residence time" (MRT) is defined as the average time a drug molecule stays in the body. This calculation, which is a function of absorption, distribution and elimination, is dependent in part, on the dosage form containing the active ingredient.

Unless specifically designated as "single dose" or at "steady-state," the pharmacokinetic parameters disclosed and claimed herein encompass both single dose and steady-state conditions. In other words, in general, the pharmacokinetic parameters under these conditions are not substantially changed with respect to single dose or steady-state conditions.

For purposes of the invention, unless further specified, the term “a patient” means that the discussion (or claim) is directed to the pharmacokinetic parameters of an individual patient and/or the mean pharmacokinetic values obtained from a population of patients.

The term “breakthrough pain” means pain which the patient experiences despite the fact that the patient is being administered generally effective amounts of the sustained release solid oral dosage forms of the invention containing hydromorphone.

The term “rescue” refers to a dose of an analgesic which is administered to a patient experiencing breakthrough pain.

The term “effective pain management” means an objective evaluation of a human patient’s response (pain experienced versus side effects) to analgesic treatment by a physician as well as subjective evaluation of therapeutic treatment by the patient undergoing such treatment. One skilled in the art will understand that effective analgesia will vary according to many factors, including individual patient variability.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

Figure 1 is a graphical representation of the dissolution (mean percent dissolved over time) for Examples 1 and 2.

Figure 2 is a graphical representation of the concentration of Example 3 (fed and fasted) over time, versus Dilaudid.

Figure 3 is a graphical representation of the concentration of Example 4 (fed and fasted) over time, versus Dilaudid.

Figure 4 is a graphical representation of the plasma concentration over time for Example 7.

Figure 5 is a graphical representation of the plasma concentration over time for Example 8.

Figure 6 provides the mean plasma concentration over time (up to 30 hours) for HHCR 12 mg, HHCR 24 mg, and Dilaudid.

Figure 7 provides the mean plasma concentration-time course data for Example 12.

Figure 8 provides the mean trough values (ng/ml) over time for HHIR and HHCR.

Figure 9 provides the mean subject drug effect (VAS, mm) over time for HHIR and HHCR.

Figure 10 provides a graphical representation of the mean plasma hydromorphone concentration (ng/ml) and mean subject drug effect (VAS, mm) over time for HHCR.

Figure 11 provides a graphical representation of the mean plasma hydromorphone concentration (ng/ml) and mean subject drug effect (VAS, mm) over time for HHIR.

DETAILED DESCRIPTION

The sustained release formulations of the present invention include hydromorphone as the therapeutically active opioid in an amount of hydromorphone hydrochloride from about 0.5 to about 100 mg or more, preferably from about 2 mg to about 84 mg, e.g. 4 mg, 8 mg, 12 mg, 16 mg, 24 mg, 32 mg, 64 mg and 84 mg. Alternatively, the dosage form may contain molar equivalent amounts of other hydromorphone salts or of the hydromorphone base.

Hydromorphone formulations in accordance with the current invention provide a highly desirable pharmacokinetic profile that includes a bi-phasic absorption pattern. In preferred embodiments, the formulation provides a rapid initial absorption phase followed by a slow absorption for sustained pain relief. The short elimination half-life of hydromorphone, combined with the rapid absorption phase of the preferred embodiments, permits prompt attainment of steady-state, a stable therapeutic profile, and an early assessment of the patient's pain status. This absorption profile affords pain relief both early and throughout the 24-hour dosing period. The disclosed hydromorphone formulations can then be used for dose titration as well as maintenance therapy.

It is contemplated that administration of the solid oral sustained release hydromorphone formulations to human patients will result in effective pain management, upon titration of the patient to an effective dosage of hydromorphone. Surprisingly, human patients can be titrated to steady-state using the sustained release dosage forms of the invention rather than titrating with immediate release hydromorphone, and steady-state is typically reached rapidly, e.g., within about 2 doses of the sustained release dosage form. In view of the many factors which must be taken into account by the health care practitioner in evaluating the treatment of a patient's pain, it is contemplated that the effective pain management of human patients using the sustained release dosage forms of the invention will nevertheless include the possibility and even the likelihood that doses of immediate release analgesics (i.e., rescue dosages) will be administered from time to time in order to treat breakthrough pain.

The sustained release hydromorphone formulations of the invention may be used to treat chronic malignant or non-malignant pain, cancer pain, postoperative pain, pain due to acute myocardial infarction, acute attacks of biliary stone pain, pain arising from sickle cell anemia, trauma, biliary and renal colic, burns, tissue, bone and rectal pain, etc. This list is merely representative and is not meant to be exclusive.

The sustained release dosage forms of the present invention generally achieve and maintain therapeutic levels substantially without significant increases in the intensity and/or degree of concurrent side effects, such as nausea, vomiting or drowsiness, which are often associated with high blood levels of opioid analgesics. There is also evidence to suggest that the use of the present dosage forms leads to a reduced likelihood of inappropriate self-administration by a drug abuser.

The sustained release hydromorphone formulations of the present invention are preferably bioavailable. It is generally recognized that the mere presence of an active substance in the gastrointestinal fluids does not, by itself, insure bioavailability. In order to be absorbed, the active drug substance must be in solution. The time required for a given proportion of an

active substance from a unit dosage form is determined as the proportion of the amount of active drug substance released from a unit dosage form over a specified time base by a test method conducted under standardized conditions. The physiologic fluids of the gastrointestinal tract are the media for determining dissolution time. The present state of the art recognizes many satisfactory test procedures to measure dissolution time for pharmaceutical compositions, and these test procedures are described in official compendia world-wide.

Although there are many diverse factors which influence the dissolution of drug substance from its carrier, the dissolution time determined for a pharmacologically active substance from the specific composition is relatively constant and reproducible. Among the different factors affecting the dissolution time are the surface area of the drug substance presented to the dissolution solvent medium, the pH of the solution, the solubility of the substance in the specific solvent medium, and the driving forces of the saturation concentration of dissolved materials in the solvent medium. Thus, the dissolution concentration of an active drug substance is dynamically modified in its steady state as components are removed from the dissolution medium through absorption across the tissue site. Under physiologic conditions, the saturation level of the dissolved materials is replenished from the dosage form reserve to maintain a relatively uniform and constant dissolution concentration in the solvent medium providing for a steady state absorption.

The transport across a tissue absorption site of the gastrointestinal tract is influenced by the Donnan osmotic equilibrium forces on both sides of the membrane since the direction of the driving force is the difference between the concentrations of active substance on either side of the membrane, i.e., the amount dissolved in the gastrointestinal fluids and the amount present in the blood. Since the blood levels are constantly being modified by dilution, circulatory changes, tissue storage, metabolic conversion and systemic excretion, the flow of active materials is directed from the gastrointestinal tract into the blood stream.

Notwithstanding the diverse factors influencing both dissolution and absorption of a drug substance, a strong correlation has been established between the in-vitro dissolution time

determined for a dosage form and (in-vivo) bioavailability. The dissolution time and the bioavailability determined for a composition are two of the most significant fundamental characteristics for consideration when evaluating sustained-release compositions. Surprisingly however, the dissolution profiles of the once-a-day sustained release oral hydromorphone formulations of the invention are not predictive of the bimodal plasma concentration curve (meaning the occurrence of a T_{max} #1 and T_{max} #2 as described herein).

Sustained release dosage forms having the desired inventive characteristics can be formulated as a pharmaceutically acceptable tablet, caplet, or multiparticulate formulation known to those skilled in the art. The sustained release dosage form may optionally include a sustained released carrier which is incorporated into a matrix along with the hydromorphone, or which is applied as a sustained release coating. The sustained release dosage forms of the current invention are preferably pH-independent, e.g. the dissolution of hydromorphone being independent of pH over the range of about 1.6 to about 7.2.

The sustained release dosage form may include a portion of the hydromorphone in sustained release form and remaining portion of the hydromorphone in immediate release form. For example, the sustained release dosage form may have a relatively larger portion of the hydromorphone in sustained release form and a smaller portion of the hydromorphone incorporated into the dosage form in immediate release form.

An oral dosage form according to the invention may be provided as, for example, granules, spheroids, beads, pellets (hereinafter collectively referred to as "multiparticulates") or a tablet. An amount of the multiparticulates effective to provide the desired dose of hydromorphone over time may be placed in a capsule or may be incorporated in any other suitable oral solid form.

In further aspects of the invention, when the hydromorphone is formulated in a capsule, the capsule can be opened and the contents sprinkled on applesauce or other soft foods for easier administration to patients who have difficulty swallowing pills. The pharmacokinetics of the hydromorphone administered in this manner are not significantly different than swallowing the

dosage form whole.

The dosage forms of the present invention may further include one or more additional drugs which may or may not act synergistically with the hydromorphone analgesics of the present invention. Examples of such additional drugs include non-steroidal anti-inflammatory agents, including ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acetaminophen, fentiazac, clidanac, oxipinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolafenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, and the like. Such non-steroidal anti-inflammatory agents also include cyclo-oxygenase inhibitors such as celecoxib (SC-58635), DUP-697, flosulide (CGP-28238), meloxicam, 6-methoxy-2 naphthylacetic acid (6-MNA), Vioxx (MK-966), nabumetone (prodrug for 6-MNA), nimesulide, NS-398, SC-5766, SC-58215, and T-614. as amantadine (1-aminoadamantine), and memantine (3,5 dimethylaminoadamantane), their mixtures and pharmaceutically acceptable salts thereof.

Other additional drugs include nontoxic NMDA receptor antagonists such as dextrorphan, dextromethorphan, 3-(1-naphthalenyl)-5-(phosphonomethyl)-L-phenylalanine, 3-(1-naphthalenyl)-5-(phosphonomethyl)-DL-phenylalanine, 1-(3,5-dimethylphenyl)naphthalene, and 2-(3,5-dimethylphenyl) naphthalene, 2SR,4RS-4-(((1H-Tetrazol-5-yl)methyl)oxy)piperidine-2-carboxylic acid; 2SR,4RS-4-(((1H-Tetrazol-5-yl)methyl)oxy)methyl)piperidine-2-carboxylic acid; E and Z 2SR-4-(O-(1H-Tetrazol-5-yl)methyl)ketoximino)piperidine-2-carboxylic acid; 2SR,4RS-4-((1H-Tetrazol-5-yl)thio)piperidine-2-carboxylic acid; 2SR,4RS-4-((1H-Tetrazol-5-yl)thio)piperidine-2-carboxylic acid; 2SR,4RS-4-(5-mercapto-1H-Tetrazol-1-yl)piperidine-2-carboxylic acid; 2SR,4RS-4-(5-mercapto-2H-Tetrazol-2-yl)piperidine-2-carboxylic acid; 2SR,4RS-4-(5-mercapto-1H-Tetrazol-1-yl)piperidine-2-carboxylic acid; 2SR,4RS-4-(5-mercapto-2H-Tetrazol-2-yl)piperidine-2-carboxylic acid; 2SR,4RS-4-(((1H-Tetrazol-5-yl)thio)methyl)piperidine-2-carboxylic acid; 2SR,4RS-4-((5-mercapto-1H-Tetrazol-1-

yl)methyl)piperidine-2-carboxylic acid; or 2SR,4RS-4-((5-mercapto-2H-Tetrazol-2-yl)methyl)piperidine-2-carboxylic acid, their mixtures and pharmaceutically acceptable salts thereof.

Other suitable additional drugs which may be included in the dosage forms of the present invention include acetaminophen, aspirin, neuro-active steroids (such as those disclosed in U.S. Serial No. 09/026,520, filed February 20, 1998, hereby incorporated by reference) and other non-opioid analgesics.

For example, if a second (non-opioid) drug is included in the formulation, such drug may be included in controlled release form or in immediate release form. The additional drug may be incorporated into the controlled release matrix along with the opioid; incorporated into the controlled release coating; incorporated as a separated controlled release layer or immediate release layer; or may be incorporated as a powder, granulation, etc., in a gelatin capsule with the substrates of the present invention. In such combination products, the hydromorphone component can be included in an amount from about 0.5 to about 100 mg, preferably from about 2 mg to about 84 mg, e.g. 4 mg, 8 mg, 12 mg, 16 mg, 24 mg, 32 mg, 64 mg or 84 mg.

Sustained Release Coatings

In certain preferred embodiments, the hydromorphone is incorporated into or onto a substrate and a sustained release coating is applied thereto. For example, the hydromorphone may be contained within or on a substrate as follows: (i) incorporated into matrix spheroids (e.g., together with a pharmaceutically acceptable spheronizing agent such as microcrystalline cellulose), (ii) coated onto inert pharmaceutically acceptable beads (e.g., nonpareil beads); (iii) incorporated into a normal release tablet core; or (iv) incorporated into a tablet core which comprises a matrix including a sustained release carrier material. Thereafter, a sustained release coating is applied onto substrates such as those mentioned in (i)-(iv) above. The dosage forms of the present invention may optionally be coated with one or more materials 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. A pH-dependent coating serves to release the opioid in desired areas of the gastro-intestinal (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. 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. 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.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the 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 shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) comprising the hydromorphone is coated with a hydrophobic 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. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. Such formulations are described, e.g., in detail in U.S. Patent Nos. 5,273,760 and 5,286,493, assigned to the Assignee of the present invention and hereby incorporated by reference. The particles are preferably film coated with a material that permits release of the hydromorphone so as to achieve, in combination with the other stated properties, a desired in-vitro release rate and in-vivo plasma levels. The sustained release coating formulations of the present invention should be capable of producing a strong, continuous film that is smooth and

elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Other examples of sustained release formulations and coatings which may be used in accordance with the present invention include Assignee's U.S. Patent Nos. 5,324,351; 5,356,467, and 5,472,712, hereby incorporated by reference in their entirety.

Alkylcellulose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads 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 in any combination, as all or part of a hydrophobic coating according to the invention.

One commercially-available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pennsylvania, U.S.A.). 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.

Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pennsylvania, U.S.A.). 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.

Acrylic Polymers

The hydrophobic material comprising the controlled release coating may comprise a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl 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.

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.

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.

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® from Röhm Tech, Inc. 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.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic

resin lacquers commercially available from Rohm Pharma under the Tradenames 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.

The Eudragit RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained 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.

Plasticizers

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material such as an alkylcellulose or an acrylic polymer, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained 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 sustained 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.

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.

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.

It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

When the aqueous dispersion of hydrophobic material is used to coat a substrate

including the hydromorphone, for example, inert pharmaceutical beads such as nu pariel 18/20 beads, a plurality of the resultant stabilized solid controlled release beads may thereafter 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. Alternatively, the substrate may be a tablet core coated with the sustained release coating, and optionally a further film-forming agent or colorant, such as Opadry®.

In formulations where an aqueous dispersion of an hydrophobic polymer such as an alkylcellulose is applied to the substrate, it is preferred that the coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer and at a relative humidity above ambient conditions, until an endpoint is reached at which the coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, in such formulations the curing time is about 24 hours or more, and the curing conditions may be, for example, about 60°C and 85% relative humidity. Detailed information concerning the stabilization of such formulations is set forth in U.S. Patent Nos. 5,273,760; 5,681,585; and 5,472,712; all of which are hereby incorporated by reference in their entireties.

In formulations where an aqueous dispersion of an acrylic polymer is applied to the substrate, it is preferred that the coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer until an endpoint is reached at which the coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, the curing time is about 24 hours or more, and the curing temperature may be, for example, about 45°C. Detailed information concerning the stabilization of such formulations is set forth in U.S. Patent Nos. 5,286,493; 5,580,578; and 5,639,476; all of which are hereby incorporated by reference in their entireties.

The sustained release profile of the coated formulations of the invention can be altered, for example, by varying the amount of overcoating with the aqueous dispersion of hydrophobic

material, altering the manner in which the plasticizer is added to the aqueous dispersion of hydrophobic material, by varying the amount of plasticizer relative to hydrophobic 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 retardant coating.

Spheroids or beads 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 Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the opioid to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropylmethylcellulose, etc. with or without colorant (e.g., Opadry®, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. 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.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic 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.

The coating solutions of the present invention preferably contain, in addition to the filmBformer, 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 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 the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

The plasticized aqueous dispersion of hydrophobic 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 sustained release of the therapeutically active agent (i.e., hydromorphone) when the 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 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.

The release of the hydromorphone from the sustained 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 material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

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.

The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The sustained 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.

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.

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Patent Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864 (all of which are hereby incorporated by reference). The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

Sustained Release Matrices

In certain preferred embodiments of the present invention, the sustained release formulation comprises a matrix including the hydromorphone and a sustained release carrier (which may comprise one or more hydrophobic materials, such as an alkylcellulose and/or an acrylic polymer as previously defined herein). The materials suitable for inclusion in a sustained release matrix will depend on the method used to form the matrix.

Suitable materials for inclusion in the sustained release matrices of the invention, in addition to the hydromorphone, include:

(A) hydrophilic and/or hydrophobic materials, such as gums; alkylcelluloses; cellulose ethers, including hydroxyalkylcelluloses and carboxyalkylcelluloses; acrylic resins, including all

of the acrylic polymers and copolymers discussed above, and protein derived materials. This list is not meant to be exclusive, and any pharmaceutically acceptable hydrophobic material or hydrophilic material which is capable of imparting the desired sustained release profile of the hydromorphone is meant to be included herein. The dosage form may comprise, e.g., from about 1% to about 80% by weight of such material.

In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl 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), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and mixtures of the foregoing. In yet other embodiments, the hydrophobic material is an alkylcellulose.

(B) digestible, long chain (C_8 - C_{50} , especially C_{12} - C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and natural or synthetic waxes, polyhydric alcohols, including polyalkylene glycols. The oral dosage form may contain up to 60% (by weight) of such material. In certain embodiments, a combination of two or more hydrocarbon materials are included in the matrix formulations. If an additional hydrocarbon material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same.

Preferred hydrocarbons are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends, and have a melting point from about 301° to about 2001° C, preferably from about 451° to about 901° C.

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 301° to

about 1001° C. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax.

The aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl, cetyl and/or cetostearyl alcohol. The amount of aliphatic alcohol, if included in the present oral dosage form, will be determined, as above, by the precise rate of hydromorphone release required. In certain embodiments, the oral dosage form contains between 20% and 50% (by wt) aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

In one 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 opioid from the formulation.

Suitable polyalkylene glycols include, for example, polypropylene glycol or 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.

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 order to facilitate the preparation of a solid, sustained release, oral dosage form according to this invention, any method of preparing a matrix formulation known to those skilled in the art may be used. For example incorporation in the matrix may be effected, for example, by (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and opioid or an opioid 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/opioid with water. In a particularly 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 opioid.

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 (Trade Mark, FMC Corporation). 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 hydroxypropylcellulose, 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 copolymer, or ethyl cellulose. In such embodiments, the sustained release coating will generally include a hydrophobic material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

Melt Extrusion Matrices

In certain preferred embodiments of the present invention, the sustained release matrices also be prepared via melt-granulation or melt-extrusion techniques. Such formulations are described in U.S. Patent Application Serial No. 08/334,209, filed November 4, 1994 and U.S. Patent Application Serial No. 08/833,948, filed April 10, 1997, both of which are hereby incorporated by reference in their entireties. Generally, melt-granulation techniques involve melting a normally solid hydrophobic material, e.g. a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate an additional hydrophobic substance, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic material. Examples of sustained release formulations prepared via melt-granulation techniques are found in U.S. Patent No. 4,861,598, assigned to the Assignee of the present invention and hereby incorporated by reference in its entirety.

The additional hydrophobic 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 constant 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 substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

In addition to the above ingredients, a sustained 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. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation. In addition to the above ingredients, a sustained release matrix incorporating melt-extruded multiparticulates 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.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986), incorporated by reference herein.

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the opioid analgesic (i.e., hydromorphone) together with at least one hydrophobic material and preferably the additional hydrophobic 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 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 sustained release of the therapeutically active agent for a time period of from about 8 to about 24 hours. The

multiparticulates may be divided into unit doses via placement into a gelatin capsule, or may be compressed into a suitable tablet form.

