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(54) Title: ABUSE-RESISTANT DELIVERY SYSTEMS

(57) Abstract: Dosage forms comprising at least one opioid agonist prone to abuse and at least one opioid antagonist, effective to enhance the therapeutic potency of the opioid agonists and reduce their abuse or providing effective therapeutic relief for at least 12 hours.

ABUSE-RESISTANT DELIVERY SYSTEMS

FIELD OF THE INVENTION

[0001] This application claims priority from U.S. provisional patent application serial no. 61/217,434 filed on June 1, 2009, which is incorporated herein by reference.

[0002] The present invention is related to abuse-resistant pharmaceutical dosage forms comprising an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent, effective to enhance the therapeutic potency of the active agent and reduce the probability of abuse of the active agent. The antagonist functions in dual roles, both to enhance the therapeutic potential and attenuate the side effects of the active agent and also to reduce the likelihood of abuse of the active agent prone to abuse.

BACKGROUND OF THE INVENTION

[0003] Prescription medications such as pain relievers, central nervous system (CNS) depressants (tranquilizers and sedatives), and stimulants are highly beneficial treatments for a variety of health conditions. For example, pain relievers enable individuals with chronic pain to lead productive lives; tranquilizers can reduce anxiety and help patients with sleep disorders; and stimulants help people with attention-deficit hyperactivity disorder (ADHD) focus their attention. Most people who take prescription medications use them responsibly. However, when abused, that is, taken by someone other than the patient for whom the medication was prescribed, or taken in a manner or dosage other than what was prescribed, prescription medications can produce serious adverse health effects and can lead to addiction.

[0004] The common abused classes of prescription drugs include opioids, central nervous system depressants, and stimulants. Commonly abused opioids include drugs such as, oxycodone (OxyContin), propoxyphene (Darvon), hydrocodone (Vicodin), hydromorphone (Dilaudid), meperidine (Demerol), and diphenoxylate (Lomotil). Common central nervous system depressants include barbiturate drugs such as, pentobarbital sodium (Nembutal), and benzodiazepines such as diazepam (Valium) and alprazolam (Xanax), and stimulants include drugs such as, dextroamphetamine (Dexedrine) and methylphenidate (Ritalin).

[0005] Opioid or the opioid agonist class of drugs include morphine, the archetypical opioid, and various others such as, for example, codeine, dihydrocodeine, hydrocodone,

hydromorphone, levorphanol, meperidine, buprenorphine, fentanyl, fentanyl derivatives, dipipanone, heroin, tapentadol tramadol, etorphine, dihydroetorphine, butorphanol, methadone, diamorphine, oxycodone, oxymorphone, pethidine and propoxyphene, and the like. Opioid agonists chemically interact with areas or binding sites of the central nervous system related to the perception of pain, to movement, mood and behavior, and to the regulation of neuroendocrinological functions. Opioid agonists exhibit pharmacological properties that provide a range of therapeutic uses for patients in addition to analgesic use. Opioid agonists have been prescribed for effective use as hypnotics, sedatives, anti-diarrheal, anti-spasmodic, and anti-tussives. Unfortunately, opioid agonists have been associated with a number of undesirable side effects; constipation, respiratory depression, nausea, vomiting, dizziness, orthostatic hypotension, drowsiness, urinary retention, itch, dry mouth, headache, miosis, changes in mood and mental clouding resulting without resulting loss of consciousness in patients, and, due to the addictive properties, has been subjected to illegal diversion for abuse by addicts.

[0006] Widely used opioid agonists include Morphine, Oxycodone, Tramadol and recently approved Tapentadol; all have been reported to have numerous side effects and are prone for diversion for abuse. Morphine has a high potential for addiction; tolerance and both physical and psychological dependence develop rapidly. Other side effects include symptoms such as, constipation, addiction, tolerance and abuse. Another opioid agonist, Oxycodone's, reported side effects include constipation, fatigue, dizziness, nausea, lightheadedness, headache, dry mouth, anxiety, pruritus, euphoria, and diaphoresis. It has also been claimed to cause dimness in vision due to miosis. Patients have also experienced loss of appetite, nervousness, abdominal pain, diarrhea, dyspnea, and hiccups.

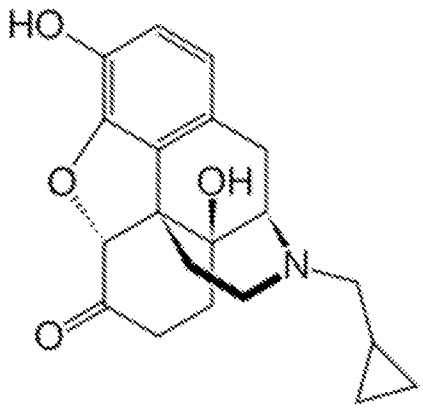
[0007] Tramadol, (±) cis-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclo-hexanol hydrochloride, is a centrally acting synthetic opioid analgesic. It is commercially available as a hydrochloride salt, Ultram (tablets). Tramadol's reported side effects include nausea, constipation, dizziness, headache, drowsiness, and vomiting. Less commonly reported side effects include itching, sweating, dry mouth, diarrhea, rash, visual disturbances, and vertigo. Attempts to prevent/reduce these side effects include prescribing lower doses of tramadol, hopefully without compromising the extent of pain relief.

[0008] Tapentadol, 3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol, is a centrally acting analgesic with a dual mode of action: ! -opioid receptor agonism and noradrenaline reuptake inhibition. Its dual mode of action provides analgesia at similar levels of more potent narcotic analgesics such as hydrocodone, oxycodone, and morphine with a more tolerable side effect profile.

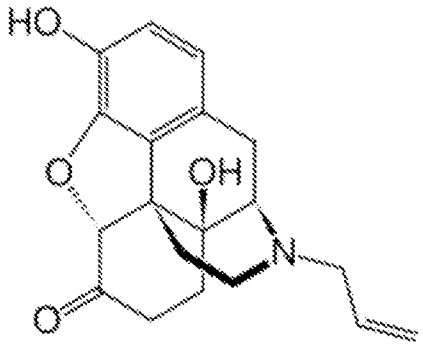
[0009] Tapentadol was first disclosed in European patent no. EP 693,475, U.S. patent no. 6,248,737 and U.S. patent no. RE39,593. Tapentadol was placed under schedule II by the FDA based on its potential for abuse. Further the most common side effects from tapentadol are nausea, dizziness, vomiting, and sleepiness. The labeling for tapentadol includes warnings about the risk of respiratory depression; addictive depressive effects on the central nervous system when taken with alcohol, other opioid, or illicit drugs; and abuse potential.

[0010] Despite the benefits derived from active agents such as opioids, stimulants, depressants, area of concerns relate to the incidence of unwanted side effects and diversion by potential abuser for their narcotic properties. Opioid analgesics, such as morphine, are sparingly prescribed for pain because of the well-known addictive effects and significant central nervous system (CNS) side effects and gastrointestinal side effects. Hence it is desirable to reduce their abuse potential by developing abuse safe formulations and also wherever possible reduce the dosage to alleviate the patients of its side effects without comprising the extent of pain relief. Thus, there is an unmet need to develop pharmaceutical dosage forms of active agents that are prone to abuse that minimize side effects and enhance analgesic effects with zero abuse potential.

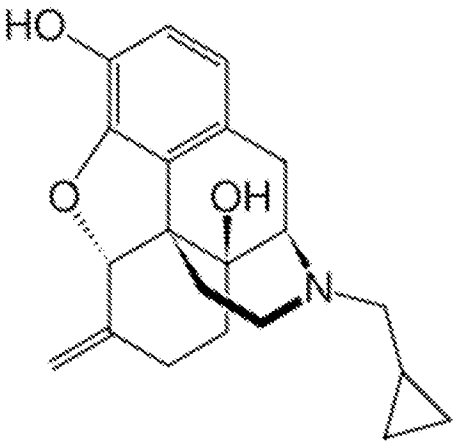
[0011] In order to alleviate the side effects and the abuse of active agents prone to abuse, antagonists of these active agents have been used in various forms. Antagonists are compounds that modify the response of their respective receptors. For example; Opioid receptors are a group of G-protein coupled receptors with opioids as ligands. Opioid antagonists include naloxone, naltrexone, diprenorphine, etorphine, dihydroetorphine, nalinefene, cyclazacine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof. Certain embodiments include the opioid antagonist is naltrexone (Formula 1), naloxone (Formula 2), and/or nalmefene (Formula 3):



Formula 1



Formula 2



Formula 3

[0012] The use of antagonists to address the potential side effects and the abuse are known in the art. For example U.S. patent no. 5,866,164 discloses a dosage system that comprises multiple layers with an opioid analgesic and the second layer comprises an antagonist for this opioid analgesic and simultaneously affecting the push function. U.S. patent no. 5,472,943 to

Crain *et al.* discloses methods of enhancing the analgesic potency of bimodally acting opioid agonists by administering the agonist with an opioid antagonist. U.S. patent no. 6,277,384 discloses a dosage form containing a combination of an opioid agonist and an opioid antagonist in a specific ratio, which brings about a negative effect on administration to an addicted person. U.S. patent no. 6,228,863 discloses a dosage form containing a combination of an opioid agonist and an opioid antagonist, such that the two compounds can in each case only be extracted together from the dosage form and then additional processes required to separate them. U.S. patent application no. 2005/0191244 discloses the opioid agonist formulations comprising an opioid agonist, antagonist and gelling agent or an irritant to prevent the abuse opioid agonist. U.S. patent No. 6,716, 449 discloses controlled release opioid agonist and controlled release opioid antagonist combinations for enhancing the analgesic potency of an opioid agonist and U.S. patent No. 7,332,142 discloses pharmaceutical composition comprising an opioid agonist, an opioid antagonist and an irritant purport to lessen the abuse.