An optional process for preparing the melt extrusions of the present invention includes directly metering into an extruder a hydrophobic material, a therapeutically active agent, and an optional binder; 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.

The diameter of the extruder aperture or exit port can also 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.

The 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 material as described herein. In this regard, 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.

In one preferred embodiment, oral dosage forms are prepared to 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 sustained release dose when ingested and contacted by gastric fluid.

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, (Arthur Osol, editor), 1553-1593 (1980), incorporated by reference herein.

In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Patent No. 4,957,681 (Klimesch, et. al.), described in additional detail above and hereby incorporated by reference.

Optionally, the sustained release melt-extruded multiparticulate systems or tablets can be coated, or the gelatin capsule can be further coated, with a sustained release coating such as the sustained release coatings described above. Such coatings preferably include a sufficient amount of hydrophobic material to obtain a weight gain level from about 2 to about 30 percent, although the overcoat may be greater depending upon the physical properties of the particular opioid analgesic compound utilized and the desired release rate, among other things.

The melt-extruded unit dosage forms of the present invention may further include combinations of melt-extruded multiparticulates containing one or more of the therapeutically active agents disclosed above before being encapsulated. Furthermore, the unit 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 the multiparticulates after preparation of the dosage forms (e.g., controlled release coating or matrix-based). The unit dosage forms of the present invention may also contain a combination of controlled release beads and matrix multiparticulates to achieve a desired effect.

The sustained 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 sustained release profile of the melt-extruded formulations of the invention

can be altered, for example, by varying the amount of retardant, i.e., hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

In other embodiments of the invention, the melt extruded material is 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.

Immediate Release Component

In certain preferred embodiments of the present invention, an effective amount of hydromorphone in immediate release form is included in the 24 hour sustained release unit dose hydromorphone formulation to be administered. The immediate release form of the hydromorphone is included in an amount which is effective to shorten the time to the first C_{max} of the hydromorphone in the blood (e.g., plasma). In such embodiments, an effective amount of the hydromorphone in immediate release form may be coated onto the substrates of the present invention. For example, where the extended release hydromorphone 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 may be coated onto the surface of substrates wherein the hydromorphone is incorporated in a controlled release matrix. Where a plurality of the sustained release substrates comprising an effective unit dose of the hydromorphone (e.g., multiparticulate systems including pellets, spheres, beads and the like) are incorporated into a hard gelatin capsule, the immediate release portion of the opioid dose may be incorporated into the gelatin capsule via inclusion of the sufficient amount of immediate release hydromorphone as a powder or granulate within the capsule. Alternatively, the gelatin capsule itself may be coated with an immediate release layer of the hydromorphone. One skilled in the

art would recognize still other alternative manners of incorporating the immediate release hydromorphone portion into the unit dose. Such alternatives are deemed to be encompassed by the appended claims. It has been discovered that by including such an effective amount of immediate release hydromorphone in the unit dose, the experience of relatively higher levels of pain in patients is significantly reduced.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

In preferred embodiments of the invention, the different dosage form strengths be dose proportional in order to facilitate safe and convenient transfer from one strength to another during therapy. In the following examples, the 12 mg and 24 mg dosage strengths exhibit pharmacokinetic linearity (dose proportionality) with respect to the maximum plasma hydromorphone concentration (C_{\max}) and total exposure (AUC). This equivalence can be inferred for the other strengths because the composition of the pellets is uniform in all capsule strengths.

The following examples illustrate various aspects of the present invention based on preliminary investigations. They are not to be construed to limit the claims in any manner whatsoever.

MELT-EXTRUSION TECHNIQUES

Typical melt extrusion systems capable of carrying-out the present invention include a suitable extruder drive motor having variable speed, torque control, and start-stop controls. In addition, the 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 system will include an extruder such as a single-screw extruder, twin-extruder which consists of two counter-rotating intermeshing screws enclosed within a cylinder

or barrel having an aperture or die at the exist thereof. The feed materials enter through a feed hopper and is moved through the barrel by the screws and is 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 a multiparticulate system. The pelletizer can consist of rollers, fixed knife, rotating cutter and the like. Suitable instruments and systems are available from distributors such as C.W. Brabender Instruments, Inc. of South Hackensack, New Jersey, or Leistritz of Somerville, New Jersey. Other suitable apparatus will be apparent to those of ordinary skill in the art.

The melt extruded product is preferably 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. It has been found that 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). It has been found that 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.

A general procedure for preparing melt extrusion formulations useful in the present invention is as follows. First, the required amount of drug (hydromorphone), hydrophobic material and binder are blended, along with any additional excipients. Next, a powder feeder is charged with the proper amount of drug/excipient blend. The temperatures of the extruder heating zones are set to the required temperature, depending on the formulation. Typically, in the Leistritz extruder, the temperatures should be set from about 701° to about 1051°C. The blend is preferably not fed into the extruder until the corresponding heating zones reach steady temperatures. Preferably, the extruder screw rotation speed may be set to, e.g., about 200 rpm,

and the feeder, the conveyor and the pelletizer are actuated. After the excipients in the blend are (preferably) softened and the drug is embedded in the softened mixture, the resultant viscous mass is extruded as spaghetti-like strands. The diameter of the extruder aperture can be adjusted to vary the thickness of the resulting strand. The conveyor belt speed may be set to an appropriate speed (e.g., 3-100 ft/min). The extruded semisolid strand(s) are allowed to congeal and/or harden while transported to the pelletizer on the conveyor belt. Additional cooling devices may be needed to ensure proper congealing (the conveyor belt may not be needed to cool the strand, if the material congeals rapidly enough). The roller knife is preferably set to an appropriate speed (e.g., to 3-100 ft/min and 100-800 rpm), and the congealed strands are preferably cut to desired size (e.g., 0.5-5 mm in diameter, e.g., 0.3.5 mm in length). The product, in the form of pellets, is then collected. A desired weight of pellets may then be filled into hard gelatin capsules to obtain an appropriate dose of the drug or, alternatively, the pellets can be milled and compressed into tablets.

Dissolution Method

The following dissolution method was used to obtain dissolution profiles for the dosage forms of the Examples: (USP II Paddle at 100 rpm at 37°C). The media is as follows: 1st hour in 700 ml simulated gastric fluid (SGF), pH 1.2 without enzyme, and thereafter, 900 ml simulated intestinal fluid (SIF), pH 7.5 without enzyme. HPLC procedures may be used for assaying.

EXAMPLES 1-2

In Examples 1-2, hydromorphone hydrochloride controlled release pellets were prepared according to the above manufacturing procedure using Eudragit RSPO and Eudragit L-100 as the retardants. The formulations are set forth in Tables 1 and 2 below. The dissolution of these formulations is set forth in Figure 1.

Table 1

<u>Ex.1 -Composition</u>	<u>Amt. (mg) per capsule</u>
Hydromorphone Hydrochloride	8
Eudragit RSPO	67.2
Eudragit L-100	11.2
Stearic Acid	33.6
Total	120

Table 2

<u>Ex. 2 - Composition</u>	<u>Amt. (mg) per capsule</u>
Hydromorphone Hydrochloride	8
Eudragit RSPO	36
Eudragit L-100	6
Stearic Acid	18
Talc	52
Total	120

Example 3

Hydromorphone HCL once-a-day capsules were produced with the formula set forth in Table 3 below, using the melt extrusion methods and technology described above.

Table 3

<u>Ingredients</u>	<u>Amt(mg)/Capsule</u>	<u>Percentage in Formula</u>
Hydromorphone HCL	8	10
Eudragit RSPO	53	66.25
Stearyl Alcohol	19	23.75
Total	80	100

Pellets of 1.0 mm in diameter and 1.0 mm in length were prepared. Each capsule holds

80 mg of pellets and contains 8 mg of hydromorphone HCL.

The above capsules were tested using the dissolution methodology described above, and were found to have the dissolution results set forth in Table 4 below:

TABLE 4

Time (hr)	1	2	4	8	12	18	24
Mean % dissolved	17	28	32	45	56	69	82

Example 4

Hydromorphone HCL once-a-day capsules were produced with the formula set forth in Table 5 below:

TABLE 5

Ingredients	Amt(mg)/Capsule	Percentage in Formula
Hydromorphone HCL	8	10
Eudragit RSPO	48	60
Stearyl Alcohol	24	30
Total	80	100

The pellet manufacturing procedure and the dissolution method are the same as described in Example 3.

The above capsules were found to have the dissolution results set forth in Table 6 below:

TABLE 6

Time (hr)	1	2	4	8	12	18	24
Mean % dissolved	23	29	40	56	69	84	96

Example 5

Hydromorphone HCL once-a-day capsules were produced with the following formula set forth in Table 7 according to the method described in Example 3 .

TABLE 7

Ingredients	Amt(mg)/Capsule	Percentage in Formula
Hydromorphone HCL	8	10
Eudragit RSPO	41.5	51.9
Eudragit L-100	8.5	10.6
Stearic Acid	22	27.5
Total	80	100

The manufacturing procedure of the pellets and the dissolution method are the same as described in Example 3. The above capsules were found to have the following dissolution results set forth in Table 8:

TABLE 8

Time (hr)	1	2	4	8	12	18	24
Mean % dissolved	4	14	36	52	64	75	84

EXAMPLE 6

A bioavailability study of hydromorphone capsules of Examples 3 and 4 was conducted using a single dose, five-way crossover study in 12 normal male volunteers. The subjects received either 8 mg of Dilaudid tablet (immediate release hydromorphone commercially available from Knoll) or 8 mg of sustained release hydromorphone capsules. Dilaudid tablets were administered after an overnight fast. Hydromorphone sustained release capsules were administered with or without food. Blood samples were taken periodically and assayed for hydromorphone concentrations using gas chromatography with mass detection (G/MS). From the data, the following pharmacokinetic parameters were calculated as set forth in Table 9 below:

TABLE 9

Treatment	AUC, ng•hr/ml	Cmax, ng/ml	Tmax, hr
Example 3, fasted	19.23	0.76	3.9
Example 3, fed	21.47	0.93	1.9
Example 4, fasted	19.00	0.72	6.8
Example 4, fed	20.10	0.75	2.4
Dilaudid, fasted	14.55	3.69	0.7

From the above data, both formulations 3 and 4 provide bioavailable formulations without a fed/fast effect which are suitable for once daily administration. The data of Example 3 is shown graphically in Figure 2 and the data of Example 4 is shown graphically in Figure 3.

EXAMPLE 7

To assess steady state plasma levels of hydromorphone, a two-way crossover study was conducted in 12 normal male volunteers. The subjects received either 4 mg of Dilaudid (immediate release) every 6 hours or 16 mg of the capsules according to Example 3 every 24 hours. Venous blood samples were taken at predetermined time points. The plasma

hydromorphone concentrations were quantitated using gas chromatography with mass detection (G/MS). From the data from day 4, the following pharmacokinetic parameters were calculated and are set forth in Table 10 below.

TABLE 10

Treatment	AUC, ng•hr/ml	Cmax, ng/ml	Cmin, ng/ml	Tmax, hr
Example 3	36.08	2.15	1.49	5.8
Dilaudid	33.53	3.44	0.94	1.6

The results are shown graphically in Figure 4. From this data it can be seen that Example 3 provides bioavailable formulations suitable for once-a-day administration.

EXAMPLE 8

To assess bioavailability and effect of food on hydromorphone sustained release capsules, a single dose, three-way crossover study was conducted in 12 normal male volunteers. The subjects received either 8 mg of Dilaudid tablet (immediate release) or 8 mg of hydromorphone sustained release capsules of Example 5. Dilaudid tablets were administered after an overnight fast. The capsules of Example 5 were administered with or without food. Venous blood samples were taken at predetermined time points. The plasma hydromorphone concentrations were quantitated using gas chromatography with mass detection (GC/MS).

From the data, the following pharmacokinetic parameters were calculated and are set forth in Table 11 below:

TABLE 11

Treatment	AUC, ng•hr/ml	Cmax, ng/ml	Tmax, hr
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Example 5, fasted	15.83	0.52	5.6
Example 5, fed	16.55	0.65	4.1
Dilaudid, fasted	16.54	3.15	0.8

From the above data it is shown that suitable for once-a-day hydromorphone product can be produced using different ingredients than are used for Examples 3 and 4. This data is shown graphically in Figure 5.

REVIEW OF BI-MODAL PLASMA CONCENTRATION

Examples 9-10

Hydromorphone HCL once-a-day capsules were produced with the following formula set forth in Table 12 (Example 9) and Table 13 (Example 10) according to the method described in Example 3. The pellets were prepared by first mixing the Hydromorphone HCl with the retardant polymers. Then, using a twin screw melt extruder (Leistritz), the material was heated and extruded into 1 mm diameter "spaghetti like" extrudate. This extrudate was cooled on a conveyor belt and cut into 1mm length pellets using a rotating knife pelletizer. These pellets were then collected and filled in capsules using a capsule filling machine at the appropriate fill weights to produce various strength capsules.

Table 12

<u>Ex. 9 -INGREDIENT</u>	<u>AMOUNT/UNIT</u>
Hydromorphone HCl	12.0 mg
Eudragit RSPO	76.5 mg
Ethocel Std. 7 Premium	4.5 mg
Stearyl Alcohol	27.0 mg
Total	120.0 mg

Table 13

<u>Ex. 10 - INGREDIENT</u>	<u>AMOUNT/UNIT</u>
Hydromorphone HCl	24.0 mg
Eudragit RSPO	153.5 mg
Ethocel Std. 7 Premium	9.0 mg
Stearyl Alcohol	54.0 mg
Total	240.0 mg

The capsules of Examples 9 and 10 were subjected to dissolution according to the following methodology - 900 ml of simulated intestinal fluid (SIF)(USP) having 3 grams/liter of NaCl at pH 7.5. The results are set forth in Table 14 below:

Table 14

<u>Time</u> <u>(hr)</u>	<u>1</u>	<u>2</u>	<u>4</u>	<u>6</u>	<u>12</u>	<u>18</u>	<u>24</u>
Ex. 9	11.3	18.2	31.8	56.0	73.8	90.3	98.9
Ex. 10	11.1	18.3	33.3	58.2	77.0	92.6	98.9

Example 11

In Example 11, a four-treatment, randomized, crossover, analytically blinded single dose study (fed and fasted) was conducted in normal human volunteers. The dosage forms administered were a 12 mg sustained release hydromorphone capsule corresponding to Example 9 (referred to as "HHCR" 12 mg); a 24 mg sustained release hydromorphone capsule corresponding to Example 10 (referred to as "HHCR" 24 mg); and immediate release

hydromorphone 8 mg tablets (bioequivalent to Dilaudid, referred to as "HHIR" 8 mg). The objective was to assess the pharmacokinetic and pharmacodynamic profile of HHCR 24 mg fed and fasted, 12 mg HHCR fasted, and dose proportioned immediate release hydromorphone fasted. The sample size was 28 normal adult males (75 - 100 KG) to complete 24. Blood samples were taken from the volunteers at times 0; 0.25; 0.5; 1; 1.5; 2; 3; 4; 5; 6; 8; 10; 12; 14; 18; 24; 36; 48; 60 and 72 hours. The assay used was a validated GC/MS for hydromorphone.

Table 15 is summary of adjusted hydromorphone pharmacokinetic parameters for HHCR 24 mg fed, HHCR 24 mg fasted, HHCR 12 mg fasted and HHIR 8 mg fasted.

Table 15

Treatment	Parameter	Arithmetic Mean (SD)		Geometric Mean
HHCR 24 mg Fasted				
	AUC (0-Last)	48.66	(13.95)	40.88
	Cmax(ng/ml)	1.27	(0.37)	1.22
	T ½ Abs. (hrs)	10.91	(10.18)	
	T ½ Elim. (hrs)	18.45	(17.18)	
	Tmax (hrs)	21.08	(9.72)	
	Peak Width @50% Cmax	38.27	(9.48)	
	Wag-Nel 50% (hrs)	24.71	(2.29)	
HHCR 24 mg Fed				
	AUC (0-Last)	48.36	(12.60)	44.88
	Cmax(ng/ml)	1.48	(0.49)	1.41
	T ½ Abs. (hrs)	3.92	(4.45)	

T ½ Elim. (hrs)	26.98	(14.03)
Tmax (hrs)	8.54	(0.95)
Peak Width @50% Cmax	26.87	(13.65)
Wag-Nel 50% (hrs)	23.99	(2.84)

HHCR 12mg Fasted

AUC (0-Last)	43.14	(14.07)	41.15
Cmax(ng/ml)	1.50	(0.50)	1.49
T ½ Abs. (hrs)	8.08	(8.34)	
T ½ Elim. (hrs)	20.14	(16.69)	
Tmax (hrs)	16.00	(8.82)	
Peak Width @50% Cmax	26.72	(8.24)	
Wag-Nel 50% (hrs)	21.02	(3.77)	

HHIR 8 mg Fasted

AUC (0-Last)	32.26	(12.23)	28.87
Cmax(ng/ml)	8.36	(3.88)	7.79
T ½ Abs. (hrs)	0.78	(0.41)	
T ½ Elim. (hrs)	1.04	(0.40)	
Tmax (hrs)	0.79	(0.29)	
Peak Width @50% Cmax	1.21	(0.40)	
Wag-Nel 50% (hrs)	6.84	(5.51)	

Note: Concentrations were dose-adjusted to 24 mg, only the AUC and Cmax are affected.
Wag-Nel denotes "Wagner-Nelson".

Table 16 is a summary of the adjusted hydromorphone pharmacokinetic parameters for HHCR 24 mg fed, HHCR 24 mg fasted, HHCR 12 mg fasted, and Dilaudid 8 mg fasted.

Table 16

Parameter		Ratio (%)*	90% CI	
			Lower	Upper
HHCR 24 mg Fed vs. HHCR 24 mg Fasted				
AUC (0-Last)	Arithmetic	95.31	88.12	102.88
	Geometric	96.29	87.38	106.12
Cmax(ng/ml)	Arithmetic	116.87	50.90	186.68
	Geometric	116.01	106.37	128.49
T ½ Abs. (hrs)	Arithmetic	35.94	6.27	65.33
T ½ Elim. (hrs)	Arithmetic	138.72	105.44	170.03
Tmax (hrs)	Arithmetic	40.56	21.61	60.49
Peak Width @50% Cmax	Arithmetic	67.61	56.81	79.19
Wag-Nel 50% (hrs)	Arithmetic	97.10	89.70	102.88

HHCR 24 mg Fasted

vs.

Dilaudid 8 mg Fasted

AUC (0-Last)	Arithmetic	150.83	130.40	161.67
	Geometric	155.31	140.93	171.18
Cmax(ng/ml)	Arithmetic	16.18	4.81	25.14
	Geometric	15.47	14.08	17.01
T ½ Abs. (hrs)	Arithmetic	1397.16	1143.4	2124.7
T ½ Elim. (hrs)	Arithmetic	1875.84	1028.3	2008.9
Tmax (hrs)	Arithmetic	2680.53	3648.0	5404.4
Peak Width @50%	Arithmetic	3160.93	2677.8	3352.5

C_{max}

Wag-Nel 50% (hrs)	Arithmetic	381.24	346.31	385.21
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HHCR 12 mg Fasted

vs.

HHCR 24 mg Fasted

AUC (0-Last)	Arithmetic	88.66	82.10	86.84
	Geometric	89.53	61.24	88.67
C _{max} (ng/ml)	Arithmetic	118.19	53.12	188.81
	Geometric	118.02	108.29	130.81
T ½ Abs. (hrs)	Arithmetic	74.06	44.25	104.30
T ½ Elim. (hrs)	Arithmetic	103.57	72.90	137.49
T _{max} (hrs)	Arithmetic	76.26	56.17	95.08
Peak Width @50% C _{max}	Arithmetic	88.82	58.58	80.84
Wag-Nel 50% (hrs)	Arithmetic	95.71	81.62	94.81

HHCR 12 mg Fasted

vs.

Dilaudid 8 mg Fasted

AUC (0-Last)	Arithmetic	133.73	123.08	148.73
	Geometric	139.06	128.18	163.24
C _{max} (ng/ml)	Arithmetic	17.84	7.88	28.28
	Geometric	18.42	10.76	20.24
T ½ Abs. (hrs)	Arithmetic	1034.74	729.05	1704.3
T ½ Elim. (hrs)	Arithmetic	1840.75	1107.2	2088.2
T _{max} (hrs)	Arithmetic	2028.85	2541.5	4301.0
Peak Width @50% C _{max}	Arithmetic	2208.87	1765.8	2440.5

Wag-Nel 50% (hrs)	Arithmetic	320.44	302.83	851.53
Note: Ratio and 90% CI are based on least squares means				
* Ratio (%): (Test mean/Reference mean) 100%				
Note: Concentrations were dose-adjusted to 24 mg, only the AUC and Cmax are affected.				
Note: Wag-Nel denotes "Wagner-Nelson"				

Table 17 provides a summary of the adjusted plasma hydromorphone concentration (ng/ml) at each sampling time by subject for HHCR 24 mg Fed. Table 18 provides a summary of the adjusted plasma hydromorphone concentration (ng/ml) at each sampling time by subject for HHCR 24 mg Fasted. Table 19 provides a summary of the adjusted plasma hydromorphone concentration (ng/ml) at each sampling time by subject for HHCR 12 mg Fasted. Table 20 provides a summary of the adjusted plasma hydromorphone concentration (ng/ml) at each sampling time by subject for Dilaudid 8 mg Fasted.

The results of this single-dose study show that the 24 mg capsule was dose proportional to the 12 mg capsule based on primary pharmacokinetic metrics. Figure 6 provides the mean plasma concentration over time (up to 30 hours) for HHCR 12 mg, HHCR 24 mg, and Dilaudid.

TABLE 17

Summary Of The Adjusted Plasma Hydromorphone Concentration (ng/mL) At Each Sampling Time By Subject

Treatment: HHCR 24mg Fed

Subject Number	0	0.25	0.5	1	1.5	2	3	4	5	6	8	10	12	14	18	24	36	48	60	72
1	0.00	0.36	0.56	2.08	1.85	1.88	1.36	1.09	0.99	0.78	0.82	0.98	1.15	1.29	1.41	1.07	0.90	0.32	0.19	0.00
3	0.00	0.00	0.14	0.39	0.83	0.82	0.52	0.25	0.32	0.38	0.31	0.48	0.45	0.29	0.22	0.44	0.93	0.23	0.32	0.13
4	0.00	0.00	0.15	0.31	0.72	0.88	0.83	0.76	0.82	0.62	0.49	0.52	0.75	1.02	0.95	0.99	0.83	0.50	0.18	0.10
5	0.00	0.13	0.21	0.79	1.16	1.31	1.48	1.23	1.19	1.01	0.92	0.78	0.90	0.96	1.04	1.54	1.40	0.78	0.49	0.26
6	0.00	0.00	0.22	0.43	0.55	0.74	1.11	0.60	0.71	0.37	1.01	0.67	0.89	0.51	0.36	0.39	0.84	0.62	0.23	0.00
7	0.00	0.00	0.14	0.90	1.22	1.28	1.08	0.79	1.17	1.03	0.69	0.59	0.50	0.49	0.93	0.88	0.75	0.41	0.29	0.25
8	0.00	0.00	0.17	0.22	0.72	0.66	1.20	0.92	0.65	0.76	1.12	0.67	0.89	0.67	0.93	0.73	0.98	0.56	0.28	0.21
9	0.00	0.00	0.19	0.37	0.78	1.00	0.91	0.77	0.47	0.69	0.53	0.26	0.45	0.23	0.52	0.70	0.93	0.25	0.18	0.00
10	0.00	0.00	0.00	0.11	0.83	0.96	1.30	1.72	1.32	1.10	0.97	0.90	0.93	0.82	1.29	1.17	1.44	0.47	0.41	0.20
11	0.00	0.21	0.44	0.72	1.14	1.15	0.92	1.11	1.04	0.96	0.69	0.74	0.46	0.58	0.78	1.42	1.17	0.48	0.26	0.17
12	0.00	0.00	0.18	0.58	0.72	1.09	2.21	1.40	1.00	0.71	0.54	0.88	0.85	1.38	1.21	0.94	0.46	0.14	0.00	0.00
13	0.00	0.00	0.00	0.28	0.30	0.73	0.57	0.77	1.11	0.78	0.64	0.54	0.38	0.43	0.73	1.17	0.82	0.28	0.16	0.00
14	0.00	0.00	0.00	0.00	0.49	1.22	1.18	1.51	1.38	1.19	1.00	0.79	0.99	0.86	0.97	1.17	1.17	0.48	0.37	0.27
15	0.00	0.00	0.00	0.00	0.00	0.10	1.25	2.12	1.48	1.35	0.95	0.85	1.03	0.80	0.82	0.84	1.01	0.65	0.40	0.22
16	0.00	0.00	0.00	0.45	1.66	2.04	2.76	2.11	2.38	1.75	1.11	1.17	1.43	1.34	1.35	1.38	1.21	0.49	0.32	0.00
17	0.00	0.00	0.15	0.52	0.79	1.00	1.29	1.08	0.99	0.94	0.87	0.84	0.83	0.83	1.14	1.44	0.85	0.49	0.26	0.22
19	0.00	0.29	0.41	0.39	0.61	0.65	0.32	0.32	0.90	0.70	0.68	0.73	0.51	0.33	0.34	0.58	0.33	0.26	0.20	0.00
21	0.00	0.00	0.00	0.00	0.46	0.96	0.99	1.06	0.99	1.29	0.76	0.78	0.72	0.68	0.85	1.07	0.90	0.45	0.30	0.23
22	0.00	0.00	0.13	0.39	0.57	0.62	1.19	1.04	1.04	0.84	0.57	0.54	0.52	0.59	0.51	0.49	0.58	0.31	0.23	0.14
23	0.00	0.00	0.00	0.35	0.99	1.34	1.11	0.89	1.10	0.99	0.72	0.70	0.79	0.92	0.96	1.14	0.82	0.56	0.22	0.00
25	0.00	0.00	0.68	0.88	1.89	1.33	1.32	0.87	0.89	1.12	1.06	1.28	1.75	1.32	1.52	1.61	0.74	0.18	0.00	0.00
26	0.00	0.00	0.00	0.12	0.27	0.42	0.67	0.65	0.78	0.60	0.51	0.48	0.50	0.39	0.62	0.65	0.42	0.21	0.25	0.49
27	0.00	0.00	0.41	1.22	1.96	1.56	1.40	1.79	1.46	1.41	0.87	0.99	1.29	1.61	1.82	1.38	1.34	0.57	0.25	0.12
28	0.00	0.00	0.00	0.59	0.43	1.23	0.90	0.82	1.01	1.74	0.87	0.66	0.78	0.56	0.69	1.13	0.75	0.63	0.36	0.28
N	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
Mean	0.00	0.04	0.17	0.50	0.87	1.03	1.16	1.07	1.05	0.96	0.78	0.74	0.82	0.79	0.92	1.01	0.90	0.43	0.26	0.14
Std. Dev	0.00	0.10	0.19	0.45	0.53	0.44	0.51	0.50	0.40	0.36	0.22	0.23	0.34	0.38	0.39	0.36	0.29	0.17	0.11	0.13
RSD %	0.00	244.45	110.84	90.30	60.46	42.89	44.27	46.48	38.10	37.85	28.15	30.99	41.46	48.51	43.03	35.06	32.48	39.55	44.34	95.49

Note: Concentrations were dose-adjusted to 24 mg.

TABLE 18

Summary Of The Adjusted Plasma Hydromorphone Concentration (ng/mL) At Each Sampling Time By Subject

Subject Number	Treatment: HHCR 24mg Fasted																			
	0	0.25	0.5	1	1.5	2	3	4	5	6	8	10	12	14	18	24	36	48	60	72
1	0.00	0.00	0.43	0.54	0.59	0.58	0.55	0.51	0.75	0.68	0.61	0.81	1.42	1.32	1.60	0.98	0.92	0.37	0.00	0.00
3	0.00	0.00	0.63	0.69	0.60	0.54	0.38	0.38	0.41	0.35	0.35	0.59	0.67	0.69	0.72	0.74	0.76	0.42	0.53	0.27
4		0.51	0.56	0.65	0.50	0.42	0.46	0.48	0.56	0.44	0.52	0.43	0.65	0.71	0.68	1.09	1.19	0.57	0.27	0.20
5	0.00	0.35	0.42	0.59	0.52	0.72	0.41	0.54	0.67				0.98	1.15	1.26	0.91	0.81	0.63	0.31	0.19
6	0.00	0.00	0.27	0.40	0.84	0.66	0.60	0.65	0.68	0.68	0.54	0.70	0.70	0.62	0.68	0.72	0.65	0.53	0.26	0.11
7	0.00	0.00	0.00	0.51	0.62	0.67	0.99	0.87	0.71	0.78	0.68	0.65	0.86	0.96	1.05	0.78	0.66	0.43	0.27	0.17
8	0.00	0.00	0.56	0.65	0.84	0.68	0.69	0.42	0.55	0.45	0.50	0.59	0.83	1.41	0.91	1.04	0.75	0.53	0.30	0.22
9	0.00	0.00	0.52	0.84	0.76	0.62	0.67	0.57	0.56	0.76	0.47	0.52	0.71	0.84	0.78	0.96	1.20	0.57	0.41	0.23
10	0.00	0.00	0.16	0.79	0.97	0.94	0.77	0.78	0.82	0.69	1.13	0.80	0.81	1.19	1.59	1.16	1.30	0.50	0.50	0.16
11	0.00	0.00	0.55	0.87	0.87	1.01	1.03	0.81	1.06	1.12	0.81	0.77	0.68	0.69	1.59	1.55	0.99	0.73	0.29	0.15
12	0.00	0.00	0.00	0.43	0.25	0.75	0.32	0.30	0.54	0.41	0.37	0.58	0.68	0.74	0.80	0.66	0.45	0.16	0.00	0.00
13	0.00	0.00	0.29	0.47	0.69	1.05	0.67	0.62	0.73	0.59	0.51	0.84	0.79	1.17	1.31	1.26	1.07	0.56	0.39	0.15
14	0.00	0.00	0.00	0.21	0.41	0.48	0.35	0.34	0.35	0.37	0.25	0.27	0.46	0.56	0.72	0.87	0.70	0.31	0.26	0.14
15	0.00	0.10	0.34	0.99	1.47	1.49	1.19	1.13	1.21	0.98	0.60	1.05	0.98	1.06	0.97	1.40	1.17	0.85	0.71	0.41
16	0.00	1.02	1.11	1.20	1.49	1.48	1.16	1.14	0.81	1.19	1.24	1.08	1.59	1.56	1.14	1.31	1.62	1.54	0.53	0.21
17	0.00	0.00	0.33	0.49	0.58	0.44	0.52	0.59	1.10	0.68	0.79	1.27	1.10	1.10	1.20	1.40	1.02	0.68	0.31	0.15
19	0.00	0.00	0.17	0.43	0.48	0.78	0.65	0.67	0.21	0.28	0.00	0.35	0.36	0.78	0.84	0.70	0.41	0.38	0.29	0.21
21	0.00	0.10	0.77	0.64	0.71	0.69	0.68	0.54	0.64	0.67	0.74	0.77	0.89	0.81	1.05	1.10	0.74	0.53	0.22	0.18
22	0.00	0.21	0.49	0.86	0.81	0.63	0.58	0.51	0.65	0.64	0.53	0.50	1.01	1.65	1.02	1.01	0.91	0.37	0.24	0.15
23	0.00	0.00	0.13	0.55	0.72	0.75	0.60	0.52	0.59	0.54	0.49	0.64	0.86	0.85	0.97	0.98	0.68	0.42	0.17	0.12
25	0.00	0.00	0.54	0.76	0.61	0.54	0.26	0.39	0.78	0.66	0.97	0.90	1.28	1.12	1.28	1.07	0.73	0.28	0.13	0.00
26	0.00	0.00	0.50	0.62	0.91	0.79	0.82	0.81	1.02	0.95	0.62	0.65	0.72	0.66	0.89	1.15	0.88	0.55	0.40	0.29
27	0.00	0.00	0.21	0.96	0.87	0.90	0.63	0.74	0.83	0.79	0.66	0.71	1.20	1.81	2.39	1.75	1.39	0.60	0.25	0.14
28	0.00	0.00	0.41	0.53	0.63	1.02	0.73	0.52	0.65	0.62	0.57	0.29	0.68	0.58	0.56	0.85	1.09	0.42	0.20	0.13
N	23	24	24	24	24	24	24	24	24	23	23	23	24	24	24	24	24	24	24	24
Mean	0.00	0.10	0.39	0.64	0.73	0.78	0.65	0.62	0.70	0.67	0.61	0.68	0.87	0.99	1.08	1.06	0.92	0.54	0.30	0.17
Std. Dev	0.00	0.23	0.26	0.22	0.29	0.28	0.24	0.22	0.23	0.24	0.27	0.25	0.29	0.36	0.41	0.28	0.29	0.26	0.16	0.09
RSD %	0.00	246.14	66.48	33.97	39.03	36.10	37.49	35.71	33.29	35.39	44.43	36.24	33.06	36.31	37.62	26.39	32.04	48.51	53.44	54.83

Note: Concentrations were dose- adjusted to 24 mg.

TABLE 19

Summary Of The Adjusted Plasma Hydromorphone Concentration (ng/mL) At Each Sampling Time By Subject

Treatment: HHCR 12mg Fasted																				
Subject Number	0	0.25	0.5	1	1.5	2	3	4	5	6	8	10	12	14	18	24	36	48	60	72
1	0.00	0.00	0.38	0.52	0.92	0.56	0.78	0.78	1.00	0.78	1.12	1.62	1.40	1.34	1.16	0.98	0.32	0.00	0.00	0.00
3	0.00	0.00	0.64	0.46	0.60	1.16	0.38	0.38	0.48	0.40	0.46	0.44	0.38	0.64	0.94	0.80	0.84	0.42	0.26	0.00
4	0.00	0.00	0.00	0.00	0.42	0.44	0.24	0.26	0.72	0.00	0.22	0.34	0.78	0.46	0.88	0.56	0.56	0.22	0.00	0.32
5	0.00	0.00	0.34	1.10	0.94	0.74	0.66	0.60	1.28	0.76	0.96	0.98	1.18	1.18	1.32	2.64	1.66	0.68	0.48	0.00
6	0.00	0.00	0.00	0.24	0.42	0.62	0.62	0.60	0.66	0.62	0.58	0.58	0.54	0.42	0.72	0.98	1.04	0.50	0.24	0.00
7	0.00	0.00	0.00	0.46	0.64	0.60	0.32	0.24	0.28	0.00	0.26	0.00	0.54	0.44	0.56	0.46	0.94	0.24	0.00	0.00
8	0.00	0.36	0.74	0.88	1.12	1.18	0.96	0.96	1.28	1.00	0.96	0.70	1.24	1.60	1.90	1.80	0.96	1.02	0.46	0.28
9	0.00	0.00	0.00	1.32	0.82	0.74	0.84	0.76	0.70	0.72	0.58	0.48	0.66	0.86	1.32	1.04	0.68	0.32	0.24	0.00
10	0.00	0.00	0.30	0.40	0.56	0.42	0.40	0.36	0.66	0.58	0.56	0.64	0.90	1.04	1.08	1.26	1.00	0.50	0.32	0.00
11	0.00	0.84	0.74	1.80	1.48	1.32	1.42	0.98	1.12	0.96	0.78	1.10	1.60	1.26	1.88	1.50	0.74	0.34	0.00	0.00
12	0.00	0.00	0.96	0.66	0.56	0.70	0.46	0.74	1.14	0.84	0.74	0.84	1.14	1.02	1.18	0.90	0.40	0.00	0.00	0.00
13	0.00	0.00	0.44	0.52	0.42	0.44	0.60	0.58	0.90	1.02	0.48	0.48	1.12	1.16	1.66	1.18	0.62	0.38	0.00	0.00
14	0.00	0.00	0.00	0.52	0.78	0.86	0.88	0.76	0.78	0.74	0.54	0.52	0.70	0.92	0.86	1.12	0.84	0.54	0.46	0.00
15	0.00	0.56	0.72	1.76	1.04	1.62	1.20	0.94	1.18	0.80	0.68	0.94	1.26	1.40	1.22	1.34	0.82	0.62	0.30	0.00
16	0.00	0.00	0.66	0.86	1.04	1.04	0.82	0.76	0.78	0.46	0.76	0.58	2.74	1.66	1.56	1.24	0.94	0.52	0.00	0.00
17	0.00	0.28	0.22	0.60	0.52	0.56	0.36	0.54	0.58	0.70	0.80	0.88	1.14	1.08	1.30	0.90	0.76	0.46	0.30	0.00
19	0.00	0.00	0.60	0.74	0.68	0.68	0.72	0.58	0.58	0.44	0.66	0.88	0.80	0.70	1.16	0.92	0.58	0.26	0.00	0.00
21	0.00	0.00	0.00	0.32	0.50	0.38	0.36	0.50	0.48	0.34	0.28	0.56	0.96	0.90	1.26	0.78	0.42	0.30	0.00	0.00
22	0.00	0.40	0.66	0.78	0.64	0.76	0.94	0.86	1.22	1.38	0.88	0.88	0.98	1.56	1.02	0.94	0.84	0.48	0.00	0.00
23	0.00	0.22	0.66	0.86	1.48	1.40	0.78	0.74	0.62	0.68	0.48	0.66	0.78	0.80	1.04	1.14	0.68	0.78	0.42	0.24
25	0.00	0.00	0.56	0.84	0.58	0.64	0.58	0.40	1.04	1.00	1.02	0.94	1.34	1.16	0.88	0.72	0.60	0.00	0.00	0.00
26	0.00	0.00	0.00	0.28	0.00	0.00	0.92	0.50	1.06	0.90	0.44	0.48	0.40	0.58	0.72	1.10	0.50	0.52	0.32	0.00
27	0.00	0.00	0.44	0.44	0.78	0.84	0.84	0.92	1.02	1.00	1.52	1.46	1.88	1.86	2.38	1.42	0.54	0.24	0.00	0.00
28	0.00	0.92	0.86	0.96	1.10	1.32	0.92	0.86	1.08	1.20	0.86	0.64	0.80	0.80	0.76	1.04	0.82	0.42	0.00	0.00
N	24	24	24	24	23	24	24	24	24	24	24	24	23	24	24	24	24	24	24	23
Mean	0.00	0.15	0.41	0.72	0.74	0.79	0.71	0.65	0.86	0.72	0.69	0.73	1.07	1.04	1.20	1.12	0.75	0.41	0.16	0.04
Std. Dev	0.00	0.28	0.32	0.44	0.35	0.38	0.29	0.22	0.29	0.33	0.30	0.35	0.52	0.40	0.43	0.44	0.28	0.24	0.19	0.10
RSD %	0.00	184.81	77.34	60.95	46.83	48.34	41.19	34.12	33.21	46.31	43.25	47.43	48.06	38.80	36.00	39.41	36.70	59.29	117.49	266.06

Note: Concentrations were dose-adjusted to 24 mg.