[0013] U.S. patent No. 6,559,159 to Carroll *et al.* describes the use of kappa receptors antagonist for the treatment of opioid related addictions. U.S. patent No. 6,309,668 describes a tablet for oral administration containing two or more layers comprising one or more drugs and one or more gelling agents within separate layers of the tablet. U.S. patent No. 6,228,863 teaches the reduction of the abuse potential of oral dosage forms of opioid analgesics by selecting the particular opioid agonist and antagonist pair, and the concentrations of the same such that the antagonist cannot be easily extracted from the agonist. U.S. patent nos. 6,277,384, 6,375,957 and 6,475,494 discloses oral dosage forms including a combination of an orally active opioid agonist and an orally active opioid antagonist in a ratio that, when delivered orally, is analgesically effective but that is aversive in a physically dependent subject. U.S. patent No. 4,457,933 discloses the reduction in the oral abuse potential of the analgesics oxycodone, propoxyphene and pentazocine by combining the analgesic with naloxone in a specific range. U.S. patent No. 3,773,955 discloses orally effective analgesic compositions which contain from about 0.1 mg to about 10 mg naloxone with an opioid analgesic. U.S. patent no. 3,493,657 to Lewenstein, *et al.* discloses compositions comprising naloxone and morphine or oxymorphone. U.S. patent no. 4,582,835 to Lewis describes a method of treating pain by administering a sublingually effective dose of buprenorphine with naloxone.

[0014] The patents discussed hereinabove, disclose dosage forms, compositions and methods that either address the side effects by using an antagonist of an active agent prone to abuse in small amounts that purport to enhance the therapeutic properties or in amounts large enough to disrupt the effects of active agent prone to abuse, if the dosage form is disrupted by abusive methods such as physical grinding. However, these patents fail to disclose a dosage form comprising an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent, wherein the antagonist performs dual roles of both enhancing the therapeutic potency of active agent prone to abuse and attenuating side effects, and to also prevent its abuse if the dosage form is tempered with.

[0015] Similarly, a method of treating pain by administering to patient in need thereof, an optimal or suboptimal amount of at least one opioid agonist, and at least one antagonist of the opioid agonist, wherein the antagonist performs dual roles of both enhancing the analgesic potency of the opioid agonist and reducing its side effects and also preventing its abuse when the dosage system is tempered upon is not disclosed.

[0016] There is a need for dosage forms comprising an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent, wherein the antagonist enhances therapeutic potency and/or attenuates one or more adverse effects and reduce the abuse of the active agent prone to abuse. There is also a need for a method of treating pain by administering to a patient in need thereof, at least one opioid agonist, and at least one opioid antagonist, to enhance analgesic potency and/or attenuate one or more adverse effects of the opioid agonist.

[0017] There is also a need for slow release dosage forms comprising an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent, to enhance therapeutic potency and/or attenuate one or more adverse effects. There is also a need for a method for treating a disease by administering to a patient in need thereof, a slow release dosage form comprising an optimal or suboptimal amount of at least one opioid agonist, and at least one opioid antagonist, to enhance therapeutic potency and/or attenuate one or more adverse effects.

[0018] In addition, there is an unmet need for a dosage forms comprising an optimal or suboptimal amount of at least one active agent prone to abuse, at least one antagonist of the active agent, and an optimal or suboptimal amount of a second active agent, wherein the

antagonist enhances the therapeutic potency and reduce the abuse of active agent. Still further, there is a need for a method of treating a disease by administering to a patient in need thereof, an optimal or suboptimal amount of an opioid agonist, an opioid antagonist and an optimal or suboptimal amount of a second active agent, wherein the antagonist enhances the analgesic potency and reduce the abuse of opioid agonist.

SUMMARY OF THE INVENTION

[0019] The instant invention provides, therapeutically enhanced dosage forms, methods and uses of such dosage forms to address the unmet needs. Such dosage forms comprise an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent, wherein the antagonist is bioavailable at a level to enhance the therapeutic potency of the active agent prone to abuse (agonist) and when the dosage form is abused, the opioid antagonist is provided at a level sufficient to reduce probability of abuse of the active agent prone to abuse.

[0020] In another embodiment, the invention provides a method for treatment of a disease in a mammal (*e.g.*, human) comprising administering to a mammal, in need of such treatment, a dosage form composition an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent, for enhancing therapeutic potency of the active agent and/or attenuating its adverse effects, and reduce probability of abuse of the active agent than other dosage forms.

[0021] In another embodiment, the invention provides a method for treatment of pain and pain related disorders in a mammal (*e.g.*, human) comprising administering to a mammal, in need of such treatment, an dosage form composition an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent, for enhancing therapeutic potency of the active agent and/or attenuating its adverse effects, and reduce probability of abuse of the active agent than other dosage forms.

[0022] In another embodiment, the invention provides dosage forms comprising an optimal or suboptimal amount of at least one active agent prone to abuse, at least one antagonist of the active agent, and an optimal or suboptimal amount of a second active agent, wherein the antagonist enhances the therapeutic potency and reduce probability of abuse of active agent.

The second active agent can include drugs such as a gamma-aminobutyric acid (GABA) analogue or an NSAID or a non-NSAID such as naproxinoid.

[0023] In another embodiment, the invention provides a method of treating a disease by administering to a patient in need thereof, an optimal or suboptimal amount of an opioid agonist, an opioid antagonist and an optimal or suboptimal amount of a second active agent, wherein the antagonist enhances the analgesic potency and reduce the abuse of opioid agonist is provided. The second active agent can be a drug such as a gamma-aminobutyric acid (GABA) analogue or an NSAID.

[0024] In another embodiment, the invention provides dosage forms and methods suitable for a desirable therapeutic potency and/or minimal adverse side effects and can reduce abuse associated with the administration of an active agent prone to abuse, in mammals (*e.g.*, humans), wherein the dosage forms include immediate release dosage forms, slow release dosage forms and combinations thereof. The dosage forms have an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent, in combination with at least one additional active agent thereof. The antagonist can perform dual roles of enhancing the therapeutic potency of the active agent prone to abuse and attenuating the side effects and also preventing the abuse if the dosage form is abused.

[0025] In another embodiment, the invention provides a dosage form of an active agent prone to abuse, which is less likely to be abused than other dosage forms.

[0026] In another embodiment, the invention provides a dosage form comprising an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent; wherein the bio availability of the antagonist is at a level just sufficient to enhance the therapeutic potency of the active agent prone to abuse and also has sufficient bio availability to reduce the effect of the active agent if the dosage form is used in an abusive manner. The present invention provides a dosage form having one or more antagonist(s), of an active agent prone to abuse, within the dosage formulation of the active agent pharmaceutical product so that, under normal conditions, the antagonist of the active agent prone to abuse has bioavailability just sufficient to enhance the therapeutic potency of the active agent prone to abuse. However, upon disruption of the dosage form, through any of a variety of means, the antagonist will have sufficient bioavailability to diminish the effects of the active agent.

[0027] In another embodiment, the invention provides a dosage form comprising an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent, wherein the antagonist enhances the therapeutic potency of the dosage form and reduces the potential for abuse of active agent prone to abuse and wherein the dosage form provides effective pain relief for at least about 12 hours, or preferably at least about 24 hours, when administered to a mammal (*e.g.*, human) patient.

[0028] In another embodiment, the invention provides a dosage form comprising an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent; such that the dosage form provides effective pain relief for at least about 12 hours, or preferably at least about 24 hours, when administered to a mammal (*e.g.*, human) patient.

[0029] In yet another embodiment, the invention provides a dosage form for both selectively enhancing the analgesic potency and simultaneously attenuating anti-analgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects associated with the administration of an active agent prone to abuse and reducing the potential for abuse of the active agent. The dosage form comprises at least one active agent prone to abuse, and at least one antagonist of the active agent; wherein the antagonist is released at a level sufficient to enhance the therapeutic potency of the agent and at a level sufficient to attenuate the anti-analgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects of the active agent.