TABLE 20

Summary Of The Adjusted Plasma Hydromorphone Concentration (ng/mL) At Each Sampling Time By Subject

Subject Number	Treatment: HHCR 8mg Fasted																			
	0	0.25	0.5	1	1.5	2	3	4	5	6	8	10	12	14	18	24	36	48	60	72
1	0.00	2.73	5.07	4.14	1.95	1.62	1.41	0.93	0.81	0.54	0.60	0.42	0.36	0.60	0.42	0.00	0.00	0.00	0.00	0.00
3	0.00	2.46	4.32	5.16	2.85	2.01	1.14	0.84	0.51	0.42	0.00	0.00	0.39	0.42	0.54	0.57	0.36	0.00	0.36	0.00
4	0.00	3.87	5.88	4.74	2.64	1.86	1.38	0.84	0.48	0.60	0.00	0.45	0.72	0.57	0.60	0.81	0.60	0.00	0.00	0.00
5	0.00	6.72	11.64	9.99	5.58	4.56	3.00	1.95	1.17	0.90	0.54	0.51	0.51	0.93	1.26	0.96	0.72	0.00	0.00	0.00
6	0.00	1.83	5.31	3.18	1.71	1.92	0.84	0.87	1.35	0.96			0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
7	0.00	3.09	5.25	3.24	3.45	1.80	0.96	1.05	0.81	0.45	0.48	0.36	0.00	0.42	0.33	0.00	0.00	0.00	0.00	0.00
8	0.00	6.75	10.20	8.10	5.91	4.50	2.37	1.80	0.87	0.93	0.72	0.54	1.23	1.11	0.96	0.99	0.42	0.36	0.36	0.00
9	0.00	4.71	8.22	6.54	4.17	3.09	1.95	1.50	0.93	0.63	0.00	0.00	0.00	0.48	0.69	0.72	0.54	0.00	0.00	0.00
10	0.00	2.40	7.86	8.19	4.62	3.51	2.55	1.83	1.23	0.93	0.81	0.68	1.35	1.02	0.81	0.78	0.60	0.00	0.00	0.00
11	0.00	4.50	13.56	11.52	4.32	2.94	2.19	1.32	1.08	0.87	0.36	0.00	0.00	0.48	1.29	0.84	0.00	0.00	0.00	0.75
12	0.00	7.17	7.59	7.89	4.11	2.67	1.86	1.29	1.02	0.78	0.45	0.33	1.05	0.54	0.45	0.30	0.00	0.00	0.00	0.00
13	0.00	3.42	10.35	6.36	3.87	2.88	2.10	1.53	0.99	0.57	0.00	0.30	0.72	0.54		0.84	0.93	0.00	0.00	0.00
14	0.00	4.41	4.44	6.51	4.14	3.21	2.46	1.77	1.17	0.81	0.42	0.00	0.36	0.66	0.81	0.48	0.33	0.00	0.00	0.00
15	0.00	4.71	2.88	8.22	3.57	3.00	1.77	0.99	0.69	0.72	0.00	0.00	0.00	0.51	0.00	0.00	0.00	0.00	0.00	0.00
16	0.00	12.72	21.51	10.68	4.86	4.77	2.67	3.33	1.59	1.17	1.05	0.42	0.39	0.30	0.78	1.26	0.45	0.00	0.00	0.00
17	0.00	0.54	3.87	6.30	3.48	3.57	1.80	0.99	1.05	0.69	0.54	0.54	0.90	0.54	0.69	0.48	0.39	0.00	0.57	0.00
19	0.00	3.00	3.09	5.76	2.49	1.65	3.12	1.56	1.23	0.81	0.69	0.57	0.45	0.54	0.48	0.75	0.39	0.00	0.00	0.00
21	0.00	2.37	5.19	4.89	2.22	1.62	2.04	1.35	0.96	0.69	0.48	0.93	0.84	0.78	0.99	0.60	0.00	0.00	0.00	0.00
22	0.00	0.84	2.22	4.35	6.18	2.46	1.08	0.96	1.05	0.75	0.39	0.45	0.63	0.75	0.63	0.00	0.00	0.00	0.00	0.00
23	0.00	1.35	3.90	9.63	4.14	3.00	1.98	1.41	0.72	0.57	0.00	0.45	0.75	0.69	0.69	0.60	0.39	0.00	0.00	0.00
25	0.00	2.52	4.29	7.05	3.81	2.22	2.07	1.32	0.96	0.99	0.63	0.60	1.02	1.05	0.93	0.36	0.00	0.00	0.00	0.00
26	0.00	0.51	1.23	6.93	5.43	4.08	2.64	1.68	1.11	0.57	0.33	0.84	0.78	0.63	0.72	0.60	0.81	0.42	0.00	0.00
27	0.00	0.00	0.51	9.00	6.36	5.07	2.13	1.77	1.68	1.20	0.66	1.11	1.32	1.53	0.87	0.78	0.33	0.00	0.00	0.00
28	0.00	1.86	1.68	11.70	6.87	3.87	2.07	1.62	0.87	0.66	0.66	0.42	0.39	0.33	0.57	0.66	0.00	0.00	0.00	0.00
N	24	24	24	24	24	24	24	24	24	24	23	23	24	24	23	24	24	24	24	24
Mean	0.00	3.52	6.25	7.09	4.11	3.00	1.98	1.44	1.01	0.76	0.43	0.43	0.59	0.64	0.67	0.56	0.30	0.03	0.05	0.03
Std. Dev	0.00	2.77	4.66	2.47	1.42	1.07	0.61	0.54	0.29	0.21	0.30	0.30	0.43	0.31	0.32	0.36	0.30	0.11	0.15	0.15
RSD %	0.00	78.80	74.51	34.87	34.61	35.64	31.01	37.27	28.46	27.23	70.88	69.53	72.12	48.97	47.69	63.87	98.39	339.89	278.33	489.90

Note: Concentrations were dose-adjusted to 24 mg.

Example 12

In Example 12, an open-label, 5-day, repeated-dose, two-treatment, randomized, cross-over, analytically blinded pharmacokinetic/pharmacodynamic comparison study of Hydromorphone HCL sustained release 12 mg capsules (HHCR 12 mg of Example 9) administered once daily and Hydromorphone HCL immediate release 3 mg tablets administered every 6 hours was conducted in normal, healthy, young male and female volunteers. The objective was to assess relative bioavailabilities (including gender effects) and to compare the pharmacokinetic / pharmacodynamic (PK/PD) profiles of HHCR 12 mg capsules administered once daily (“q24h”) and HHIR 3 mg tablets administered every 6 hours (“q6h”) under apparent steady-state (multiple-dose) conditions. A total of 26 subjects (15 males and 11 females) were enrolled and completed the study. All were included in the both the PK/PD and safety analysis.

The hydromorphone hydrochloride controlled-release capsule (HHCR) tested in this example provides favorable release characteristics and plasma concentration-time profiles for once-daily administration. In Example 11, the results of the single-dose study showed that the 24 mg capsule was dose proportional to the 12 mg capsule based on primary pharmacokinetic metrics, and the pharmacokinetic profiles support once-daily dosing. The present study demonstrates the same results for the same formulation tested under steady-state conditions. Blood samples for determination of hydromorphone concentrations were obtained within 15 minutes before dosing (0 hour) on Days 2-5 of each study period, and at 0.25, 0.5, 1, 2, 3, 4, 6, 6.25, 6.5, 7, 8, 9, 10, 12, 12.25, 12.5, 13, 14, 15, 16, 18, 18.25, 18.5, 19, 20, 21, 22, and 24 hours (± 2 minutes) after the 8 a.m. dose on Day 5 of each study period. Hydromorphone concentrations were determined using a validated APCI LS/MS/MS technique.

With respect to pharmacokinetics, measurements included: Area under the plasma concentration time course curve from dosing to 24h at steady-state [$AUC_{ss,(0-24)}$], maximum plasma concentration at steady-state [$C_{ss,max}$], minimum plasma concentration at steady-state [$C_{ss,min}$], minimum plasma concentration prior to steady-state [$C_{t,min}$], time to maximum plasma concentration at steady-state [$t_{ss,max}$], % fluctuation at steady-state, and time from

initiation of therapy to steady-state [Tss].

Table 21 provides a summary of adjusted hydromorphone pharmacokinetic metrics (mean and standard deviation) for HHCR 12 mg and HHIR 3 mg.

Table 21		
Metric	Arithmetic mean (SD)	
	HHCR 12 mg	HHIR 3 mg
	q24h	q6h
AUC _{ss} , (0-24) (ng/mL·h)		
Arithmetic Mean (SD)	34.86 (10.15)	34.40 (8.93)
Geometric Mean	33.89	33.20
C _{ss} ,max (ng/mL)		
Arithmetic Mean (SD)	2.12 (0.64)	2.89 (0.96)
Geometric Mean	2.03	2.73
C _{ss} ,min (ng/mL)		
Arithmetic Mean	0.99 (0.35)	0.70 (0.21)
Geometric Mean	0.92	0.66
C _t ,min (ng/mL)	1.26 (0.41)	0.99 (0.23)
t _{ss} ,max (h)	8.44 (6.34)	0.86 (0.52)
% Fluctuation	125.80 (62.04)	327.92 (124.32)
T _{ss} (d)	3	3
Trough (ng/ml)		
Arithmetic Mean (SD)	1.26 (0.41)	0.99 (0.23)
Geometric Mean	1.18	0.96

SD = Standard deviation

The pharmacokinetic metrics used in the study are defined as follows:

AUC_{ss}, (0-24) (ng/mL·h) - The area under the plasma concentration-time course curve at

steady-state from 0 to 24 hours (within one dosing interval).

Css,max (ng/mL) B The maximum observed plasma concentration at steady-state.

Css,min (ng/mL) B The minimum observed plasma concentration at steady-state (between 8 am on Day 5 and 8 a.m. on Day 6).

Ct,min (ng/mL) - The minimum plasma concentrations prior to steady-state (8 am on Days 2 - 5).

tss,max (hr) - The time from dosing at steady-state to Css,max.

Fluctuation (%) - The difference between Css,max and Css,min expressed as a percentage of Css,min.

Tss (days) - The time from initiation of therapy to steady-state (the first day between Days 2 and 5 when the slope of Ct,min values no longer increases).

A summary of AUCss,(0-24) and Css,max and primary pharmacokinetic metrics (mean and standard deviation) and 90% confidence intervals around ratios (test/reference) of least squares means derived from logarithmic-transformed data are presented below in Table 22.

Table 22

Metric	Arithmetic mean (SD)		LSM Ratio (%) ^a	90% CI ^b	
	HHCR 12 mg q24h	HHIR 3 mg q6h			
AUCss,(0-24) (ng/mL·h)	34.86 (10.15)	34.40 (8.93)	101.36	96.31	106.40
Css,max (ng/mL)	2.12 (0.64)	2.89 (0.96)	73.33	64.31	82.34

SD = Standard deviation.

^a Ratio (%) (test/reference) of least square means (ANOVA) derived from logarithmic-transformed data.

^b 90% confidence interval (CI) around least squares means ratio.

The Ct,min data is presented in Table 23. Steady-state appeared to have been reached between Day 3 and 4 for both treatments.

Table 23

Summary of Mean Ct,min (ng/mL) (Mean, N=26)

Treatment	<u>Study Day</u>				<u>Overall</u>
	2	3	4	5	Mean
HHCR	0.69	0.99	1.26	1.26	1.05
HHIR	0.55	0.77	0.89	0.99	0.80

A summary of the time to maximum concentration (Tmax) by subject (HHCR 12 mg and HHIR 3 mg) is provided in Table 25. A summary of the maximum concentration (Cmax) by subject is provided in Table 26. A summary of the minimum concentration (Cmin) is provided in Table 27. A summary of the area under the curve (0-24 hours) by subject is provided in Table 28. A summary of the percent fluctuation in concentration (Cmin) by subject is provided in Table 29. A summary of the trough concentration values (day 5) by subject is provided in Table 30.

Mean plasma concentration-time course data for Example 12 are presented in Figure 7. Each of the 4 daily administrations of HHIR 3 mg tablets produced an initial increase in plasma drug concentration (tss,max by 1 hour) followed by a decline over the remaining 5 hours of the dosing interval. Each daily administration of HHCR capsules resulted in a rise to an initial early peak concentration, followed by a second broader peak with plateau concentrations maintained to 24 hours. A summary of the plasma hydromorphone concentration (ng/ml) values at each sampling time by subject is provided in Table 24.

Comparisons of AUC_{ss,(0-24)} indicated that HHCR 12 mg q24h and HHIR 3 mg q6h are bioequivalent in terms of extent of absorption over a 24 hour period at steady-state. Mean AUC_{ss,(0-24)} values differed between treatments by < 1% (CI = 96 B 106). Comparison of C_{ss,max} values indicated that HHCR 12 mg capsules q24h had a 26% lower C_{ss,max} than HHIR 3 mg tablets q6h (CI = 64 B 82), consistent with the sustained release characteristics of HHCR. The mean C_{ss,min} of HHCR 12 mg capsules q24h was higher than that of HHIR 3 mg tablets q6h (0.99 and 0.70 ng/mL, respectively), consistent with the controlled release characteristics of HHCR. The mean C_{t,min} of HHCR 12 mg capsules q24h was higher than that of HHIR 3 mg tablets q6h (1.26 and 0.99 ng/mL, respectively), consistent with the controlled release characteristics of HHCR capsules. The mean t_{ss,max} of HHCR 12 mg capsules q24h was considerably longer than that of HHIR 3 mg tablets (8.44 and 0.86 h, respectively). Considering the anticipated within-subject variability of t_{ss,max}, this observation was not of any significance. The fluctuation between C_{ss,max} and C_{ss,min} resulting from HHCR 12 mg capsules q24h was less than that from HHIR 3 mg tablets q6h (125.80 and 327.92 hours, respectively), consistent with the controlled release characteristics of HHCR capsules. The time to steady-state for most subjects was 3 days after the first dose of either treatment. Two subjects who received HHIR 3 mg tablets q6h and two subjects who received HHCR 12 mg q24h did not appear to reach steady-state on Day 3. All subjects had reached steady-state prior to the pharmacokinetic sampling period on Day 5. Figure 8 provides the mean trough values (ng/ml) over time for HHIR and HHCR.

Relationships between the time course of plasma drug concentrations and pharmacodynamics (visual analog scale (VAS) "Drug Effects") were assessed. The "drug effect" visual analog scale was chosen as the pharmacodynamic outcome because of its high correlation with plasma opioid concentrations relative to other subjective and objective assessments utilized in normal volunteer studies. The VAS "drug effect" measured just prior to blood sampling on Day 5 at baseline (within 30 minutes prior to dosing) and within 5 minutes prior to all scheduled times of blood draws. "Drug effect" consisted of one question, rated by the subject: "Do you feel any effects of the drug?" Just prior to blood sampling, the subject rated drug effect by placing a vertical mark along a 100 mm visual analog scale (VAS) anchored on one end by "not at all" and on the other end by "an awful lot". With respect to pharmacokinetic-pharmacodynamic metrics, PD_{max} (maximum observed effect score) and PD_{auc} (area under the effect curve from 0 to 24 hours) were estimated based on subject VAS drug effect scores. Figure 9 provides the mean subject drug effect (VAS, mm) over time for HHIR and HHCR. Figure 10 provides a graphical representation of the mean plasma hydromorphone concentration (ng/ml) and mean subject drug effect (VAS, mm) over time for HHCR. Figure 11 provides a graphical representation of the mean plasma hydromorphone concentration (ng/ml) and mean subject drug effect (VAS, mm) over time for HHIR.

TABLE 24
Summary Of The Plasma Hydromorphone Concentration (ng/mL) Values At Each Sampling Time By Subject

Subject Number	Treatment: HHCR 12 mg																			
	-4	-3	-2	-1	0	0.25	0.5	1	2	3	4	6	6.25	6.5	7	8	9	10	12	
1	0.0	0.7	1.0	1.3	1.1	1.1	1.4	1.4	1.4	1.5	1.2	1.6	1.6	1.5	1.2	1.0	0.8	1.4	1.9	
2	0.0	0.4	1.0	1.0	1.3	1.2	1.5	1.4	1.4	1.4	1.3	1.1	1.2	1.2	1.2	1.0	0.8	0.9	0.9	
3	0.0	0.5	0.7	0.7	1.0	0.9	1.1	1.3	1.3	1.2	1.1	0.9	1.0	1.0	0.9	0.9	0.8	1.2	0.9	
4	0.0	0.3	0.4	0.5	0.6	0.7	0.8	0.9	0.9	1.0	0.8	0.7	0.8	0.7	0.7	0.6	0.7	0.8	0.7	
5	0.0	0.5	0.8	1.0	1.2	1.1	1.2	1.3	1.6	1.6	1.5	1.3	1.4	1.4	1.3	1.2	1.2	1.2	1.0	
6	0.0	0.8	1.5	1.8	2.0	1.9	2.2	2.3	2.4	2.4	1.6	1.7	1.7	1.7	1.6	1.5	1.5	1.9	2.5	
7	0.0	0.9	1.0	1.4	1.4	1.4	1.5	1.7	2.0	2.0	1.7	1.8	1.8	1.8	1.8	1.5	1.5	1.4	1.9	
8	0.0	1.2	1.4	1.6	2.0	1.8	1.8	2.4	2.4	2.4	2.1	2.0	1.9	1.7	1.7	1.5	1.6	1.5	1.6	
9	0.0	1.0	1.1	2.0	1.6	1.4	1.5	2.0	2.2	1.9	1.7	1.7	1.7	1.6	1.5	1.4	1.2	1.3	1.2	
10	0.0	0.5	1.2	1.7	1.3	1.3	1.5	1.6	2.5	2.1	1.7	1.5	1.5	1.6	1.4	1.4	1.2	1.3	2.2	
11	0.0	0.7	0.9	1.2	1.4	1.5	1.6	1.8	1.9	2.0	1.8	1.7	1.6	1.5	1.6	1.2	1.3	1.3	1.4	
12	0.0	0.8	1.1	1.2	1.6	1.6	1.9	1.8	2.2	1.9	1.6	1.4	1.4	1.5	1.4	1.2	1.2	1.4	1.6	
13	0.0	0.6	0.7	1.2	1.2	1.4	1.5	1.6	2.2	1.6	1.4	1.2	1.4	1.3	1.2	1.0	0.9	1.1	1.1	
14	0.0	0.7	1.2	1.3	1.2	1.3	1.5	1.7	2.4	2.2	1.2	1.9	1.8	1.9	1.6	1.3	1.2	1.6	1.8	
15	0.0	0.7	1.0	1.2	1.2	1.3	1.4	1.5	2.0	1.7	1.4	1.2	1.3	1.3	1.3	1.3	1.3	1.4	2.2	
16	0.0	1.2	1.4	1.5	1.6	1.5	1.5	1.9	2.5	2.2	1.7	1.7	1.6	1.6	1.6	1.8	1.9	2.0	2.7	
17	0.0	0.7	1.0	1.2	0.3	0.4	0.7	0.8	1.1	1.0	0.8	0.8	0.8	0.8	0.7	0.6	0.6	1.2	0.8	
18	0.0	0.6	1.2	1.2	0.7	0.7	1.1	1.2	1.3	1.2	1.1	0.9	0.9	0.8	1.1	1.0	1.0	1.2	1.1	
19	0.0	0.5	0.7	1.1	1.1	1.1	1.1	1.0	1.6	1.3	1.1	1.2	0.7	0.9	0.9	0.8	0.8	0.9	0.8	
20	0.0	0.7	0.8	1.3	1.1	1.2	2.1	1.7	1.8	1.5	0.9	1.2	1.1	1.3	1.2	1.4	1.1	1.6	2.0	
21	0.0	0.6	0.9	0.8	1.0	1.2	1.7	1.7	2.1	1.8	1.5	1.5	1.5	1.5	1.4	1.5	1.5	1.9	2.1	
22	0.0	0.4	1.0	1.2	1.4	1.4	1.5	1.7	2.0	2.0	1.6	1.4	1.4	1.4	1.4	1.2	1.2	1.3	1.3	
23	0.0	0.7	0.6	1.1	1.4	1.3	1.6	1.4	1.7	1.9	1.4	1.5	1.5	1.4	1.3	1.2	1.1	1.2	1.2	
24	0.0	0.6	1.1	1.2	1.5	1.9	2.3	2.4	2.4	2.4	1.9	1.6	1.6	1.5	1.4	1.2	1.3	1.8	3.0	
25	0.0	0.6	0.9	1.2	1.0	0.9	1.0	1.2	1.2	1.3	1.1	1.1	1.2	1.1	1.1	1.0	1.1	1.4	1.1	
26	0.0	1.2	1.5	2.1	2.1	2.3	2.1	2.7	3.1	3.2	2.7	2.6	2.5	2.6	2.4	2.2	1.9	2.0	2.4	
N	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	
Mean	0.00	0.69	0.99	1.26	1.26	1.30	1.50	1.63	1.90	1.77	1.45	1.43	1.42	1.40	1.33	1.23	1.16	1.39	1.59	
Std. Dev	0.00	0.25	0.28	0.36	0.41	0.41	0.42	0.47	0.53	0.50	0.42	0.42	0.40	0.40	0.35	0.34	0.33	0.33	0.65	
RSD%	0.00	35.37	26.66	28.40	32.55	31.49	27.82	28.68	27.98	28.37	28.73	29.34	28.19	28.35	26.03	28.01	28.78	23.69	41.26	