[0030] In yet another embodiment, the present invention provides a dosage form comprising an optimal or suboptimal amount of a bimodally-acting opioid agonist, and an opioid receptor antagonist, wherein the opioid antagonist enhances the analgesic potency of the bimodally-acting opioid agonist and attenuates one or more of the anti-analgesia, hyperalgesia, hyperexcitability, physical dependence, tolerance effects of the bimodally-acting opioid agonist in a subject administered the composition and reduce the abuse of opioid agonist.

[0031] In yet another embodiment, the present invention provides a method for treatment of analgesia comprising administering to the subject an optimal or suboptimal amount of at least one active agent prone to abuse, and an amount of at least one excitatory antagonist effective to enhance the therapeutic potency of the active agent and attenuates one or more of anti-

analgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects of the active agent.

[0032] In yet another embodiment, provides a dosage form comprising an optimal or suboptimal amount of at least one active agent prone to abuse, and an amount of at least one excitatory antagonist of said active agent in an amount effective to reduce the potential for abuse of the active agent.

[0033] In yet another embodiment, the present invention is provides a dosage form comprising an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent; wherein the antagonist attenuates an adverse side effect associated with the administration of the active agent to a human subject and reduces the abuse of the active agent prone to abuse. Adverse side effects (of opioid agonists) include, but are not limited to, nausea, vomiting, dizziness, headache, somnolence (sedation) or pruritis. Analgesic potency of the agonist may be maintained while one or more side effects are attenuated, without increasing or decreasing the cumulative daily dose of the active agent.

[0034] Antagonists useful in the present invention include, for but not limited to, antagonists for opioids, non-opioid narcotics, stimulants, central nervous system (CNS) depressants, tranquilizers, and barbiturates and cold and cough drugs such as pseudoephedrine, etc.

[0035] One object of the present invention is to provide method for treating pain with a dosage form comprising an optimal or suboptimal amount of at least one opioid agonist, and at least one antagonist of the opioid agonist, wherein the antagonist enhances the analgesic potency of the opioid agonist and reduces the potential for abuse of said opioid agonist and the dosage form provides effective pain relief for at least about 12 hours, or preferably at least about 24 hours, when administered to a mammal (*e.g.*, human) patient.

[0036] In yet another embodiment, present invention provides a method for treatment of pain with a dosage form comprising an optimal or suboptimal amount of at least one opioid agonist, and at least one antagonist of the opioid agonist, wherein the antagonist is delivered from the dosage form at a level just sufficient to enhance the analgesic effects of the opioid agonist and the antagonist is delivered from the dosage form at a level sufficient quantity to

diminish the effects of the opioid agonist, when the dosage form is physically or otherwise disrupted through use in a manner not intended by the drug manufacturer.

[0037] In yet another embodiment, the present invention provides a dosage form comprising an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one opioid antagonist, wherein the dosage form, upon oral administration, results in an adverse event profile which is better than the adverse event profile resulting from the administration of a dosage form without an antagonist.

[0038] In yet another embodiment, the present invention provides a method for administering to a subject a dosage form comprising an optimal or suboptimal amount of at least one opioid agonist, and at least one antagonist of the opioid agonist, wherein the antagonist(s) enhance the analgesic potency of the opioid agonist and attenuates one or more of anti-analgesia, hyperalgesia, hyperexcitability, physical dependence, or tolerance effects of the opioid agonist.

[0039] In yet another embodiment, the present invention provides a method for enhancing the potency of at least one opioid agonist, in a mammal, (*e.g.*, a human) subject by administering to the subject an optimal or suboptimal amount of at least one opioid agonist, and at least one antagonist of the opioid agonist, wherein the antagonist is effective to enhance the analgesic potency of the opioid agonist.

[0040] The opioid antagonists include but not limited to, naltrexone, naloxone, nalmefene, nalide, nalmexone, nalorphine, nalorphine dinicotinate, cyclazocine, levallorphan, pharmaceutically acceptable salts thereof, antagonists of stimulants, antagonists of depressants and the like. Preferred opioid antagonists include naltrexone, naloxone, or nalmefene.

[0041] In yet another embodiment, the present invention provides a dosage form comprising an optimal or suboptimal amount of at least one opioid agonist, and at least one opioid antagonist, wherein the dosage form, upon oral administration, provides an adverse event profile which is better than the adverse event profile resulting from the administration of a dosage form without an opioid antagonist.

[0042] In yet another embodiment, the present invention provides a dosage form comprising an optimal or suboptimal amount of at least one opioid agonist, and at least one opioid antagonist, wherein the dosage form, upon oral administration, results in fewer

occurrences of dizziness or vertigo than would result from the administration of a dosage form without an opioid antagonist.

[0043] In yet another embodiment, the present invention provides a dosage form comprising an optimal or suboptimal amount of at least one opioid agonist, and at least one opioid antagonist, wherein the dosage form, upon oral administration, results in fewer occurrences of nausea than would result from the administration of a dosage form without an opioid antagonist.

[0044] In yet another embodiment, the present invention provides a dosage form comprising a an optimal or suboptimal amount of an at least one opioid agonist, and at least one opioid antagonist, wherein the dosage form, upon oral administration, results in fewer occurrences of vomiting than would result from the administration of a dosage form without an opioid antagonist.

[0045] In yet another embodiment, the present invention provides a dosage form comprising an optimal or suboptimal amount of at least one opioid agonist, and at least one opioid antagonist, wherein the dosage form, upon oral administration, results in fewer occurrences of headache than would result from the administration of a dosage form without an opioid antagonist.

[0046] In yet another embodiment, the present invention provides a dosage form comprising an optimal or suboptimal amount of an opioid agonist and an opioid antagonist wherein the dosage form comprises about 25, about 50, about 75, about 100, about 125, about 150, about 175, about 200, about 225, about 250, about 275, about 300, about 325, about 350, about 375, about 400, about 425, about 450, about 475, about 500, about 525, about 550, about 575, about 600, about 625, about 650, about 675, about 700, about 725, about 750, about 775, or about 800 mg of an opioid agonist.

[0047] In yet another embodiment, the present invention provides dosage forms and methods for enhancing analgesic potency of an opioid agonist in combination with an opioid antagonist, and at least one additional drug, wherein the dosage forms are useful for attenuating (*e.g.* reducing, blocking, inhibiting or preventing) its adverse effects, particularly its adverse side effects in humans. Principle adverse side effects of opioid agonist in humans include dizziness, nausea, constipation, headache, somnolence (sedation), vomiting, pruritis, CNS

stimulation, seizures, asthenia, dyspepsia, diarrhea, dry mouth, sweating or any combination thereof.

[0048] In yet another embodiment, the present invention provides dosage forms and methods for enhancing therapeutic potency of compositions comprising at least one active agent prone to abuse, at least one antagonist of the active agent, and at least one additional drug, wherein the composition reduces the potential for abuse of said active agent.

[0049] Suitable antagonists for practicing the present invention include, but are not limited to, antagonists for opioids, non-opioid narcotics, stimulants, central nervous system (CNS) depressants, tranquilizers, and barbiturates and cold and cough drugs such as pseudoephedrine, and the like.

[0050] In yet another embodiment, the present invention provides a pharmaceutical composition comprising at least one active agent prone to abuse, at least one antagonist of the active agent, and at least pharmaceutical excipient, wherein in the composition is in micellar form.

[0051] In another embodiment of this invention, the dosage form includes at least one bittering agent; gelling agent; irritant, a micellar forming compound or a combination of thereof.

[0052] In a preferred embodiment, the present invention comprises a slow release dosage form that provides at least one active agent prone to abuse over an extended period of time. In another preferred embodiment, the present invention comprises a slow release dosage form that delivers at least one active agent prone to abuse over an extended period of time. In certain preferred embodiments, the present invention comprises a slow release dosage form that delivers both active agent prone to abuse and an antagonist for the active agent, over an extended period of time from about 12 hours to about 24 hours.

[0053] In a preferred embodiment, the opioid agonist is selected from the group consisting of tapentadol, tramadol, hydromorphone, oxycodone, hydrocodone, fentanyl, morphine, pharmaceutically acceptable salts thereof and mixtures thereof. Still further, in certain preferred embodiments, the opioid agonist is a bimodally acting opioid agonist selected from, e.g., morphine, codeine, fentanyl analogs, pentazocine, buprenorphine, methadone, enkephalins, tapentadol, tramadol, dynorphins, endorphins, and similarly acting opioid alkaloids and opioid

peptides. In certain preferred embodiments, the opioid antagonist is selected from the group consisting of naltrexone, naloxone, nalmefene, pharmaceutically acceptable salt thereof or a combination thereof.

[0054] In other preferred embodiments the present invention provides, a dosage form comprising a transdermal delivery system, an oral mucosal delivery system, a composition for intranasal administration, buccal delivery system, an injectable composition, and a solid oral composition.

[0055] In another embodiment of this invention, the dosage forms include but not limited to granules, spheroids, pellets, multiparticulates, aerosols, capsules, patches, tablets, sachets, controlled release suspensions, or in any other suitable dosage form incorporating such granules, spheroids, pellets or multiparticulates.

BRIEF DESCRIPTION OF THE FIGURES

[0056] The invention is illustrated by the following figures. The figures are for illustrative purposes and they do not limit the scope of the invention. A person skilled in the art can readily modify the descirption herein with alternatives that are within the scope of the instant invention.

[0057] FIG 1 illustrates the dissolution profile of Example 2 evaluated in a dissolution study in a USP Type II paddle apparatus at 100 rpm at 37°C in 900 ml SGF/SIF combination;

[0058] FIG 2 illustrates the dissolution profile of Example 7 evaluated in a dissolution study in a USP Type II paddle apparatus at 100 rpm at 37°C in 900 ml SIF.

[0059] FIG. 3 illustrates the 4-hour Total Pain Relief Scores (TOTPAR) for Group 1: Placebo with Placebo, Group 2: positive control (ST) (Example 2) (100 mg) with Placebo, Group 3: ST (Example 2) (100 mg) with NTX (0.01 mg), Group 4: ST (Example 2) (100 mg) with NTX (0.1 mg), Group 5: ST (Example 2) (100 mg) with NTX (1 mg), Group 6: Example 4 and Group 7, Example 1.

[0060] FIG. 4 illustrates the hourly pain relief scores from 0-12, 0-8 and 0-4 hours for Group 1: Placebo with Placebo, Group 2: ST (Example 2) (100 mg) with Placebo, Group 3: ST (Example 2) (100 mg) with NTX (0.01 mg), Group 4: ST (Example 2) (100 mg) with NTX (0.1 mg), Group 5: ST (Example 2) (100 mg) with NTX (1 mg Group 6: Example 4 and Group 7, Example 1.

[0061] FIG. 5 illustrates Changes in the " mean pain relief scores at four hours and at eight hours and twelve hours for Group 1: Placebo with Placebo, Group 2: ST (Example 2) (100 mg) with Placebo, Group 3: ST (Example 2) (100 mg) with NTX (0.01 mg), Group 4: ST (Example 2) (100 mg) with NTX (0.1 mg), Group 5: ST (Example 2) (100 mg) with NTX (1 mg) Group 6: Example 4 and Group 7, Example 1

DETAILED DESCRIPTION OF THE INVENTION

[0062] The term "analgesic" as used herein means to include any drug used to relieve pain including paracetamol (acetaminophen), the non-steroidal anti-inflammatory drugs (NSAIDs) such as the salicy135lates, narcotic drugs such as morphine, synthetic drugs with narcotic properties such as tramadol, GABA analogues like pregabalin, gabapentin and various others other classes of drugs not normally considered analgesics are used to treat neuropathic pain syndromes; these include tricyclic antidepressants and anticonvulsants.

[0063] The term "active agent or active agent prone to abuse" as used herein means to include any drug that is abused and has potential for abuse. These include opioids, non-opioid narcotics, stimulants, central nervous system (CNS) depressants, tranquilizers, and barbiturates and cold and cough drugs such as pseudoephedrine, etc. include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tapentadol, axamadol, and, tramadol, mixtures or salts of any of the foregoing. These include at least one form of the active agent including optically active enantiomers of active agent, such as for example, (+) or (-) forms, racemic mixtures thereof, active metabolites, pharmaceutically acceptable salts thereof, such as for example, acid addition or base addition salts of active

agent. Acids commonly employed to form acid addition salts are inorganic acids, such as for example, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

[0064] Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutylate, caproate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutylate, citrate, lactate, g-hydroxybutylate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, napththalene-2-sulfonate, mandelate and the like.

[0065] Base addition salts include those derived from inorganic bases, such as for example, ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

[0066] The term “opioid agonist or opioid agonists” as used herein mean any entity that brings out biological response by acting on an opioid receptors. These include but not limited to opioid agonists useful in the present invention include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum,

pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tapentadol, axamadol, and, tramadol, mixtures or salts of any of the foregoing,.

[0067] The term "antagonist or antagonists" as used in this invention means to include any drug that is used to prevent the abuse of an active agent prone to abuse. These include antagonists for opioids, non-opioid narcotics, stimulants, central nervous system (CNS) depressants, tranquilizers, and barbiturates and cold and cough drugs such as pseudoephedrine, etc. The term is not limited to just opioid antagonists but also include antagonist of any drug that is abused or has the potential for abuse.

[0068] The term "bimodally-acting opioid agonists" is used for opioid agonists that bind to and activate both inhibitory and excitatory opioid receptors on nociceptive neurons, which mediate pain. Activation of inhibitory receptors by said agonists causes analgesia. Activation of excitatory receptors by said agonists results in anti-analgesia, hyperexcitability, hyperalgesia, as well as development of physical dependence, tolerance and other undesirable side effects.

[0069] The term "active agent" or "drug" as used herein, refers to the compound that is to be administered to the patient in need thereof. These terms are used interchangeably.

[0070] The term "excitatory opioid receptor antagonists" as used herein, refers to compounds that bind to and act as antagonists of excitatory but not inhibitory opioid receptors on nociceptive neurons that mediate pain. That is, excitatory opioid receptor antagonists are compounds that bind to excitatory opioid receptors and selectively block excitatory opioid receptor functions of nociceptive types of DRG neurons at 1,000 to 10,000-fold lower concentrations than are required to block inhibitory opioid receptor functions in these neurons.

[0071] The term "excitatory antagonists" as used herein, refers to active agents which bind to and acts as antagonists of excitatory but not inhibitory receptors on nociceptive neurons. For example, excitatory opioid receptor antagonists are compounds that bind to excitatory opioid receptors and selectively block excitatory opioid receptor functions of nociceptive types of DRG neurons at 1,000 to 10,000-fold lower concentrations than are required to block inhibitory opioid receptor functions in these neurons.

[0072] The term "dosage form" as used herein is refers to a pharmaceutical preparation or system in which doses of medicine or active drug are included. A dosage form includes but is not limited to, for example, at least one slow release dosage form including various slow release forms such as, osmosis controlled-release dosage form, erosion controlled-release dosage form, dissolution controlled-release dosage form, diffusion controlled-release dosage form, controlled-release matrix core, controlled-release matrix core coated with at least one release-slowing coating, enteric coated dosage form, one sustained dosage, a dosage form surrounded by at least one delayed-release coating, capsules, minitablets, caplets, uncoated microparticles, microparticles coated with release-slowing coating, microparticles coated with delayed-release coating or any combination, administered through transdermal, buccal, intranasal, oral, intramuscular, sublingual, suppository routes. The dosage forms disclosed herein refer to dosage forms as defined hereinabove comprising an effective amount of opioid agonist for treating a patient in need thereof. An effective amount of the active agents (opioid agonists) can be an amount normally used to treat a patient in need of such treatment and such amounts are known to the practitioners in the medical field. The amount can vary based on the chosen active agent and the enhancement of the therapeutic potency that occurs when combined with the opioid agonist.

[0073] The term "suboptimal" us used herein refers to an amount of active agent that is below the optimal dosage for that compound when used in single-compound therapy.

[0074] The term "optimal" as used herein, refers to an amount of active agent that is the optimal dosage for that compound when used in single-compound therapy.

[0075] . The term "treatment of a disease" as used herein, refers to the management and care of a patient having developed a disease, condition or disorder. The purpose of treatment is to combat the disease, condition or disorder. Treatment includes the administration of the active compounds to eliminate or control the disease, condition or disorder as well as to alleviate the symptoms or complications associated with the disease, condition or disorder.

[0076] The term "osmotic dosage form", "osmotic delivery device", "controlled-release osmotic dosage form" or "osmosis-controlled extended-release systems" as used herein is defined to mean dosage forms which forcibly dispense an active agent all or in part by pressure created by osmosis or diffusion of fluid into a core which forces active agent to be dispensed from the osmotic dosage form. The term "osmotic dosage form", "osmotic delivery device" or

"controlled-release osmotic dosage form" also encompasses such forms that will desirably be coated with at least one "release-slowing" coating.

[0077] The term "polyoxyethylene ethers" (also referred to as polyethylene glycols) include, but are not limited to, any of several condensation polymers of ethylene glycol with the general formula $HOCH_2$ (CH_2 OCH_2) or CH_2OH or H (OCH_2 CH_2) or OH, with number average molecular weights from 200 to 6000. Also suitable are polyoxyethylene alcohols and esters; many of the polyoxyethylene ethers, alcohols and esters are sold under the trade name Brij, *i.e.*, Brij 30, 52, 56, 58, 72, 76, 700, 721, 92, 93, 96, 97, 98, 99, etc. Any of these compounds can be used in the compositions of the present invention. Preferred are polyoxyethylene ethers; most preferred is polyoxyethylene 9-lauryl ether.

[0078] The term "micelle or micelles" or "mixed micelles" refers to at least one or more than one different types of micelle(s), each of which has been formed using at least one micelle forming compounds. For example, in one embodiment, the dosage forms comprise a mix of micelles formed between the pharmaceutical agent and alkali metal alkyl sulfate, and micelles formed between the pharmaceutical agent and polyoxyethylene ether or bile salt. It will be understood that each individual micelle can be formed from more than one micelle-forming compound as well.