TABLE 24 (cont'd)
Summary Of The Plasma Hydromorphone Concentration (ng/mL) Values At Each Sampling Time By Subject

Subject Number	Treatment: HHCR 12 mg																21	22	24
	12.25	12.5	13	14	15	16	18	18.25	18.5	19	20								
1.0	2.0	1.9	1.7	1.7	1.6	1.8	1.2	1.3	1.2	1.1	1.3	1.1	1.2	1.3					
2.0	1.0	0.9	0.9	1.1	1.0	0.9	0.7	0.7	0.7	0.8	0.9	1.0	0.9	0.9					
3.0	0.9	0.8	0.7	0.6	0.6	0.6	0.4	0.5	0.5	0.5	0.5	0.5	0.4	0.4					
4.0	0.8	0.8	0.7	0.8	1.0	0.8	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6					
5.0	1.2	1.2	1.2	1.2	1.3	1.4	1.1	1.0	1.0	0.9	0.9	1.0	0.8	1.2					
6.0	2.5	2.5	2.6	2.9	2.6	2.5	2.1	2.4	2.2	2.4	2.1	2.2	1.9	1.8					
7.0	1.8	1.7	1.4	1.5	1.4	1.4	1.3	1.2	1.2	1.1	1.2	1.3	1.4	1.6					
8.0	1.8	1.9	1.8	2.1	2.5	2.3	1.7	1.7	1.7	1.6	1.7	1.4	1.6	1.8					
9.0	1.2	1.2	1.3	1.4	1.8	1.5	1.2	1.2	1.2	1.2	1.2	1.4	1.8	2.2					
10.0	2.2	2.2	1.9	2.0	1.6	2.2	2.1	2.0	1.9	1.8	1.3	1.5	1.4	1.3					
11.0	1.4	1.5	1.6	1.5	1.6	1.3	1.3	1.5	1.7	2.2	1.7	1.6	1.6	1.5					
12.0	1.4	1.4	1.3	1.3	1.6	1.4	1.2	1.0	0.9	1.1	1.1	1.3	1.0	1.3					
13.0	0.9	1.2	1.0	1.0	1.4	1.2	1.1	1.0	1.1	1.1	1.0	1.0	0.9	1.1					
14.0	1.9	1.7	1.5	1.7	1.9	2.0	1.4	1.4	1.5	1.5	1.5	1.2	1.2	1.0					
15.0	1.9	2.3	2.4	1.7	1.9	1.8	1.7	1.6	1.6	1.5	1.3	1.2	1.3	1.3					
16.0	2.9	2.8	1.4	2.6	2.4	2.9	1.9	1.8	1.8	1.6	1.7	1.7	1.7	1.4					
17.0	0.9	0.9	0.8	0.8	0.8	0.6	0.6	0.6	0.5	0.5	0.9	0.6	0.6	0.8					
18.0	1.1	1.0	1.2	1.2	1.2	1.1	1.2	1.3	1.2	1.0	1.1	1.1	0.9	0.9					
19.0	0.7	0.8	0.9	1.2	1.7	1.1	1.4	1.5	1.5	1.4	1.2	1.1	1.2	0.8					
20.0	1.9	2.1	1.9	2.7	2.2	2.2	1.6	1.5	1.4	1.4	1.1	0.9	0.9	1.2					
21.0	2.0	2.1	2.0	2.2	2.2	2.0	1.7	1.8	1.6	1.7	1.6	1.4	1.4	1.4					
22.0	1.5	1.3	2.8	1.4	2.0	1.6	1.6	1.6	1.5	1.6	1.5	1.4	1.3	1.2					
23.0	1.2	1.3	1.2	1.2	1.3	1.1	1.3	1.4	1.4	1.3	1.4	1.2	1.2	1.6					
24.0	2.9	3.1	3.0	2.7	2.2	2.0	1.4	1.4	1.2	1.3	1.2	1.1	1.1	1.0					
25.0	1.2	1.1	1.1	1.1	1.5	1.7	1.5	1.5	1.5	1.6	1.6	1.3	1.1	0.9					
26.0	2.4	2.5	2.6	3.5	3.6	2.6	2.1	2.2	2.1	2.4	2.2	2.4	2.4	2.6					
N	26	26	26	26	26	26	26	26	26	26	26	26	26	26					
Mean	1.60	1.62	1.57	1.66	1.73	1.61	1.36	1.36	1.33	1.35	1.30	1.23	1.23	1.26					
Std. Dev	0.64	0.67	0.66	0.74	0.63	0.62	0.46	0.47	0.45	0.50	0.41	0.42	0.43	0.47					
RSD%	40.15	41.23	42.03	44.42	36.73	38.81	33.53	34.44	34.15	36.95	31.91	34.03	35.05	37.57					

TABLE 24 (cont'd)

Summary Of The Plasma Hydromorphone Concentration (ng/mL) Values At Each Sampling Time By Subject

Treatment: HHCR 3 mg

Subject Number	12.25	12.5	13	14	15	16	18	18.25	18.5	19	20	21	22	24
1.0	1.5	1.8	2.3	2.1	1.9	1.3	0.9	1.0	1.0	1.1	1.8	1.4	1.1	1.1
2.0	1.5	1.8	1.2	1.2	1.1	0.9	0.6	1.2	1.1	1.3	1.1	0.8	0.7	0.8
3.0	0.9	1.3	1.4	1.0	1.1	0.8	0.6	0.6	0.7	1.1	1.6	1.3	1.0	0.8
4.0	0.5	0.5	0.8	0.8	0.7	0.7	0.5	0.5	0.8	0.9	0.8	0.6	0.5	0.4
5.0	0.7	0.8	1.3	1.6	1.6	1.4	1.2	1.5	1.4	1.7	1.7	1.6	1.3	1.3
6.0	0.9	1.0	1.7	2.6	2.4	2.0	1.6	1.7	1.7	2.7	2.4	1.9	1.6	1.3
7.0	0.8	1.1	1.6	2.2	1.9	1.2	0.8	2.4	2.3	1.8	1.6	1.3	1.1	1.0
8.0	4.9	4.7	3.7	2.6	1.6	1.1	0.8	2.3	3.1	3.0	2.7	1.9	1.5	1.2
9.0	1.0	1.9	2.3	2.2	1.7	1.4	1.1	2.0	2.1	1.9	1.4	1.3	1.2	1.2
10.0	1.5	1.8	2.9	3.0	2.6	1.9	1.4	2.4	2.3	3.0	2.0	1.9	1.5	1.0
11.0	1.5	1.8	2.0	2.4	2.3	1.9	1.1	3.5	2.6	2.0	1.9	1.4	1.4	1.2
12.0	0.6	1.5	1.5	1.4	1.0	0.9	0.6	0.7	0.7	1.5	0.8	0.8	0.7	1.1
13.0	0.6	0.7	0.8	1.6	1.7	1.2	0.8	1.0	1.2	1.3	1.2	1.0	0.8	0.9
14.0	0.7	0.6	1.0	2.3	1.6	1.2	0.7	1.2	2.1	2.0	1.1	1.1	1.0	0.8
15.0	1.4	1.7	3.1	2.9	2.3	1.6	1.0	1.1	2.3	2.3	2.1	1.7	1.4	1.3
16.0	1.2	2.4	2.5	2.1	1.6	1.4	1.0	2.5	2.4	3.7	2.7	2.7	2.6	2.0
17.0	0.8	1.7	1.5	1.2	0.7	0.6	0.5	1.4	1.6	1.8	1.4	1.2	1.0	0.6
18.0	1.5	1.4	1.8	2.1	1.9	1.4	1.2	3.6	2.5	2.0	1.4	1.3	1.1	1.0
19.0	1.0	1.5	2.3	1.7	1.5	1.3	0.9	1.0	2.5	2.4	2.1	2.0	1.7	0.8
20.0	4.4	4.0	3.4	2.6	1.5	1.2	0.8	1.7	3.9	2.7	2.3	1.7	1.5	0.9
21.0	1.2	1.1	1.2	1.5	1.7	2.1	1.3	1.5	2.5	2.3	2.1	1.5	1.3	0.8
22.0	2.2	3.2	3.0	2.5	2.0	1.6	0.9	2.5	2.8	2.5	1.7	1.4	1.2	1.0
23.0	2.2	2.0	2.2	1.8	1.5	1.3	0.9	0.8	0.7	1.5	1.6	1.4	1.0	0.7
24.0	1.9	2.4	2.7	2.1	2.0	1.5	1.0	1.5	1.5	2.2	2.1	1.7	1.6	1.2
25.0	0.7	0.9	1.1	1.3	1.2	0.9	0.6	0.8	0.7	1.5	1.6	1.4	1.4	1.0
26.0	2.6	3.3	3.4	2.9	2.7	1.9	1.2	1.3	2.2	2.7	2.7	2.0	1.7	1.1
N	26	26	26	26	26	26	26	26	26	26	26	26	26	26
Mean	1.49	1.79	2.02	1.99	1.68	1.34	0.92	1.59	1.87	2.03	1.75	1.46	1.26	1.02
StdDev	1.09	1.04	0.85	0.61	0.52	0.41	0.28	0.83	0.84	0.68	0.54	0.46	0.42	0.30
RSD%	72.76	58.00	42.23	30.78	31.24	30.85	30.68	52.38	45.21	33.52	30.51	31.25	33.44	29.05

TABLE 24 (cont'd)
Summary Of The Plasma Hydromorphone Concentration (ng/mL) Values At Each Sampling Time By Subject

Treatment: HHCR 3 mg																			
Subject Number	-4	-3	-2	-1	0	0.25	0.5	1	2	3	4	6	6.25	6.5	7	8	9	10	12
1	0.0	0.5	0.7	1.0	1.0	1.2	2.2	2.4	1.7	1.3	0.9	1.0	1.4	2.2	2.1	1.4	1.0	0.8	1.1
2	0.0	0.6	0.6	0.8	0.9	0.7	0.8	1.4	1.2	1.0	0.7	0.4	0.3	0.4	0.7	0.7	0.8	0.9	0.6
3	0.0	0.6	0.5	0.5	0.6	0.9	1.8	1.5	1.2	0.9	0.6	0.5	0.4	0.4	0.6	0.8	0.8	1.0	0.5
4	0.0	0.4	0.4	0.4	0.5	0.6	0.9	1.1	1.1	0.7	0.6	0.4	0.6	0.6	1.2	1.0	0.6	0.6	0.5
5	0.0	0.5	0.6	0.7	0.9	0.9	1.4	1.6	1.3	1.2	0.9	0.6	0.7	0.7	1.9	1.7	1.2	1.1	0.7
6	0.0	0.7	1.2	1.4	1.4	2.5	2.8	2.3	2.4	1.8	1.3	1.0	1.1	1.2	3.7	2.0	1.4	1.1	1.0
7	0.0	0.7	1.0	1.0	1.1	1.4	2.1	2.3	2.2	1.5	1.0	1.0	0.9	0.8	1.0	2.1	1.3	1.1	0.8
8	0.0	0.8	1.2	1.4	1.2	2.9	2.9	2.6	2.3	1.7	1.0	0.9	0.9	1.1	2.3	2.1	1.7	1.5	1.5
9	0.0	0.5	0.8	1.0	1.1	1.1	1.6	1.9	2.4	2.0	1.4	1.1	1.3	1.4	1.7	1.9	1.7	1.3	1.0
10	0.0	0.5	0.7	0.8	0.9	1.1	1.9	2.2	2.3	1.3	0.9	0.7	0.8	1.2	1.8	2.2	1.4	1.7	1.4
11	0.0	0.7	0.9	1.2	1.0	1.3	2.2	2.5	2.0	1.4	1.1	0.8	0.8	0.8	1.6	1.5	1.2	1.1	1.3
12	0.0	0.6	0.7	0.9	1.0	1.0	2.1	2.4	1.7	1.3	1.0	0.9	1.4	1.9	1.6	1.4	0.8	0.8	0.6
13	0.0	0.4	0.7	0.7	0.8	0.9	1.8	1.8	1.3	1.0	0.9	0.8	0.7	1.0	1.4	1.5	1.1	0.9	0.6
14	0.0	0.5	0.6	0.5	0.8	1.7	2.1	1.8	1.4	0.9	0.7	0.5	0.6	1.6	2.1	1.3	0.7	0.7	0.7
15	0.0	0.6	1.0	1.1	1.1	2.3	3.5	3.0	2.6	1.6	1.1	0.9	1.1	2.0	3.6	2.2	1.6	1.3	1.0
16	0.0	0.4	0.9	0.7	1.1	1.3	2.5	3.7	3.1	1.9	1.3	1.0	1.1	0.8	1.9	2.5	1.5	1.2	0.7
17	0.0	0.7	0.9	0.4	1.1	1.2	1.4	2.5	2.1	2.1	1.4	0.9	1.7	2.4	2.1	1.4	1.0	0.7	0.4
18	0.0	0.4	0.6	0.8	1.0	4.1	2.8	2.2	1.4	1.3	1.1	0.8	1.2	2.2	1.6	1.2	1.1	1.1	1.1
19	0.0	0.5	0.8	1.1	0.9	1.2	1.7	1.7	1.4	0.9	0.7	0.6	0.7	1.0	1.9	1.3	0.9	0.7	0.7
20	0.0	0.5	0.8	1.1	0.9	1.4	2.4	2.8	1.5	1.2	0.8	0.6	0.7	0.9	2.7	1.7	1.3	0.8	1.0
21	0.0	0.4	0.6	1.1	1.0	1.8	3.1	2.7	1.8	1.2	0.8	0.7	0.8	0.9	3.5	2.3	1.5	1.5	1.1
22	0.0	0.5	0.7	1.1	1.1	1.1	1.4	1.7	2.2	1.9	1.3	1.0	0.9	0.9	1.6	1.5	1.8	1.4	1.2
23	0.0	0.5	0.5	0.6	0.8	0.9	3.6	2.2	1.5	1.2	0.9	0.6	0.7	0.6	1.1	1.5	1.0	0.9	0.7
24	0.0	0.5	0.7	0.9	1.1	3.0	3.5	2.6	1.9	1.4	1.1	1.2	1.3	2.6	2.2	2.0	1.8	1.8	1.5
25	0.0	0.7	0.7	0.6	1.0	0.9	1.5	1.8	1.3	1.1	0.8	0.7	0.7	0.6	0.6	1.0	1.1	0.9	0.5
26	0.0	0.6	1.1	1.3	1.7	3.2	1.7	3.5	2.4	2.2	1.4	1.1	1.2	1.5	2.0	3.0	2.8	2.9	2.8
N	26.0	25.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0
Mean	0.0	0.6	0.8	0.9	1.0	1.6	2.1	2.2	1.8	1.4	1.0	0.8	0.9	1.2	1.9	1.7	1.3	1.2	1.0
Std.Dev	0.0	0.1	0.2	0.3	0.2	0.9	0.8	0.6	0.5	0.4	0.3	0.2	0.3	0.6	0.8	0.5	0.5	0.5	0.5
RSD%	0.0	21.6	27.0	31.8	23.2	57.8	35.6	28.1	29.0	28.9	26.2	28.4	36.0	52.5	44.4	32.4	36.9	42.0	51.3

TABLE 25

SUMMARY OF THE TIME TO MAXIMUM CONCENTRATION (TMAX) BY SUBJECT
HHCR 12MG AND HHIR 3MG

Subject Number	Tmax (hrs)		Ratio (%)
	Treatment		
	HHCR 12mg	HHIR 3mg	HHCR 12mg / HHIR 3mg
1	12.25	1.00	1225.00
2	0.50	0.50	100.00
3	1.00	0.50	200.00
4	3.00	1.00	300.00
5	3.00	1.00	300.00
6	14.00	1.00	1400.00
7	2.00	0.25	800.00
8	15.00	0.25	6000.00
9	2.00	2.00	100.00
10	2.00	2.00	100.00
11	19.00	0.25	7600.00
12	2.00	1.00	200.00
13	1.00	1.00	100.00
14	2.00	2.00	100.00
15	13.00	1.00	1300.00
16	12.25	1.00	1225.00
17	10.00	1.00	1000.00
18	2.00	0.25	800.00
19	15.00	0.50	3000.00
20	14.00	0.25	5600.00
21	15.00	1.00	1500.00
22	13.00	0.50	2600.00
23	3.00	0.50	600.00
24	12.50	0.50	2500.00

* Value in parenthesis is the ratio of the treatment means.

TABLE 26

SUMMARY OF THE MAXIMUM CONCENTRATION (C_{MAX}) BY SUBJECT
HHCR 12MG AND HHIR 3MG

Subject Number	Cmax (ng/ml)		Ratio (%) HHCR 12mg / HHIR 3mg
	Treatment		
	HHCR 12mg	HHIR 3mg	
1	2.00	2.38	84.03
2	1.51	1.59	94.97
3	1.30	1.76	73.86
4	1.02	1.16	87.93
5	1.58	1.90	83.16
6	2.89	3.70	78.11
7	2.03	2.39	84.94
8	2.46	4.91	50.10
9	2.18	2.40	90.83
10	2.48	2.98	83.22
11	2.16	3.53	61.19
12	2.19	2.43	90.12
13	1.61	1.83	87.98
14	2.43	2.30	105.65
15	2.38	3.55	67.04
16	2.92	3.72	78.49
17	1.17	2.52	46.43
18	1.32	4.12	32.04
19	1.67	2.45	68.16
20	2.71	4.44	61.04
21	2.23	3.53	63.17
22	2.77	3.23	85.76
23	1.86	3.62	51.38
24	3.06	3.47	88.18

* Value in parenthesis is the ratio of the treatment means.

TABLE 27

SUMMARY OF THE MINIMUM CONCENTRATION (C_{MIN}) BY SUBJECT
HHCR 12MG AND HHIR 3MG

Subject Number	Cmin (ng/ml)		Ratio (%) HHCR 12mg / HHIR 3mg
	Treatment		
	HHCR 12mg	HHIR 3mg	
1	0.84	0.80	105.12
2	0.68	0.31	219.61
3	0.37	0.41	90.44
4	0.56	0.42	135.01
5	0.82	0.64	129.45
6	1.49	0.95	157.01
7	1.11	0.77	143.97
8	1.42	0.84	169.25
9	1.15	0.98	117.47
10	1.21	0.72	168.99
11	1.19	0.76	157.62
12	0.94	0.60	157.10
13	0.88	0.59	150.34
14	0.99	0.49	204.11
15	1.15	0.90	128.06
16	1.40	0.72	193.64
17	0.26	0.41	65.02
18	0.68	0.82	82.99
19	0.70	0.60	116.45
20	0.92	0.58	156.68
21	0.99	0.70	141.39
22	1.19	0.93	128.37
23	1.07	0.59	181.36
24	1.01	1.04	97.12

TABLE 28

SUMMARY OF THE AREA UNDER THE CURVE (0-24 HRS) BY SUBJECT
HHCR 12MG AND HHIR 3MG

Subject Number	AUC (0-24hrs)		
	Treatment		Ratio (%)
	HHCR 12mg	HHIR 3mg	HHCR 12mg / HHIR 3mg
1	33.35	32.79	101.70
2	24.38	21.18	115.14
3	18.87	22.00	85.75
4	17.54	16.48	106.46
5	28.81	30.39	94.79
6	50.62	42.99	117.75
7	36.99	33.41	110.70
8	44.73	45.07	99.24
9	36.77	37.25	98.69
10	40.72	42.21	96.47
11	37.51	37.70	99.49
12	33.54	26.73	125.45
13	28.40	25.85	109.85
14	37.86	27.19	139.23
15	37.11	43.86	84.60
16	47.52	46.43	102.35
17	18.40	29.17	63.08
18	25.86	35.08	73.71
19	26.63	31.76	83.86
20	36.37	38.86	93.60
21	41.40	37.99	108.99
22	36.79	39.32	93.58
23	31.94	29.68	107.62
24	43.68	42.49	102.82

* Value in parenthesis is the ratio of the treatment means.

TABLE 29

SUMMARY OF THE PERCENT FLUCTUATION IN CONCENTRATION (CMIN) BY SUBJECT
HHCR 12MG AND HHIR 3MG

Subject Number	% Fluctuation		
	Treatment		Ratio (%)
	HHCR 12mg	HHIR 3mg	HHCR 12mg / HHIR 3mg
1	137.53	197.13	69.77
2	121.08	411.25	29.44
3	252.30	331.37	76.14
4	81.17	178.18	45.56
5	92.21	199.21	46.29
6	93.96	289.88	32.41
7	82.88	209.99	39.47
8	73.24	485.22	15.09
9	89.57	145.15	61.71
10	104.96	316.20	33.19
11	81.51	367.55	22.18
12	132.73	305.68	43.42
13	82.13	211.22	38.88
14	144.47	372.28	38.81
15	106.96	295.32	36.22
16	108.57	414.52	26.19
17	343.18	520.69	65.91
18	94.69	404.28	23.42
19	138.23	306.98	45.03
20	196.17	660.27	29.71
21	124.35	402.13	30.92
22	132.77	248.44	53.44
23	73.83	513.56	14.38
24	202.97	233.65	86.87

* Value in parenthesis is the ratio of the treatment means.

TABLE 30

SUMMARY OF TROUGH CONCENTRATION VALUES (DAY 5) BY SUBJECT
HHCR 12MG AND HHIR 3MG

Subject Number	Trough (ng/ml)		
	Treatment		Ratio (%)
	HHCR 12mg	HHIR 3mg	HHCR 12mg / HHIR 3mg
1	1.12	1.01	110.89
2	1.26	0.89	141.41
3	0.96	0.62	155.43
4	0.63	0.48	130.17
5	1.21	0.92	132.24
6	1.99	1.42	140.14
7	1.36	1.12	121.43
8	1.99	1.15	173.04
9	1.60	1.08	148.15
10	1.28	0.92	139.13
11	1.41	1.00	141.00
12	1.55	0.99	156.41
13	1.17	0.76	154.15
14	1.20	0.78	154.64
15	1.19	1.09	109.17
16	1.55	1.05	147.62
17	0.26	1.09	24.22
18	0.68	0.96	70.33
19	1.07	0.85	125.44
20	1.14	0.95	120.63
21	0.99	0.97	102.69
22	1.35	1.05	128.57
23	1.35	0.83	163.44
24	1.47	1.06	138.68

* Value in parenthesis is the ratio of the treatment means.

Example 13

Bioequivalence, plasma concentrations, and peak-to-trough fluctuations in plasma hydromorphone concentration were evaluated in a 5-day, steady-state pharmacokinetic study comparing Example 9 (hydromorphone 12 mg) administered every 24 hours to 3 mg of immediate-release hydromorphone (bioequivalent to Dilaudid) administered every 6 hours in healthy human subjects. The two treatments were found to be equivalent in terms of extent of hydromorphone absorption ($AUC_{0-24\text{ hr}}$) (Table 30). Approximately 80% of the steady-state plasma concentration was achieved within 48 hours, and full steady-state was achieved by 3 to 4 days of dosing. Hydromorphone did not accumulate significantly after multiple dosing with once daily administration.

Table 31

Treatment	AUC (ng•h/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	Fluctuation (%)
Example 9 (12 mg q 24h)	34.9 [10]	2.1 [0.6]	1.0 [0.4]	126 [62]
Immediate-release Hydromorphone (3 mg q6h)	34.4 [8.9]	2.9 [1.0]	0.7 [0.2]	328 [124]

In comparison with immediate-release hydrocodone, Example 9 showed a smaller percent fluctuation in plasma concentrations at steady-state. Specifically, lower maximum plasma concentrations (C_{max}) and higher minimum plasma concentrations (C_{min}) than those of the immediate-release product result in a markedly lower fluctuation index, which is only 38% of that observed for the immediate-release product administered every 6 hours at the same daily dose.

Example 14

For metabolism investigations, hydromorphone and its metabolites from human urine, human plasma and human hepatocyte incubations were evaluated using LC/MS/MS technology and where available, reference standards and NMR support. Since reference standards were not

available for all metabolites, comparative results between the immediate release hydromorphone and controlled release hydromorphone are given as estimates based on relative abundance of peak areas generated by the mass spectrometer.

To compare the metabolites and their relative abundance for the controlled-release and the immediate-release formulations, plasma samples from the same time points of both formulations were pooled and analyzed under the same conditions. Results indicate that the metabolites identified from both controlled-release and immediate release formulations are the same. Their estimated abundance relative to parent hydromorphone varied, but are the same trend (see Table 32). Therefore, the hydromorphone metabolite profile from the controlled release formulation is not different from that generated by the immediate-release formulation.

The proposed metabolism pathway is as follows: following absorption, hydromorphone is metabolized to hydromorphone-3-glucuronide, dihydromorphine-6-glucuronide, hydromorphone-3-glucoside, and dihydromorphine-6-glucoside, and to a lesser extent, to dihydromorphine and dihydro-iso-morphine. On the basis of the metabolites identified, two metabolic pathways from hydromorphone (1) are proposed. The first is the 3-conjugation pathway. This led to formulation of hydromorphone-3-glucoside (2) and hydromorphone-3-glucuronide (3). The second pathway is the carbonyl reduction which leads to formulation of dihydro-iso-morphine (7) and dihydromorphine (4). Conjugation of the dihydromorphine forms dihydromorphine-6-glucoside (5) and dihydromorphine (6). The metabolites of m/z 450 and m/z 464 are only temporarily assigned to dihydromorphine-6-glucoside and dihydromorphine-6-glucuronide, respectively (there are four possible structures for each of the m/z 450 and m/z 464). It is interesting to note that by using the LCQ LC/MSⁿ in these investigations, additional metabolites, dihydromorphine-6-glucuronide and two O-glucosides, hydromorphone-3-glucoside, and dihydromorphine-6-glucoside have been found, in addition to those metabolites previously reported.

Hydromorphone-N-oxide was observed from human patient urine samples. However,

due to the spontaneous formulation of hydromorphone-N-oxide from hydromorphone, and the corresponding lability of the hydromorphone-N-oxide as hydromorphone metabolite could not be made.

TABLE 32

	Abundant Rel. to Parent	RT (minutes)	MS [M+H] ⁺	MS/MS Fragment	MS/MS/MS Fragment
From Controlled- Release:					
Hydromorphone	100%	13.9	286	185; 211; 229	157
Hydromorphone-3- glucuronide	890%	4.8	462	286	185; 229; 243
Dihydromorphine-6- glucuronide ^a	120%	4.7	464	288	187; 213; 231
Dihydromorphine	10%	8.3	288	187; 213; 231	
Dihydro-iso-morphine	32%	13.4	288	187; 213; 231	
Hydromorphone-3- glucuronide	450%	7.6	448	286	185; 229; 243
Dihydromorphine-6- glucuronide ^a	67%	7.2	450	288	187; 213; 231

From Immediate- Release:					
Hydromorphone	100%	13.5	286	185; 211; 229	157
Hydromorphone-3-Glucuronide	1550%	4.7	462	286	185; 211; 243
Dihydromorphone-6-glucuronide ^a	290%	4.6	464	288	187; 211; 213
Dihydromorphone	1.6%	8.4	288	231	
Dihydro-iso-morphine	66%	13.2	288	187; 213; 231	
Hydromorphone-3-Glucoside	610%	7.7	448	286	185; 211; 243
Dihydromorphone-6-glucoside ^a	155%	7.1	450	288	187; 211; 213

^a Proposed structure, not confirmed.

WHAT IS CLAIMED IS:

1. A solid sustained release once-a-day oral dosage form comprising hydromorphone or a pharmaceutically acceptable salt thereof, together with a sustained release carrier, the dosage providing a first peak plasma concentration of hydromorphone (C_{max} #1) in about 0.3 to about 4 hours after oral administration of the dosage form (T_{max} #1), followed by a second peak plasma concentration (C_{max} #2) of hydromorphone which occurs in about 10 to about 19 hours after oral administration of the dosage form (T_{max} #2), said dosage form providing a therapeutic effect for about 24 hours or more after administration to a human patient.
2. A solid sustained release once-a-day oral dosage form comprising hydromorphone or a pharmaceutically acceptable salt thereof, together with a sustained release carrier, the dosage providing a first peak plasma concentration of hydromorphone (C_{max} #1) in about 0.3 to about 5 hours after oral administration of the dosage form (T_{max} #1), followed by a second peak plasma concentration (C_{max} #2) of hydromorphone which occurs in about 10 to about 24 hours after oral administration of the dosage form (T_{max} #2), said dosage form providing a therapeutic effect for about 24 hours or more after administration to a human patient.
3. The dosage form of claims 1 or 2, wherein the T_{max} #1 occurs in about 1 to about 3 hours.
4. The dosage form of claims 1 or 2, wherein the plasma concentration of hydromorphone at C_{max} #1 is from about 1 to about 3 ng/ml, per administration of a 12 mg dosage of hydromorphone hydrochloride.

5. The dosage form of claims 1 or 2, wherein the plasma concentration of hydromorphone at C_{max} #1 is from about 0.4 to about 2.5 ng/ml, per administration of a 12 mg dosage of hydromorphone hydrochloride.
6. The dosage form of claims 1 or 2, wherein T_{max} #2 occurs in about 12.5 to about 24 hours after oral administration of the dosage form.
7. The dosage form of claims 1 or 2, wherein T_{max} #2 occurs in about 12.5 to about 16 hours after oral administration of the dosage form.
8. The dosage form of claims 1 or 2, wherein the plasma concentration of hydromorphone at C_{max} #2 is from about 1.0 to about 3.6 ng/ml, per 12 mg hydromorphone hydrochloride.
9. The dosage form of claims 1 or 2, wherein the plasma concentration of hydromorphone at C_{max} #2 is from about 0.5 to about 3.0 ng/ml, per 12 mg hydromorphone hydrochloride.
10. The dosage form of claims 1 or 2, wherein the W₅₀ of the plasma curve at C_{max}#1 is from about 1.5 to about 4.5 hours, preferably from about 2.5 to about 3.5 hours.
11. The dosage form of claims 1 or 2, wherein the W₅₀ of the plasma concentration curve at 50% of the height of C_{max} #2 is from about 4.5 to about 9 hours, preferably from about 5.5 to about 7.0 hours.

12. The dosage form of claims 1 or 2, wherein the W50 of the plasma concentration curve at 50% of the height of C_{max} #2 is from about 6.0 to about 20 hours, preferably from about 6.5 to about 10 hours.

13. The dosage form of claims 1 or 2, which provide an in-vitro dissolution of from about 5% to about 25% hydromorphone released after 1 hour; from about 40% to about 75% hydromorphone released after 8 hours; and not less than about 80% hydromorphone released after 18 hours.

14. The dosage form of claims 1 or 2, which provides a percent fluctuation of plasma hydromorphone concentration from about 20% to about 220%, preferably from about 60% to about 180% and most preferably about 125%.

15. The dosage form of claims 1 or 2, which provides a mean resonance time (MRT, the average time a drug molecule spends in the body) of hydromorphone from about 15 to about 35 hours, more preferably from about 25 to about 30 hours.

16. The dosage form of claims 1 or 2, further comprising an effective amount of a second drug selected from the group consisting of an opioid other than hydromorphone, an NSAID, an NMDA antagonist, a neurosteroid, acetaminophen and mixtures thereof.

17. The dosage form of claims 1 or 2, wherein the amount of hydromorphone included in said dosage form is from about 4 mg to about 100 mg.

18. The use of hydromorphone in the preparation of a solid sustained release once-a-

day oral dosage form providing a first peak plasma concentration of hydromorphone (C_{max} #1) in about 0.3 to about 4 hours after oral administration of the dosage form (T_{max} #1), followed by a second peak plasma concentration (C_{max} #2) of hydromorphone which occurs in about 10 to about 19 hours after oral administration of the dosage form (T_{max} #2), the W50 of the plasma concentration curve at 50% of the height of C_{max} #2 being from about 4.5 to about 9 hours, preferably from about 5.5 to about 7.0 hours, to provide a reduction in pain intensity within 1 to 2 hours after administration followed by a prolonged phase of absorption at a later time during the dosage interval at which later time it may be expected that the patient may experience breakthrough pain, in order to provide pain relief both early and throughout the 24-hour dosing period.

19. The use of hydromorphone in the preparation of a solid sustained release once-a-day oral dosage form providing a first peak plasma concentration of hydromorphone (C_{max} #1) in about 0.3 to about 5 hours after oral administration of the dosage form (T_{max} #1), followed by a second peak plasma concentration (C_{max} #2) of hydromorphone which occurs in about 10 to about 24 hours after oral administration of the dosage form (T_{max} #2), the W50 of the plasma concentration curve at 50% of the height of C_{max} #2 being from about 6 to about 20 hours, preferably from about 6.5 to about 10.0 hours, to provide a reduction in pain intensity within 1 to 2 hours after administration followed by a prolonged phase of absorption at a later time during the dosage interval at which later time it may be expected that the patient may experience breakthrough pain, in order to provide pain relief both early and throughout the 24-hour dosing period.

20. The use of hydromorphone in claims 18 or 19, to provide a first peak plasma concentration (C_{max} #1) of hydromorphone at bedtime, and to provide a second peak plasma concentration (C_{max} #2) of hydromorphone during waking hours, when the dosage form is

administered at night.

21. The use of hydromorphone in claims 18 or 19, to provide a first peak plasma concentration (C_{max} #1) of hydromorphone during waking hours, and to provide a second peak plasma concentration (C_{max} #2) of hydromorphone at bedtime, when the dosage form is administered in the morning.

22. A method of treating pain in humans, comprising administering to a human patient a solid sustained release oral dosage form of hydromorphone on a once-a-day basis, said dosage form providing a first peak plasma concentration of hydromorphone (C_{max} #1) in about 0.3 to about 4 hours after oral administration of the dosage form (T_{max} #1), followed by a second peak plasma concentration (C_{max} #2) of hydromorphone which occurs in about 10 to about 19 hours after oral administration of the dosage form (T_{max} #2), the W50 of the plasma concentration curve at 50% of the height of C_{max} #2 being from about 4.5 to about 9 hours, preferably from about 5.5 to about 7.0 hours, to provide a reduction in pain intensity within 1 to 2 hours after administration followed by a prolonged phase of absorption at a later time during the dosage interval at which later time it may be expected that the patient may experience breakthrough pain, in order to provide pain relief both early and throughout the 24-hour dosing period.

23. A method of treating pain in humans, comprising administering to a human patient a solid sustained release oral dosage form of hydromorphone on a once-a-day basis, said dosage form providing a first peak plasma concentration of hydromorphone (C_{max} #1) in about 0.3 to about 5 hours after oral administration of the dosage form (T_{max} #1), followed by a second peak plasma concentration (C_{max} #2) of hydromorphone which occurs in about 10 to about 24 hours after oral administration of the dosage form (T_{max} #2), the W50 of the plasma concentration

curve at 50% of the height of C_{max} #2 being from about 6 to about 20 hours, preferably from about 6.5 to about 10.0 hours, to provide a reduction in pain intensity within 1 to 2 hours after administration followed by a prolonged phase of absorption at a later time during the dosage interval at which later time it may be expected that the patient may experience breakthrough pain, in order to provide pain relief both early and throughout the 24-hour dosing period.

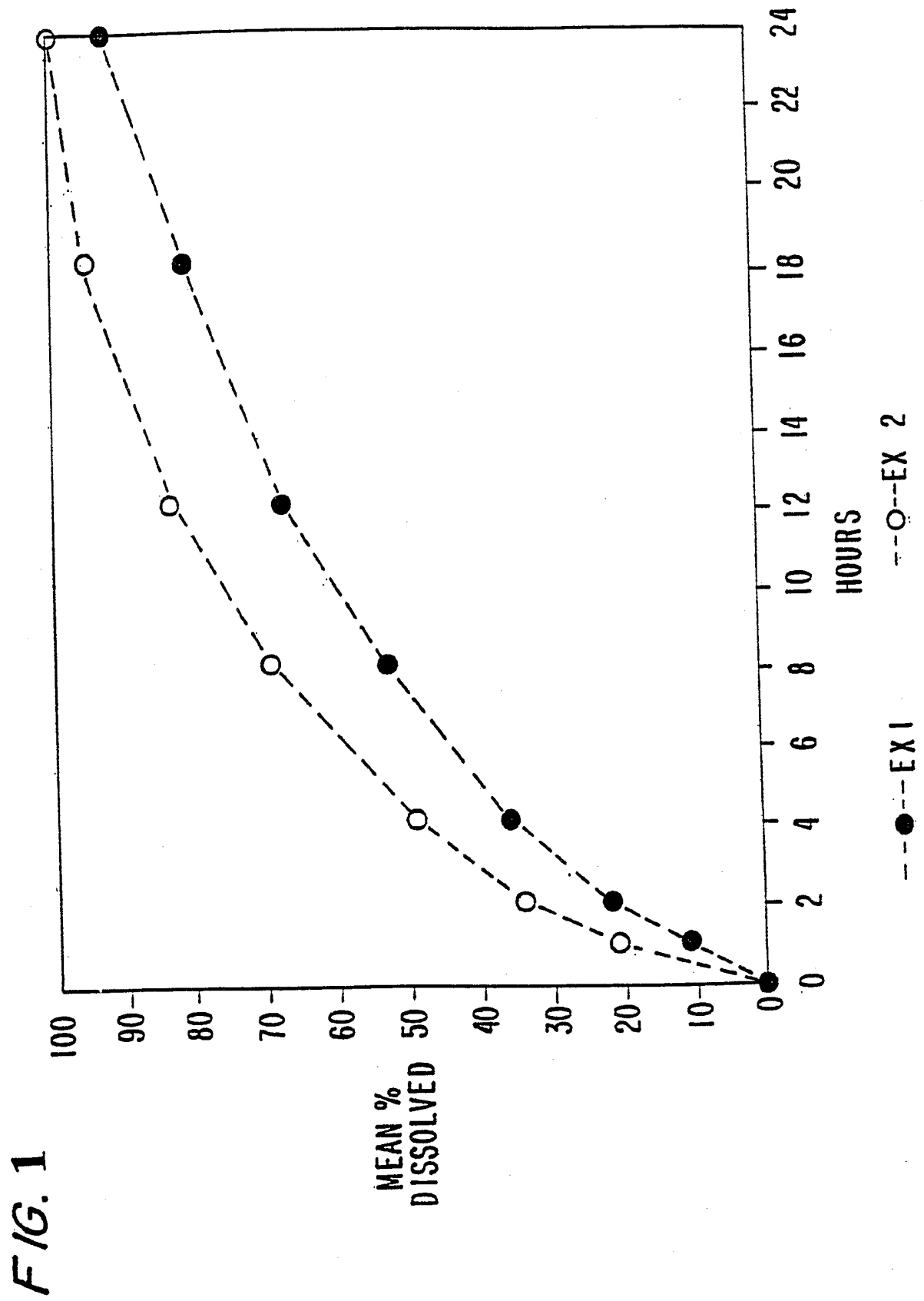
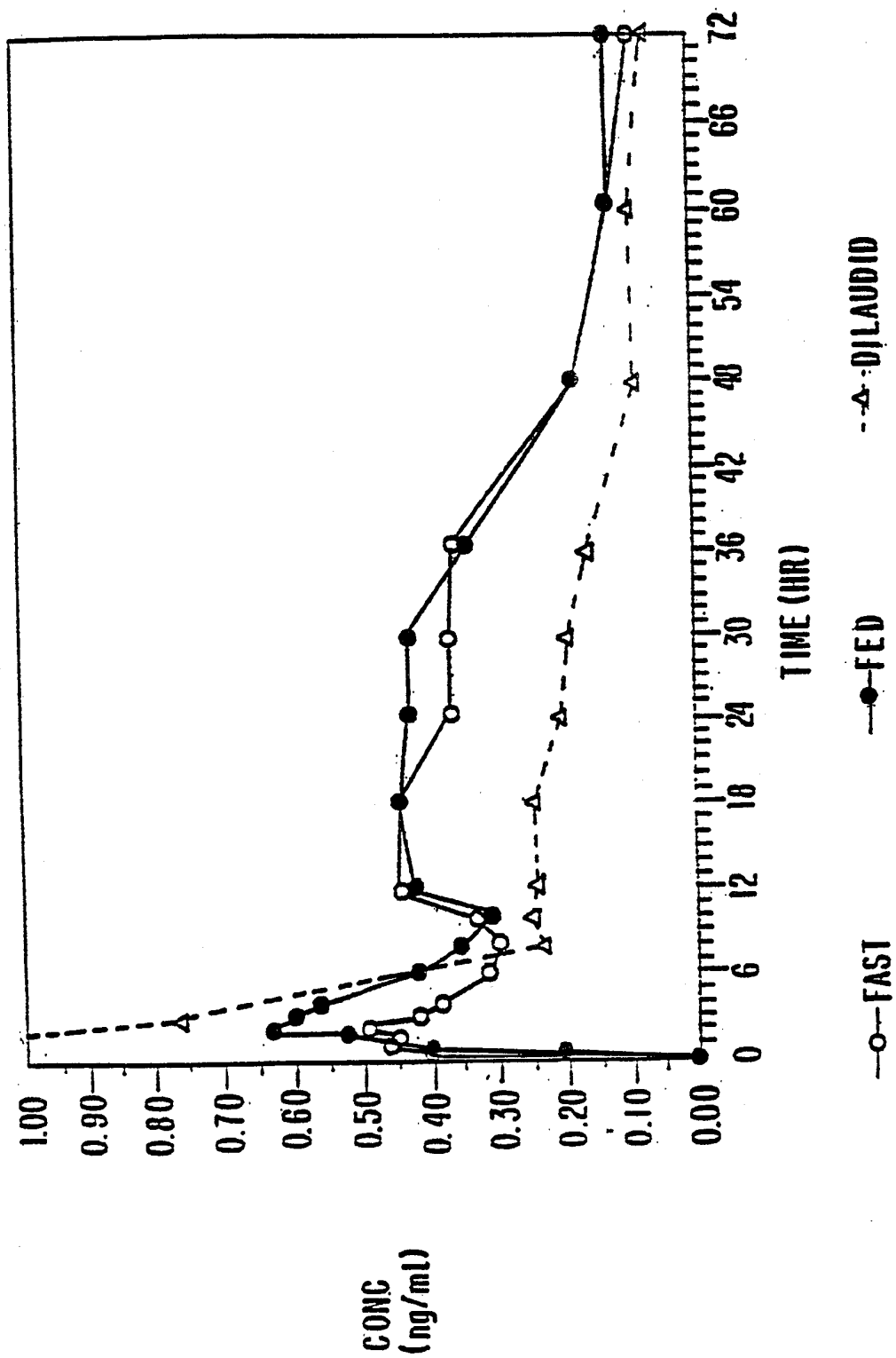