[0079] The term "prevention of a disease" as used herein, refers to the management and care of an individual at risk of developing the disease prior to the clinical onset of the disease. The purpose of prevention is to combat the development of the disease, condition or disorder, and includes the administration of the active compounds to prevent or delay the onset of the symptoms or complications and to prevent or delay the development of related diseases, conditions or disorders.

[0080] The term "pain and pain related conditions" as used herein, refers to any pain due to a medical conditions including neuropathic pain, osteoarthritis, rheumatoid arthritis, fibromyalgia, and back, musculoskeletal pain, ankylosing spondylitis, juvenile rheumatoid arthritis, migraines, dental pain, abdominal pains, ischemic pain, postoperative pain or because of an anesthetic or surgical condition

[0081] The term "extended release material" as used herein, refers to the inner solid particulate phase and the outer solid continuous phase refers to one or more hydrophilic

polymers and/or one or more hydrophobic polymers and/or one or more other type hydrophobic materials, such as, for example, one or more waxes, fatty alcohols and/or fatty acid esters. The "extended release material" present in the inner solid particulate phase may be the same as or different from the "extended release material" present in the outer solid continuous phase.

[0082] The term "slow-release" herein refers to any release from a formulation, which is other than an immediate release wherein the release of the active agent is slow in nature. The slow-release formulations release the active agent at a gradual rate in the first once daily controlled-release dosage form or the at least one means for controllably releasing the active agent in a substantially controlled manner per unit time *in-vivo*. The rate of release of the active agent is controlled by features of the dosage form and/or in combination with physiologic or environmental conditions rather than by physiologic or environmental conditions alone. The term "slow-release" includes various terms used interchangeably in the pharmaceutical context such as, extended release, delayed release, sustained release, controlled release, timed release, specific release, prolonged release and targeted release and the like. Examples of a slow release include a core where an active agent is released at a rate where the peak plasma levels of the active agent are achieved approximately from about 6 hours to about 12 hours after administration.

[0083] The "controlled-release dosage forms" or dosage forms which exhibit a "controlled-release" of opioid agonist as used herein, refers to dosage forms administered once daily that release drug at a relatively constant rate and provide plasma concentrations of the active drug that remain substantially invariant with time within the therapeutic range of the active drug over about a 12-hour to 24-hour period.

[0084] The "sustained-release dosage forms" or dosage forms which exhibit a "sustained-release" of the active agent and "delayed-release dosage forms" or dosage forms which exhibit a "delayed-release" of as used herein is refer to dosage forms administered once daily that do not substantially release drug immediately following administration but at a later time and provide release of the drug at a rate sufficient to provide a therapeutic dose after administration, and then a gradual release over an extended period of time such that the sustained-release dosage form provides therapeutic benefit over about a 12-hour to 24-hour period. The sustained-release or delayed-release dosage forms can provide a time delay prior to the commencement of drug-absorption. Such dosage forms will preferably be coated with a

delayed-release coating. This time delay is referred to as "lag time" is different from term "onset time" which represents latency, that is, the time required for the drug to reach a minimum effective concentration.

[0085] The "extended-release dosage forms" or dosage forms which exhibit an "extended release" of drug as used herein is defined to mean dosage forms administered once daily that release drug slowly, so that plasma concentrations of the drug are maintained at a therapeutic level for an extended period of time such that the sustained-release dosage form provides therapeutic benefit over about a 12-hour to 24-hour period.

[0086] The term "modified-release dosage forms" or dosage forms which exhibit a "modified-release" of the drug as used herein refers to dosage forms whose drug release characteristics of time course and/or location are designed to accomplish therapeutic or convenience objectives not offered by an immediate-release dosage forms. Modified-release dosage forms or dosage forms are typically designed to provide a quick increase in the plasma concentration of the drug which remains substantially constant within the therapeutic range of the drug for at least over about a 12-hour to 24-hour period. Alternatively, modified-release dosage forms will desirably be designed to provide a quick increase in the plasma concentration of the drug, which although may not remain constant, declines at rate such that the plasma concentration remains within the therapeutic range for at least about a 12-hour to 24-hour period.

[0087] An "immediate release" coating, as used herein, refers to a coating, which has substantially or appreciably no influence on the rate of release of active agent from the dosage form *in-vitro* or *in-vivo*. The excipients comprising the immediate release coat have no substantial control of the release, dissolution, or erosion and swelling properties, which means that the composition of the coat has no substantial influence on the rate of release of the active agent(s).

[0088] The term "multiparticulate" or "microparticle" as used herein, refers to a plurality of drug-containing units, such as for example microspheres, spherical particles, microcapsules, particles, microparticles, granules, spheroids, beads, pellets, or spherules.

[0089] The "prolonged-release dosage forms" or dosage forms which exhibit a "prolonged release" of the drug as used herein, refers to mean dosage forms administered once daily which

provide for absorption of the drug over a longer period of time than from an immediate-release dosage form and which provide therapeutic benefit over about a 12-hour to 24-hour period.

[0090] The term "bioequivalence" as used herein is defined as there being about a 90% or greater probability that the bioavailability (AUC) of the active agent, as determined by standard methods, is about 80 to about 125% of the second orally administrable dosage form comprising the same dose of opioid agonist and that there is a about 90% or greater probability that the maximum blood plasma concentration (Cmax) of opioid agonist as measured by standard methods is about 80 to about 125% of the second orally administrable dosage form.

[0091] The term "FDA guidelines" refers to the guidance, Guidance for Industry Bioavailability and Bioequivalence Studies approved by the US Food and Drug Administration at the time of filing of this patent application.

[0092] The term "candidate for sustained release" encompasses all the characteristics of a drug which make it a candidate for formulating it into an extended release fashion like a short elimination half life and consequent dosing of more than once a day, a single dose product given in an extended fashion to achieve better clinical results and avoid side effects associated with an immediate release etc.

[0093] The term "enhanced absorption dosage forms" or dosage forms which exhibit an "enhanced absorption" of the drug as used herein, refers to dosage forms that when exposed to similar conditions, will show higher (*e.g.*, more rapid) release and/or higher absorption of the drug as compared to other dosage forms with the same or higher amount of active agent.

[0094] The term "binding agent" as used herein, refers to any conventionally known pharmaceutically acceptable binder such as polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, ethylcellulose, polymethacrylate, polyvinyl alcohol, waxes and the like. Mixtures of the aforementioned binding agents may also be used. The preferred binding agents are water-soluble materials such as polyvinyl pyrrolidone having a weight average molecular weight of 25,000 to 3,000,000. The binding agent may comprise approximately about 0 to about 40% of the total weight of the core and preferably about 3% to about 15% of the total weight of the core. In one embodiment, the use of a binding agent in the core is optional.

[0095] The term "pharmaceutically acceptable derivative" as used herein, refers to various pharmaceutical equivalent isomers, enantiomers, salts, hydrates, polymorphs, esters and the like, of opioid agonist or an active drug.

[0096] The term "gelling agent" as used herein refers to a material or a combination of materials used to impart gel-like or thickening quality upon tempering of a dosage form.

[0097] The term "irritant or an irritating agent" as used herein refers to a material or a combination of materials used to provide an irritating sensation to a potential abuser of a controlled substance.

[0098] The term "bittering agent" as used herein refers to a material or a combination of material used to provide a bitter taste to a potential abuser of a controlled substance.

[0099] The term "aversive agent" as used herein refers to a material or a combination of material used to create an aversion to the dosage in a potential abuser of a controlled substance.

[00100] The term "bioavailability just sufficient" in the context of this invention is intended to mean that the antagonist interferes with opioid agonist in a meaningful way just sufficient to enhance analgesic potency of an active agent prone to abuse and attenuate the side effects. The person to whom the dosage form is administered is not burdened with a significant loading of antagonist but is administered a sufficient quantity to enhance the analgesic activity and reduce the side effects of an opioid agonist.

[00101] The term "significant bioavailability" in the context of this invention is intended to mean that the bioavailability of the antagonist is sufficient that it interferes with an active agent prone to abuse in a meaningful way and that the person to whom the dosage form is administered is provided with a significant loading of antagonist to prevent the abusive effects of the active agent prone to abuse.

[00102] The term "therapeutically effective amount" means an amount that elicits a therapeutic response in a mammal including the suboptimal amount.

[00103] The term "therapeutic potential" means clinical response of administering an active agent in a mammal including the administration of suboptimal amount of an active agent.

[00104] The term "hydrophilic polymers" as used in this specification include, but are not limited to hydroxypropylmethylcellulose, hydroxypropylcellulose, sodium, carboxymethyl-cellulose, carboxymethylcellulose calcium, ammonium alginate, sodium alginate, potassium

alginate, calcium alginate, propylene glycol alginate, alginic acid, polyvinyl alcohol, povidone, carbomer, potassium pectate, potassium pectinate, and the like. Examples of hydrophobic polymers include, but are not limited, to ethyl cellulose, hydroxyethylcellulose, amino methacrylate copolymer (Eudragit RL® or Eudragit RS®), methacrylic acid copolymers (Eudragit L® or Eudragit S®), methacrylic acid-acrylic acid ethyl ester copolymer (Eudragit L 100-5® methacrylic acid esters neutral copolymer (Eudragit NE 30D®) dimethylaminoethyl-methacrylate-methacrylic acid ester copolymer (Eudragit E 100®), vinyl methyl ether/malefic anhydride copolymers, their salts and esters (Gantrez®), and the like.

[00105] The term "osmotic dosage form", "osmotic delivery device", "controlled-release osmotic dosage form" or "osmosis-controlled extended-release systems" as used herein refer to dosage forms which forcibly dispense the drug all or in part by pressure created by osmosis or diffusion of fluid into a core which forces the drug to be dispensed from the osmotic dosage form. The term "osmotic dosage form", "osmotic delivery device" or "controlled-release osmotic dosage form" also encompass such forms that will desirably be coated with at least one "release-slowing" coat.

[00106] Other hydrophobic materials which may be employed in the inner solid particulate phase and/or outer solid continuous phase include, but are not limited, to waxes such as beeswax, carnauba wax, microcrystalline wax, and ozokerite; fatty alcohols such as cetostearyl alcohol, stearyl alcohol; cetyl alcohol myristyl alcohol etc; and fatty acid esters such as glyceryl monostearate, glycerol monooleate, acetylated monoglycerides, tristearin, tripalmitin, cetyl esters wax, glyceryl palmitostearate, glyceryl behenate, hydrogenated castor oil, and the like.

[00107] The present invention also provides an oral dosage form comprising at least active agent prone to abuse, and at least one antagonist of the active agent; wherein the antagonist bioavailability is just sufficient to enhance the therapeutic potency of the active agent and has bioavailability sufficient to reduce the abuse of the active agent. This is achieved by placing one or more antagonist of the active agent within the dosage formulation of the active agent pharmaceutical product so that, under normal conditions, the antagonist bioavailablity is just sufficient to enhance the therapeutic potency of the active agent. However, disruption of the formulation, through any of a variety of means, will release the antagonist at levels sufficient enough to diminish the harmful effects of the active agent. The instant oral dosage forms comprising an optimal or suboptimal amount of at least one active agent prone to abuse and at

least one antagonist of the active agent(s), such that the antagonist enhances the therapeutic potency of the dosage form and reduces the abuse of the active agent and the dosage form provides effective clinical relief for at least about 12 hours, or preferably for at least about 24 hours, when orally administered to a mammal (*e.g.*, human) patient.

[00108] Sill further the oral dosage forms comprising an optimal or suboptimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent such that the antagonist enhances the therapeutic potency of the dosage form and reduces the abuse of the active agent prone to abuse and the dosage form provides effective pain relief for at least about 12 hours, or preferably for at least about 24 hours, when administered to a mammal (*e.g.*, human) patient.

[00109] While physical disruption of dosage forms, for example "grinding them up," is an important path undertaken for the abuse or inappropriate use of drugs, non-physical means may also be employed. These efforts include dissolution in solvent systems or filtering in order to extract drug may be performed. It is preferred that the dosage forms of the present invention release their antagonist component when subjected to such solvent action, if the particular intended activity of the antagonist is to counteract the effects of this solvent disruption. Conceivably, a dosage form could be melted or sublimed to release a drug. In such cases, it may be preferred that dosage forms be available which can release antagonist under such conditions if this is the particular activity that is intended to be counteracted by inclusion of the antagonist in the dosage form. The antagonist can be formulated to protect against one or more such disruption activities

[00110] The dosage forms of the present invention include, but are not limited to, a transdermal delivery system, an oral mucosal delivery system, a composition for intranasal administration, a buccal delivery system, an injectable composition, a solid oral composition, and the like.

[00111] The present invention provides the antagonist in an amount such that the antagonist has selective antagonist action at excitatory, but not inhibitory, receptors, and when a potential abuser tries to abuse at least one active agent prone to abuse, the larger reservoir of antagonist of the active agent is released to prevent such an abuse. However, since the dosage form of present invention has an antagonist of the active agent performing dual roles of enhancing the

therapeutic potency and preventing the substance abuse, the active agent becomes effective when administered at reduced doses, which would otherwise be sub-optimal.

[00112] It may be possible to achieve a therapeutic effect with doses of the (bimodally acting) said active agent with the excitatory antagonists disclosed that are from about 10 to about 100 times lower than doses used when the active agent is administered alone. This is because the excitatory antagonists can enhance its therapeutic effects by attenuating the anti-analgesic excitatory side effects of the active agent. Therefore, in certain preferred embodiments of the invention, the active agent included in the dosage form is delivered in an amount, which is less than that which has been typically administered for therapeutic benefit.

[00113] In certain embodiments of the invention, opioid agonist is delivered such that the amount of opioid agonist included in the dosage form is, *e.g.*, from about 10 to about 100 times less than the amount of opioid agonist typically dosed over the dosing interval.

[00114] The combination comprising at least active agent prone to abuse and at least one antagonist of the active agent may be formulated as a slow release oral dosage form such as tablets and capsules. The active agents prone to abuse useful in the present invention include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, mixtures of any of the foregoing, salts of any of the foregoing, and the like. In a preferred embodiment, the bimodally acting opioid agonist is selected from the group consisting of tapentadol, tramadol, morphine, codeine, fentanyl analogs, pentazocine, methadone, buprenorphine, enkephalins, dynorphins, and endorphins and similarly acting opioid alkaloids and opioid peptides.

[00115] Useful antagonists include, but are not limited to, naloxone, naltrexone, diprenorphine, etorphine, dihydroetorphine, nalinefene, cyclazacine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof. In a preferred embodiment, the opioid antagonist is naloxone or naltrexone.

[00116] In a preferred embodiment, the ratio of active agent prone to abuse to its antagonist is 1:0.3. That is antagonist is present three times the amount of an active agent prone to abuse. This ratio is provided because antagonist performs dual roles of enhancing the therapeutic potency of the active agent prone to abuse such as opioid agonist and attenuate the side effects and also prevent its abuse whenever the dosages form is tempered upon.

[00117] In another preferred embodiment, the slow release oral dosage form is provided comprising at least one active agent prone to abuse, and at least one antagonist of the active agent, released over a period of time, such that when the dosage form is administered to a mannal, the blood level of an active agent is maintained throughout the dosing period at an optimal or suboptimal level, and the antagonist at a level sufficient to decrease the side effects associated with the active agent but not sufficient to negate the therapeutic effect of the active agent. The ratio of an active agent with the antagonist is about 1:1 to about 5000:1 by weight, more preferably from about 50:1 to about 1000:1 and still more preferably from about 50:1 to about 500:1. In a preferred embodiment of the invention the amount of the antagonist administered is about 100 to about 10,000 fold less than the amount of the active agent administered.

[00118] The disclosed slow release oral dosage forms may be formulated using the standard methods available to one skilled in the art. For example, the slow release tablets comprise at least one active agent prone for to abuse, and at least one antagonist of the active agent in a slow release matrix. The slow release matrix of this invention may include hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials; the list is not meant to be exclusive, and any pharmaceutically acceptable hydrophobic material or hydrophilic material which is capable of imparting slow release of an active agent may be deployed. Preferrably, the hydrophobic material includes 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. To achieve the desired release profile, it may be necessary to use a combination of two co-polymers.

[00119] The instant invention can also use alkyl celluloses to achieve the desired release profile. In one embodiment, the formulation uses ethyl cellulose though the persons skilled in the art would easily substitute an alternate material and such substitutes are encompassed in the present invention. Commercially available aqueous dispersions of ethylcellulose include Aquacoat® or Surelease®, prepared according to standard techniques known in the art. These may be optionally mixed with a plasticizer prior to coating.

[00120] 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 1, 2-propylene glycol. Other plasticizers which are suitable for enhancing the elasticity of the films formed from acrylic films, *e.g.*, Eudragit RL/RS® lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, triacetin, and the like. A preferred plasticizer of this invention in aqueous dispersions is triethyl citrate.

[00121] The instant invention envisages the use of film coat, in combination with the others, to achieve a desired in-vitro release rate. The slow release coating formulations of the present invention may also include ingredients such as coating additives that are non-toxic, inert, and tack-free.

[00122] The disclosed dosage forms, comprising at least one active agent prone to abuse and at least one antagonist of the active agent may optionally be coated with one or more materials to control the release of an active agent protect the formulation. In an embodiment of this invention, the formulations are coatings are provided to enable either pH-dependent or pH-independent release, upon exposure to stomach fluids. The use of a pH-sensitive coating serves to release the active agent in the targeted areas of the gastro-intestinal tract such that the absorption profile is capable of providing at least from about eight hours to up to about twenty-four hours of clinical effect to a patient. However, when a pH-insensitive coating is used, the coating is prepared in way to facilitate an optimal release of an active agent regardless of pH-changes in the GI tract. It is also possible to formulate instant inventions such that a portion of

the dose is released in one targeted area of the GI tract and the reminder of the dose is released in another targeted area of the GI tract such as the small intestine.