FIG. 2



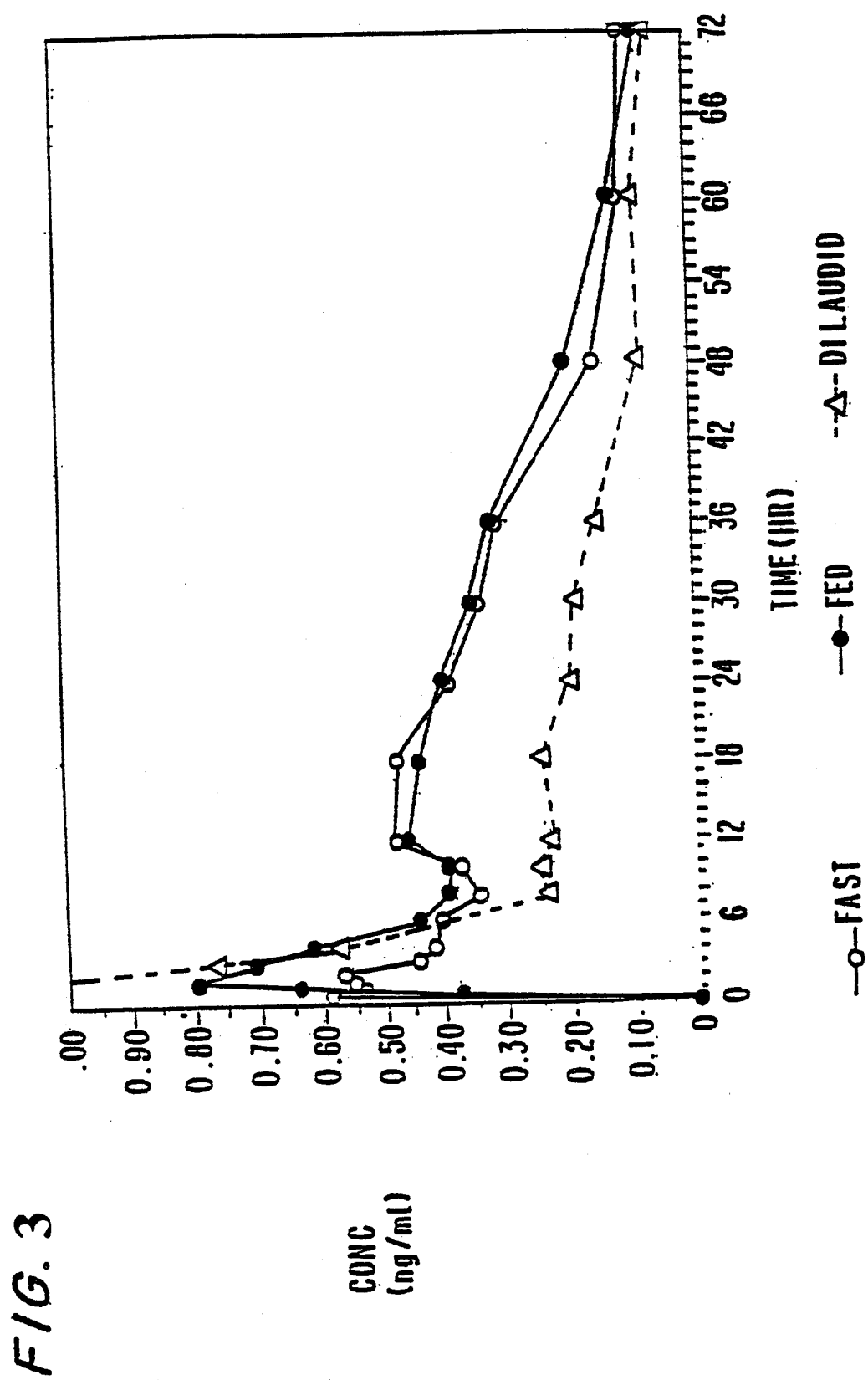


FIG. 4

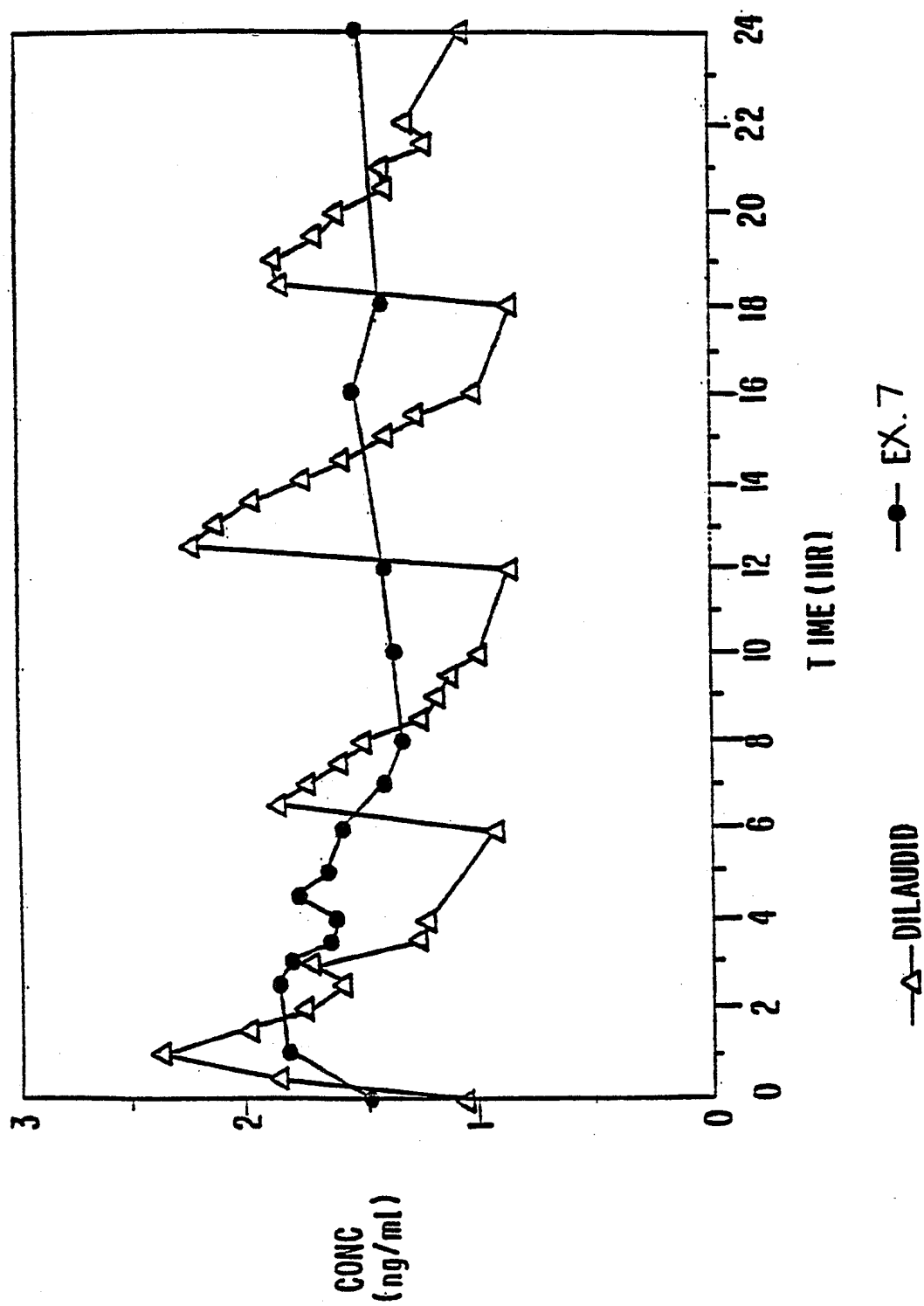
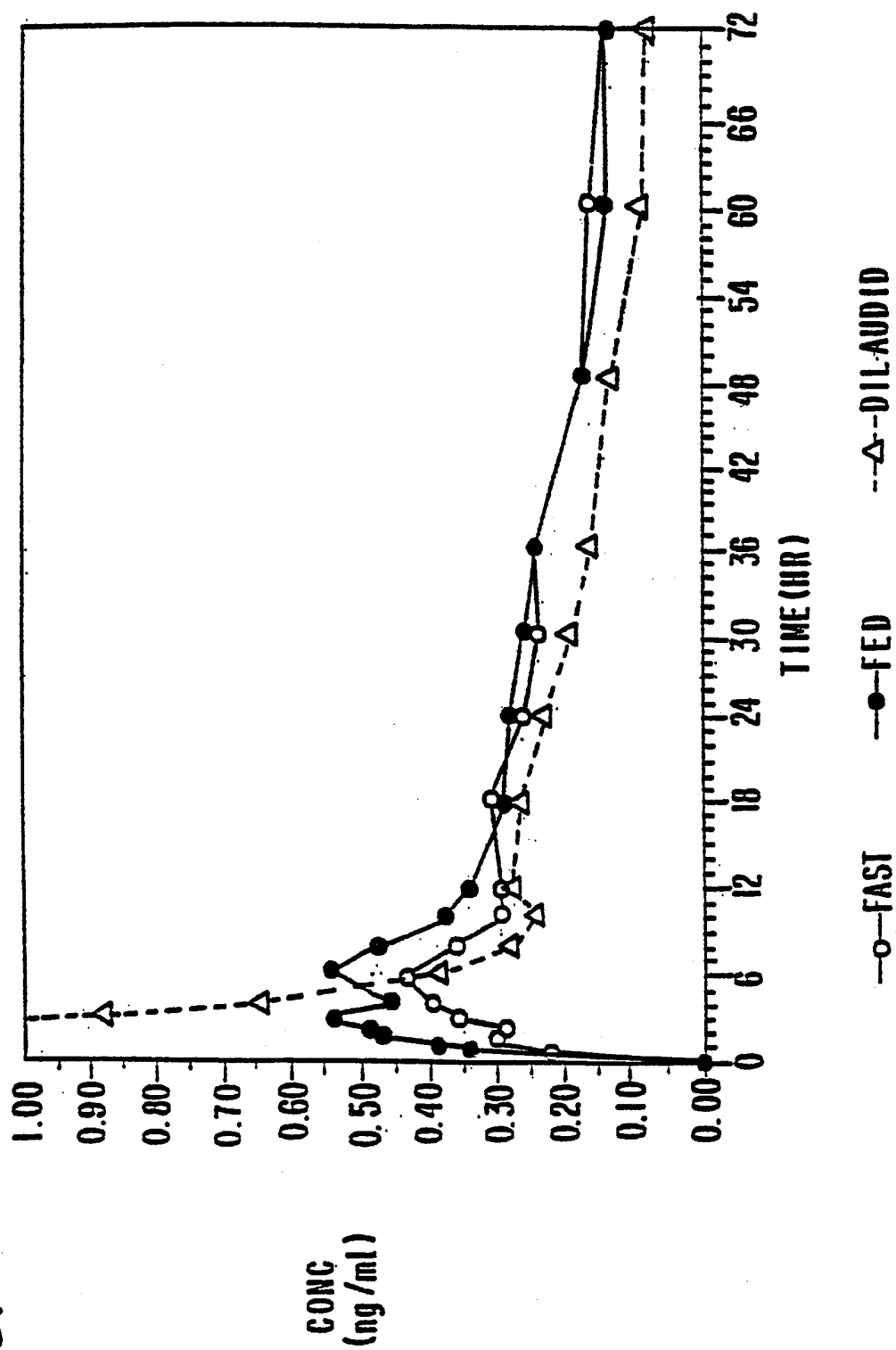


FIG. 5



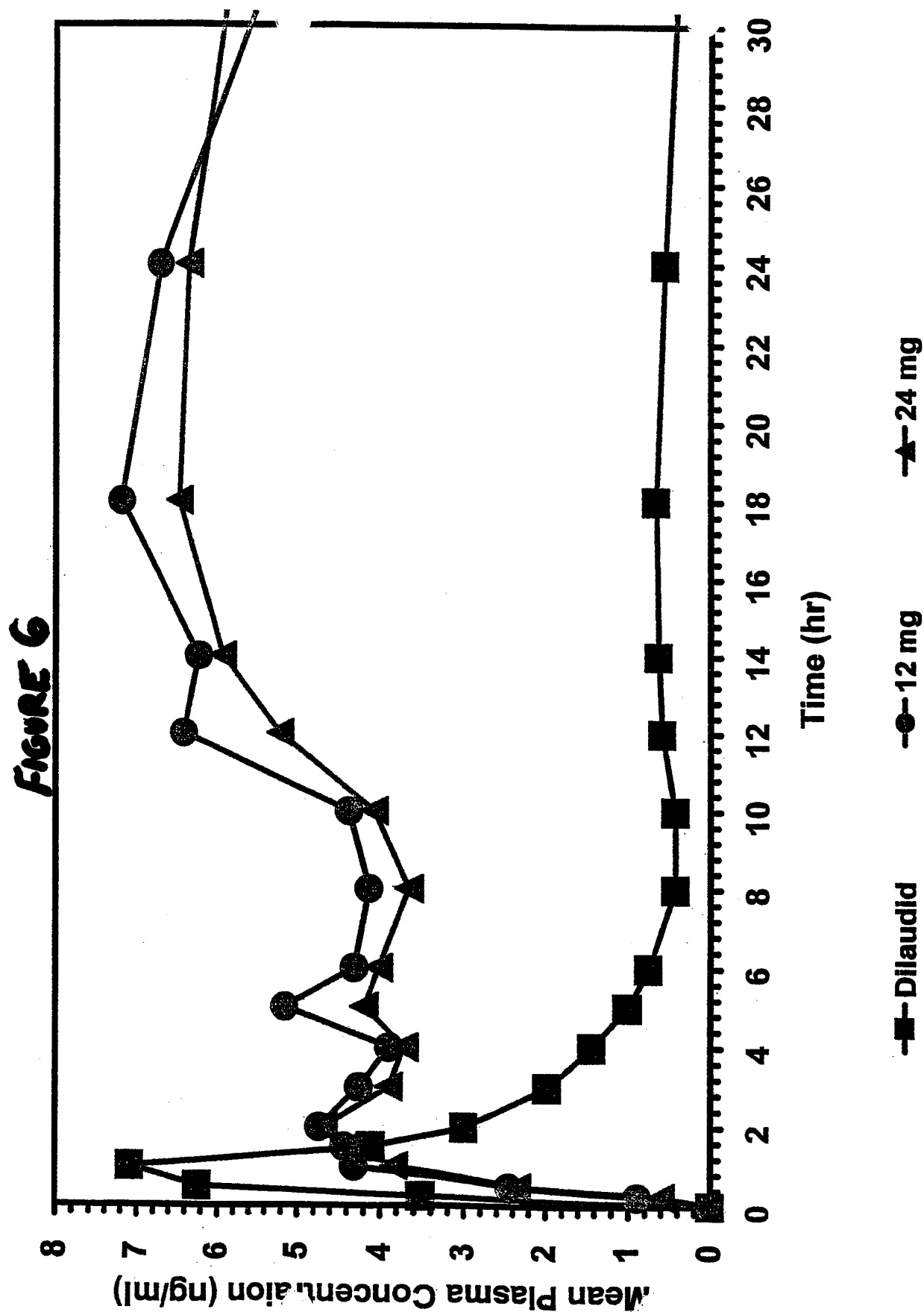
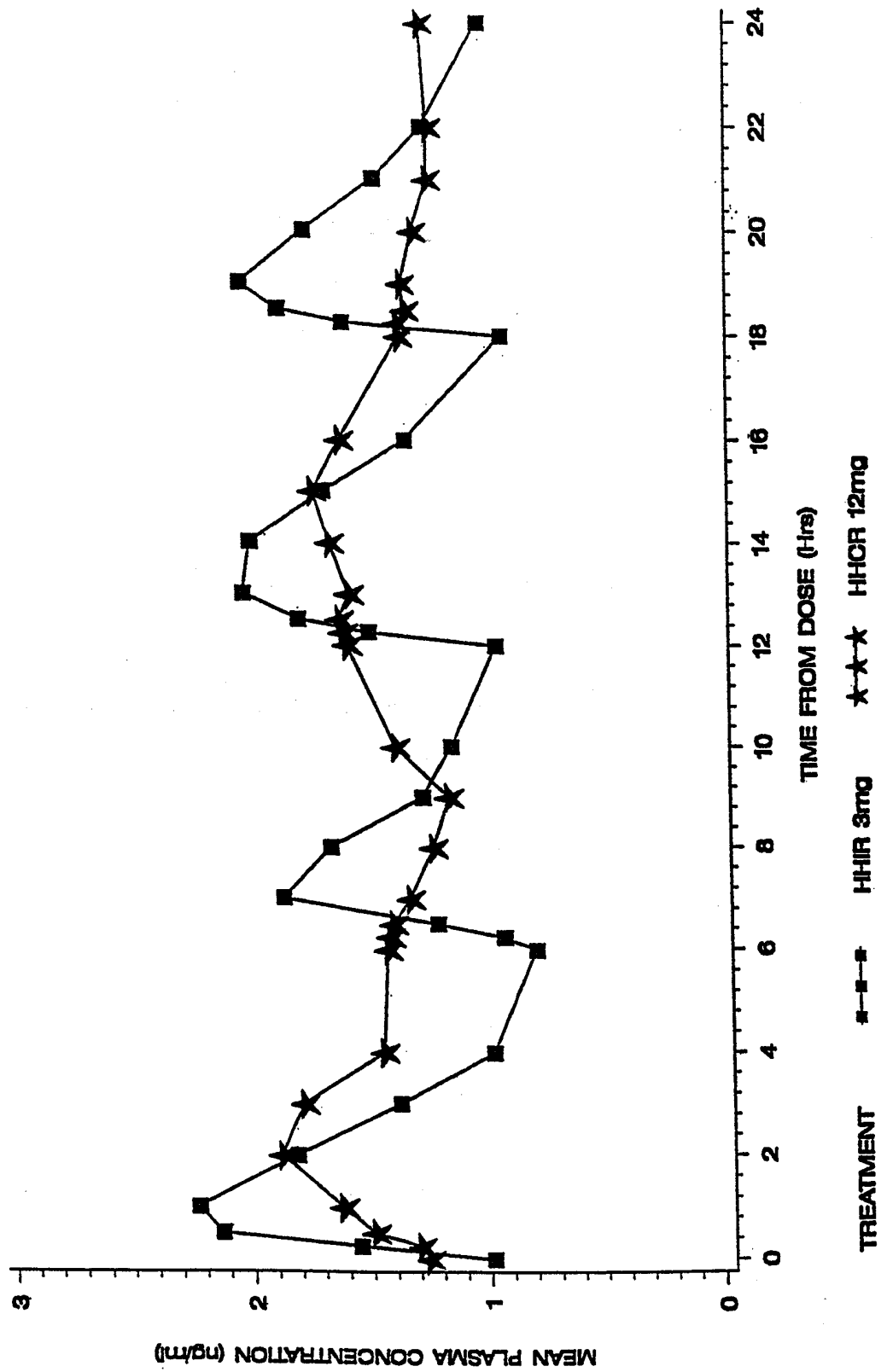
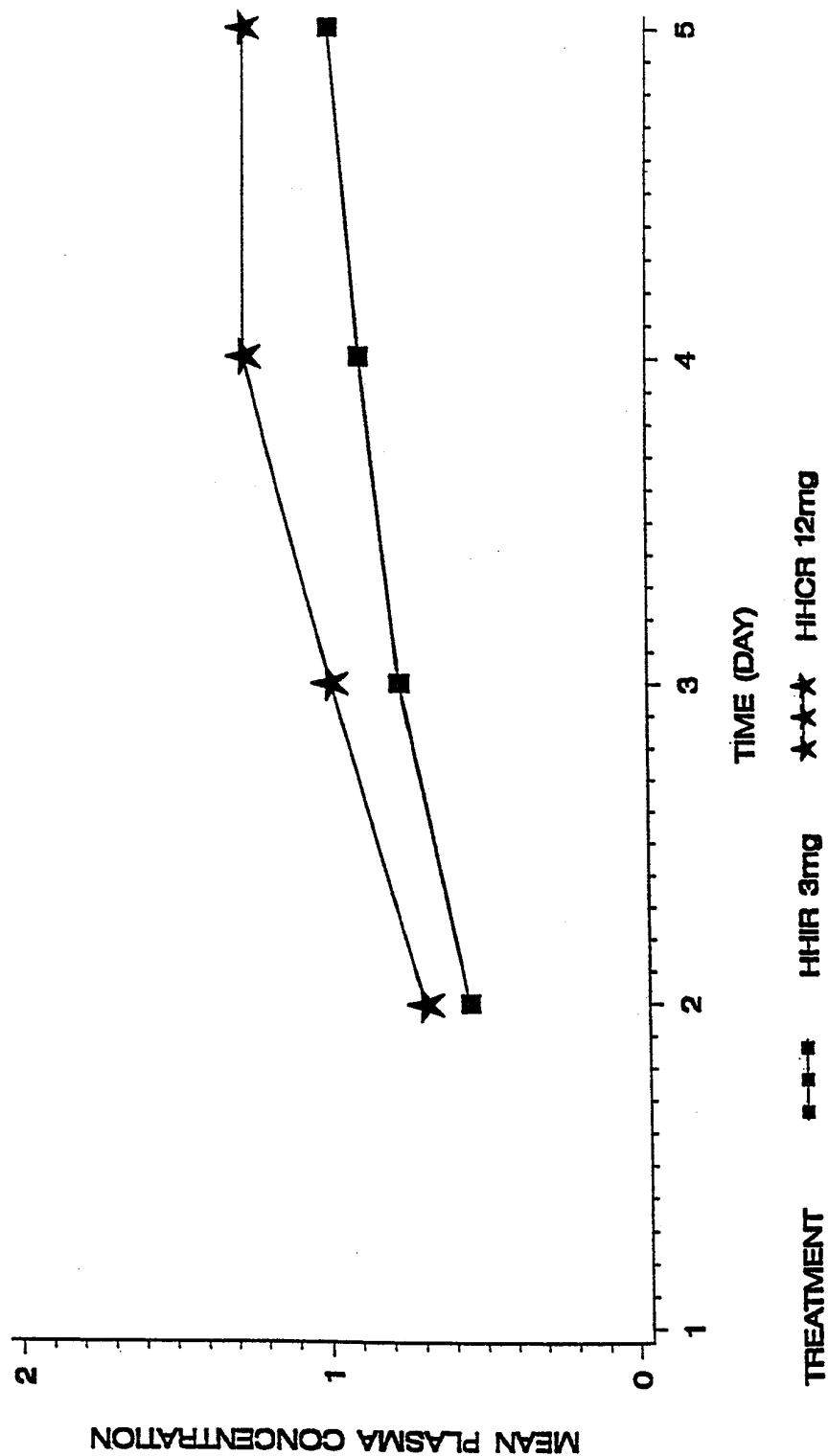


FIGURE 7
MEAN PLASMA HYDROMORPHONE CONCENTRATIONS (NG/ML) OVER TIME



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FIGURE 8
MEAN TROUGH VALUES (NG/ML) OVER TIME



Note: 1=Day 1 2=Day 2 3=Day 3 4=Day 4 and 5=Day 5

FIGURE 9
MEAN SUBJECT DRUG EFFECT (VAS,MM) OVER TIME

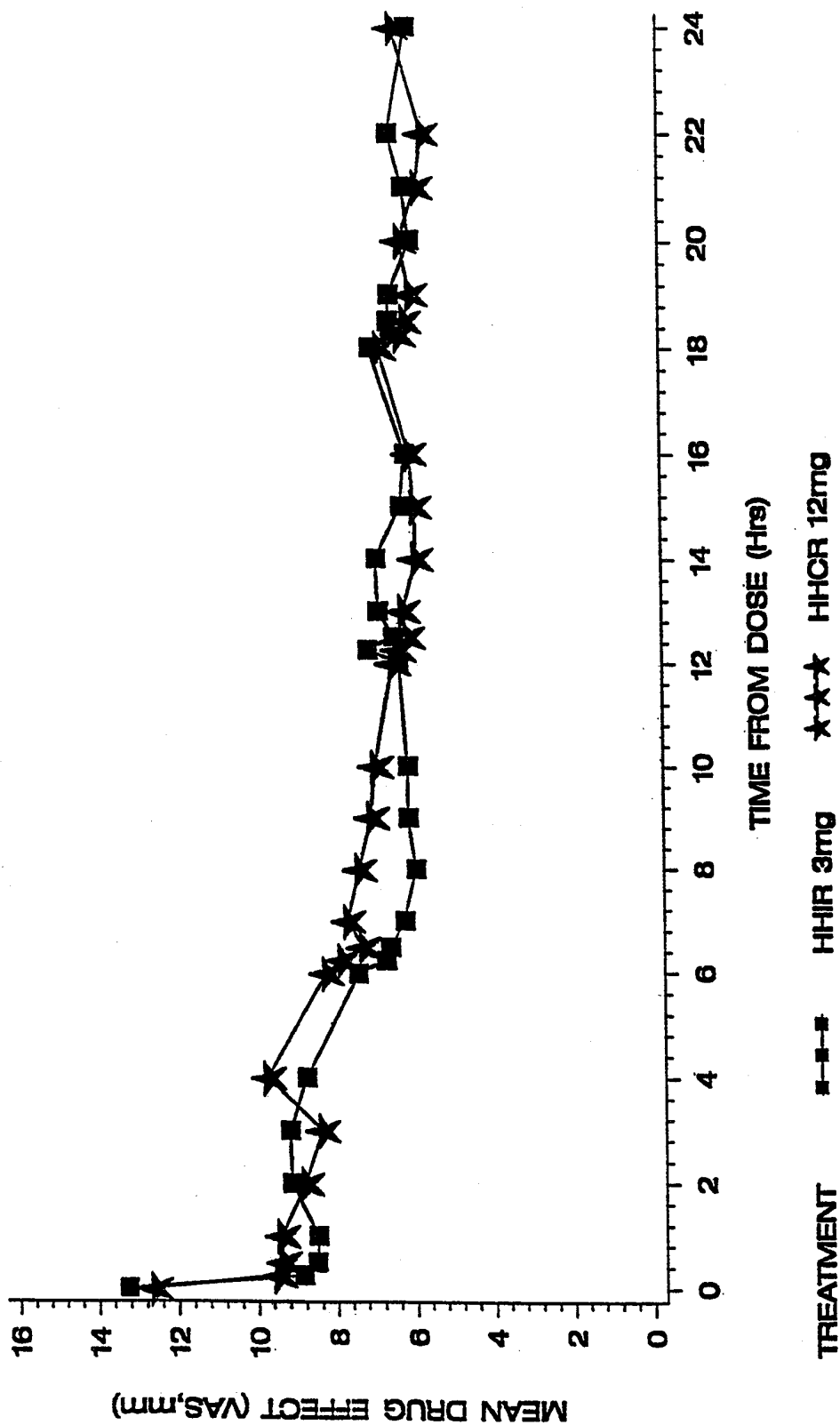
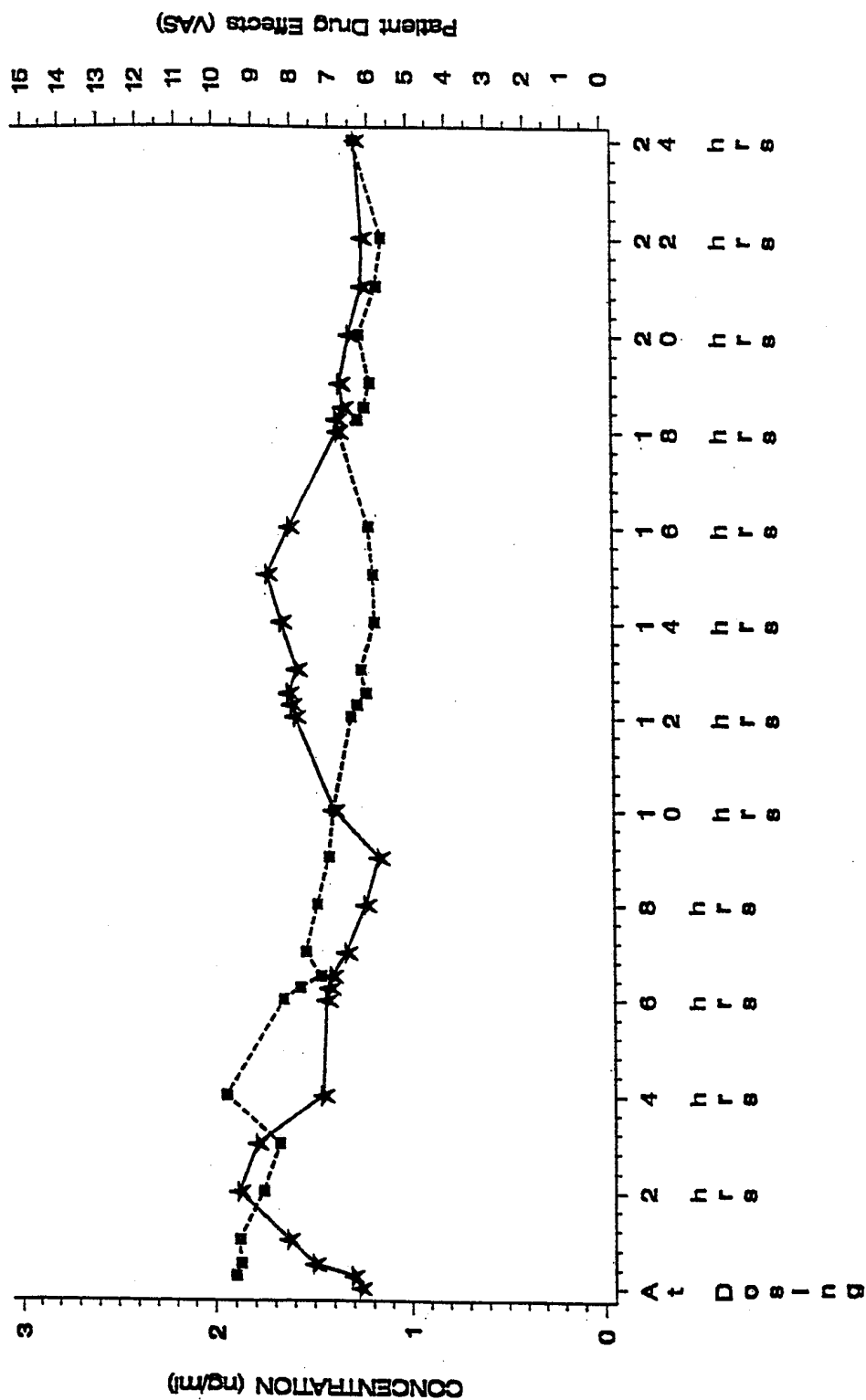


FIGURE 10

MEAN PLASMA HYDROMORPHONE CONCENTRATION (NG/ML) AND MEAN SUBJECT DRUG EFFECT (VAS,MM)

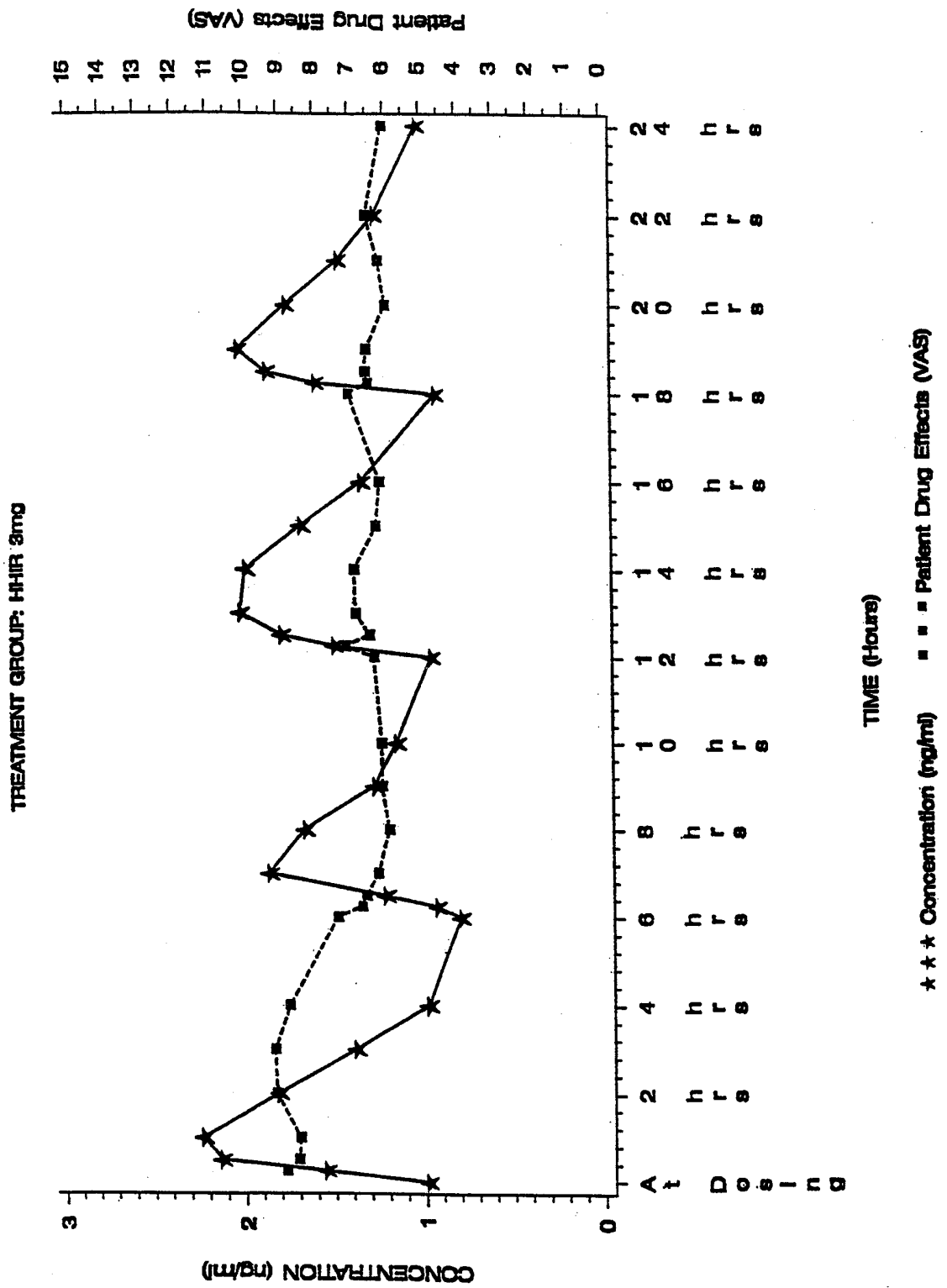
TREATMENT GROUP: HHCR 12mg



TIME (Hours)

*** Concentration (ng/ml) ■ ■ ■ Patient Drug Effects (VAS)

FIGURE 11
MEAN PLASMA HYDROMORPHONE CONCENTRATION (NG/ML) AND MEAN SUBJECT DRUG EFFECT (VAS,MM)



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22189**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) :A61K 9/48, 9/52, 9/54, 9/62

US CL :424/461, 456, 457, 458

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)

U.S. : 424/461, 456, 457, 458

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, EMBASE, DRUGU, TOXLIT, USPATFULL

search terms: hydromorphone, opioid, sustained release, delayed release, pellet, capsule, granule

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,672,360 A (SACKLER et al) 30 September 1997, see entire document.	1-23
Y	US 5,478,577 A (SACKLER et al) 26 December 1995, see entire document.	1-23
A,E,	US 5,958,459 A (CHASIN et al) 28 September 1999, see entire document.	1-23
Y,P	US 5,914,131 A (MERRILL et al) 22 June 1999, see entire document.	1-23
Y	US 4,844,909 A (GOLDIE et al) 04 July 1989, see entire document.	1-23



Further documents are listed in the continuation of Box C.



See patent family annex.

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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)	*Z* document member of the same patent family
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	

Date of the actual completion of the international search

17 NOVEMBER 1999

Date of mailing of the international search report

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