[00123] The disclosed formulations that utilize pH-sensitive coatings may use, among other things ingredients such as shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like. There are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters that are commercially available as Eudragit® from Rohm Tech, Inc. There are several different types of Eudragit.R® that swell at different pH and there others such as Eudragit.R® RL and Eudragit.R® RS that are though water swellable, are pH-insensitive in a dosage form.

[00124] In another embodiment, the substrate in a tablet core bead or a matrix particle containing at least one active agent prone to abuse and at least one antagonist of the active agent combination is coated with a hydrophobic material such as alkyl cellulose, an acrylic polymer or a combination thereof. The disclosed coating may be an organic or an aqueous solution or dispersion and to extent from about 2 to about 35% of the substrate weight in order to achieve a desired sustained release profile.

[00125] The disclosed composition may be presented, for example, as granules, spheroids, pellets, multiparticulates, capsules, patches, tablets, sachets, controlled release suspensions, aerosols, or in any other suitable dosage form incorporating such granules, spheroids, pellets or multiparticulates.

[00126] The one or more of active ingredient(s) in the combination may suitably be incorporated in a matrix. This may be any matrix, known to a person skilled the art, that affords slow release active agent over at least about a twelve-hour period and preferably that affords in-vitro dissolution rates and in vivo absorption rates of opioid agonist within the therapeutically effective ranges. The combination according to the present invention may preferably use a slow release matrix. Alternatively, normal release matrices having a coating which provides for slow release of the active agent may be used.

[00127] The disclosed slow release matrix employed in the combination may also contain other pharmaceutically acceptable ingredients which are conventional in the pharmaceutical arts such as diluents, lubricants, binders, granulating aids, colorants, flavorants, surfactants, pH

adjusters, anti-adherents and glidants, *e.g.*, dibutyl sebacate, ammonium hydroxide, oleic acid and colloidal silica. Any known diluent, *e.g.*, microcrystalline cellulose, lactose and dicalcium phosphate may be used to prepare this combination. Suitable lubricants are *e.g.*, magnesium stearate and sodium stearyl fumarate. Suitable binding agents include, *e.g.*, hydroxypropyl methyl cellulose, polyvidone and methyl cellulose. Suitable disintegrating agents include, *e.g.*, starch, sodium starch glycolate, and crospovidone and croscarmellose sodium.

[00128] The surface active agents that are suitable include, *e.g.*, Poloxamer 188®, polysorbate 80 and sodium lauryl sulfate. The suitable flow aids for this invention include, *e.g.*, talc, or colloidal anhydrous silica. Similarly, the suitable water soluble polymers that may be used to prepare the matrix include, *e.g.*, PEG with molecular weights in the range 1000 to 6000. The combination comprising at least one active agent and at least one antagonist provided may conveniently be film coated using any film coating material conventional in the pharmaceutical art but preferably an aqueous film coating is used.

[00129] The disclosed oral dosage forms may further include, in addition to at least one active agent prone to abuse, and at least one antagonist of the active agent, a second drug that may or may not be synergistic with the active agent. The second drug to include any drug used to relieve a disease these include pain drugs including paracetamol (acetaminophen), the non-steroidal anti-inflammatory drugs (NSAIDs) 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, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, and NON-NSAIDs such as Naproxinod and the like. Useful dosages of these drugs are well known to those skilled in the art. Others such as morphine, synthetic drugs with narcotic properties such as tramadol, GABA analogues like pregabalin, gabapentin and various others other classes of drugs not normally considered analgesics are used to treat neuropathic pain syndromes; these include tricyclic antidepressants and anticonvulsants. Still further the additional drugs include antitussive; N-methyl-D-aspartate (NMDA) receptor antagonists, expectorant, decongestant, antihistamine drugs, local anesthetics, and the like types.

[00130] The disclosed dosage form, in addition to at least one active agent prone to abuse, and at least one antagonist of the active agent, may further include one or more drugs including a combination of two active agents prone to abuse. For example, the dosage form may include two active agents having different properties, such as half-life, solubility, potency, and a combination of any of the foregoing. In yet further embodiments, one or more active agent is included and a further an active agent that is not prone to abuse is also included, in addition to the antagonist. Such non-opioid drugs would preferably provide additional analgesia, and include, for example, aspirin, acetaminophen; non-steroidal anti-inflammatory drugs ("NSAIDS"), for example, ibuprofen, ketoprofen, etc.; N-methyl-D-aspartate (NMDA) receptor antagonists, *e.g.*, a morphinan such as dextromethorphan or dextrorphan, or ketamine; cycooxygenase-II inhibitors; Non-NSAIDS such as Naproxinod and/or glycine receptor antagonists.

[00131] In certain preferred embodiments of the invention, the slow release oral dosage form comprises an opioid agonist and an opioid antagonist in combination with acetaminophen. It is possible that the slow release formulations prepared in accordance with the present invention include a wide range of dosages of acetaminophen, known to a person skilled in art, such as dose than the 50-650 mg dose, but that dose will be released in a slow release manner over a longer dosing interval over 8 hours or more.

[00132] The disclosed combinations may comprise a normal release matrix having a slow release coating. Preferably the combination comprises film-coated spheroids containing the active ingredient and a spheronising agent. The spheronising agent may be any suitable pharmaceutically acceptable material, which may be spheronised together with the active ingredient to form spheroids. A preferred spheronising agent as per this invention is microcrystalline cellulose. The microcrystalline cellulose used may suitably be, for example, Avicel PH 101 or Avicel PH 102 (Trade Marks, FMC Corporation). The spheroids may optionally contain other pharmaceutically acceptable ingredients conventional in the pharmaceutical art such as binders, bulking agents and colorants. Suitable binders may include water soluble polymers, water soluble hydroxyalkyl celluloses such as hydroxypropylcellulose or water insoluble polymers (which may also contribute controlled release properties) such as acrylic polymers or copolymers for example ethylcellulose. Suitable bulking agents include lactose.

[00133] The spheroids are coated with a material, which permits release of the active ingredient at a slow rate in an aqueous medium. Suitable slow release coating materials that may be used in this invention include water insoluble waxes and polymers such as polymethylacrylates (for example Eudragit polymers,) or water insoluble celluloses, particularly ethylcellulose. Optionally, water-soluble polymers such as polyvinylpyrrolidone or water-soluble celluloses such as hydroxypropylmethylcellulose or hydroxypropylcellulose may be included. Optionally other water-soluble agents such as polysorbate 80 may be added.

[00134] In an alternative embodiment, a flux-enhancing agent can also be included in the membrane or slow release coating can include one of the above-described polymers. The flux-enhancing agent can increase the volume of fluid imbibed into the core to enable the dosage form to dispense substantially all of the active agent and/or antagonist through the passage and/or the porous membrane. The flux-enhancing agent can be a water-soluble material or an enteric material. Examples of the preferred materials that are useful as flux enhancers include but not limited to sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycols (PEG), propylene glycol, hydroxypropyl cellulose, hydroxypropyl methycellulose, hydroxypropyl methycellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers, poloxamers (such as LUTROL F68, LUTROL F127, LUTROL F108 which are commercially available from BASF) and mixtures thereof. A preferred flux-enhancer used in this invention is PEG 400.

[00135] The flux-enhancer may also be a water miscible/soluble drug such as an opioid agonist or a stimulant or its pharmaceutically acceptable salts, or the flux enhancer may be a drug that is soluble under intestinal conditions. If the flux-enhancer is an active agent prone to abuse, the present pharmaceutical composition has an added advantage of providing an immediate release of the drug that has been selected as the flux-enhancer. The flux-enhancing agent dissolves or leaches from the membrane or sustained release coating to form channels in the membrane or sustained release coating, which enables fluid to enter the core and dissolve the active ingredient. In the preferred embodiment, the flux-enhancing agent comprises approximately 0 to about 40% of the total weight of the coating, most preferably about 2% to about 20% of the total weight of the coating.

[00136] Commonly known excipients, such as plasticizers may also be used for preparing the membrane or slow release coating Some commonly known plasticizers include but are not

limited to adipate, azelate, enzoate, citrate, stearate, isoebucate, sebacate, triethyl citrate, tri-n-butyl citrate, acetyl tri-n-butyl citrate, citric acid esters, and those described in the Encyclopedia of Polymer Science and Technology, Vol. 10 (1969), published by John Wiley & Sons. The preferred plasticizers include triacetin, acetylated monoglyceride, grape seed oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate and the like. The amount used depends on the type of plasticizer used. Typical amounts of plasticizer used are from 0 to about 25 wt%, and preferably from about 2 to about 15 wt %, based upon the total weight of the membrane or sustained release coating.

[00137] Generally, the membrane or slow release coating around the core will comprise from about 1 to about 20 wt% and preferably about 2 to about 10 wt% based upon the total weight of the core and coating.

[00138] The membrane or sustained release coating surrounding the core can further include a passage that will allow for controlled release of the drug from the core. As used herein the term passage includes an aperture, orifice, bore, hole, weakened area or a credible element such as a gelatin plug that erodes to form an osmotic passage for the release of an active agent and /or antagonist from the dosage form. Suitable passages used herein with the disclosed dosage forms are well known and are described, *e.g.*, in U.S. patent nos. 3,845,770; 3,916,899; 4,034,758; 4,077,407; 4,783,337 and 5,071,607.

[00139] The following examples are shown for illustrating the invention related to a dosage form comprising a optimal or sub-optimal amount of at least one active agent prone to abuse, and at least one antagonist of the active agent, a slow release dosage form comprises of an optimal or suboptimal amount of at least one active agent prone to abuse and at least one antagonist of the active agent, and a dosage form comprising an optimal or suboptimal amount of at least one active agent prone to abuse and at least one antagonist of the active agent and an additional drug. All formulations are intended to enhance therapeutic potency and/or attenuate one or more adverse effects. In one embodiment, the dosage form comprising at least one active agent prone to abuse and at least one antagonist of the active agent; wherein the bioavailability of the antagonist is just sufficient to enhance the analgesic potency of the active agent and by its sufficient bioavailability reduces the potential for abuse of the active agent.

[00140] The examples further illustrate a method of treating pain and pain related conditions by administering to a patient in need thereof, an optimal or suboptimal amount of at least one opioid agonist, and at least one opioid antagonist, to enhance analgesic potency and/or attenuate one or more adverse effects of the opioid agonist. The invention also provides a method for treating pain and pain related conditions by administering to a patient in need thereof, an optimal or suboptimal amount of at least one opioid agonist, and at least one opioid antagonist and a second drug. The person skilled in the art will know how the combination may be modified using other drugs not illustrated in the following examples and using other manufacturing methods known in the art.

Example 1

[00141] **Example 1:** A dosage form comprising slow release tapentadol hydrochloride and an amount of naltrexone hydrochloride effective to enhance the analgesic potency of tapentadol and an amount of an opioid antagonist effective to reduce the abuse of tapentadol was prepared according to Table 1;

TABLE 1

Tapentadol Beads	
Tapentadol Beads	**Unit Quantity mg**
Tapentadol HCl	50
Polyvinylpyrrolidone	4
Inert Beads	20
Eudragit RS30	2
Lactose	15
Opadry II (Colorcon)	5
Water	35
Slow Release Coat	
Eudragit RS30+ Eudragit RL30D (9.5:1)	5.12
Ethyl Citrate (Aldrich W308307)	1.01
Talc	1.77
Opadry II (Colorcon)	5.5
Water	8
Tapentadol Bead Weight	125.4

Enhancing Naltrexone Beads	
Naltrexone HCl	1
Sugar Spheres NF (Paulaur (Cranbury, NJ)	75
Talc	10
Polyvinylpyrrolidone (Plasdone 28-32)	0.95
Water	25
Opadry II (Colorcon)	5
Slow Release Coat	
Eudragit RS30D	14.1
Polysorbate 20	0.05
Acetyl Tributyl Citrate (ATBC)	3.38
Talc	12.5
Opadry II (Colorcon)	5
Water	45
Enhancing Naltrexone Beads Weight	127.98
Anti-abuse Naltrexone Beads	
Naltrexone HCl	50
Eudragit RS30D	30
Triethyl Citrate	4.5
Talc	15
Water*	35
Seal Coat	
Opadry White Y	8
Water*	45
Anti-abuse Naltrexone Beads Weight	107.5
Abuse Safe Slow Release Tapentadol and Slow Release Naltrexone Dosage	
Tapentadol HCl Beads	125.4
Enhancing Naltrexone HCl Beads	127.98
Anti-Abuse Naltrexone HCl Beads	107.5
Total Weight	**359.88**

*Removed during processing

[00142] **Manufacturing Process:** Tapentadol HCl beads and Enhancing naltrexone HCl beads were prepared according to the formula in Table 1. Specifically tapentadol and polyvinylpyrrolidine were dissolved in water and mixed with others before applying to sugar beads at 60'C using standard procedures. The tapentadol beads were coated with a coating solution comprising Eudragit, Ethyl Citrate, and talc dispersion. Naltrexone beads were prepared by mixing all constituents in a mixer. The fine mixture was granulated with water,

extruded in an extruder at desired size and classified by a screener. The screened naltrexone hydrochloride beads were coated with a coating solution prepared by dissolving Eudragit RS30D, Polysorbate 20, Acetyl Tributyl Citrate (ATBC) and dispersing talc.

[00143] The Anti-abuse naltrexone hydrochloride beads were prepared by dissolving naltrexone hydrochloride and Opadry in water and applying to sugar beads. The sugar beads were coated with coating solution containing Eudragit, Triethyl Citrate and Talc in water. After Non-releasable coating, the beads were dried and incorporated into capsules along with tapentadol HCl beads and enhancing naltrexone beads to prepare dosage form that comprises tapentadol and an amount of an opioid antagonist effective to enhance the analgesic potency of tapentadol and an amount of Naltrexone hydrochloride effective to reduce the abuse of tapentadol. The enhancing beads and the anti abuse beads of naltrexone hydrochloride can be optionally color coated to make look indistinguishable from another.

[00144] **Example 2:** A dosage form comprising slow release morphine sulfate and an amount of naltrexone hydrochloride effective to enhance the analgesic potency of morphine and an amount of naltrexone hydrochloride effective to reduce the abuse of morphine was prepared according to Table 2.

TABLE 2

Morphine Beads	
Morphine Beads	**Unit Quantity mg**
Morphine Sulfate	60
Polyvinylpyrrolidone	4.1
Inert Beads	20
Eudragit RS30	2
Lactose	15
Opadry II (Colorcon)	4.8
Water	35
Slow Release Coat	
Eudragit RS30+ Eudragit RL30D (9.5:1)	5.4
Ethyl Citrate (Aldrich W308307)	1.01
Talc	1.77
Opadry II (Colorcon)	6.1
Water	18
Morphine Bead Weight	156.18

Enhancing Naltrexone Beads	
Naltrexone HCl	2
Sugar Spheres NF (Paulaur (Cranbury, NJ)	75
Talc	10
Polyvinylpyrrolidone (Plasdone 28-32)	0.95
Water	25
Opadry II (Colorcon)	5
Slow Release Coat	
Eudragit RS30D	14.1
Polysorbate 20	0.05
Acetyl Tributyl Citrate (ATBC)	3.38
Talc	12.5
Opadry II (Colorcon)	5
Water	45
Enhancing Naltrexone Beads Weight	127.98
Anti-abuse Naltrexone Beads	
Naltrexone HCl	60
Sugar Spheres NF (Paulaur (Cranbury, NJ)	95
Eudragit RS30D	33
Triethyl Citrate	4.4
Talc	13.5
Water	35
Seal Coat	
Opadry White Y	8
Water	45
Anti-abuse Naltrexone Beads Weight	213.9
Abuse Safe Slow Release Morphine and Slow Release Naltrexone Dosage	
Morphine Sulfate Beads	156.18
Enhancing Naltrexone HCl Beads	127.98
Anti-Abuse Naltrexone HCl Beads	213.9
Total Weight	**498.06**

[00145] **Manufacturing Process;** A dosage form comprising morphine sulfate and naltrexone hydrochloride according Example 2 was prepared as per the manufacturing process disclosed under Example 1.

[00146] **Example 3:** In another example a dosage form comprising morphine sulfate and an amount of naltrexone hydrochloride effective to enhance the analgesic potency of morphine and an amount of an opioid antagonist effective to reduce the abuse of morphine was prepared by preparing suitably coated pellets and incorporating them into a final dosage form according to Table 3.

TABLE 3

Morphine Pellets	
Core	**Unit Quantity mg**
Morphine Sulfate	60
Polyvinylpyrrolidone	4.1
Inert Beads	20
Eudragit RS30	2
Lactose	15
Opadry II (Colorcon)	4.8
Water	35
Slow Release Coat	
Ethyl Cellulose (Surelease Aqueous dispersion, Colorcon)	10
GMS	2
Talc	1.77
Titanium Dioxide	2.5
Morphine Pellet Weight	122.17
Enhancing Naltrexone Pellets	
Naltrexone HCl	2
Sugar Spheres NF (Paulaur (Cranbury, NJ)	75
Talc	10
Polyvinylpyrrolidone (Plasdone 28-32)	0.95
Water	25
Opadry II (Colorcon)	5
Slow Release Coat	
Eudragit RS30D	14.1
Polysorbate 20	0.05
Acetyl Tributyl Citrate (ATBC)	3.38
Talc	12.5
Opadry II (Colorcon)	5
Water	45
Enhancing Naltrexone Pellet Weight	127.98

Anti-abuse Naltrexone Pellets	
Naltrexone HCl	20
Lactose	95
Avicel microcrystalline cellulose	33
HPC	4.4
Non Releasable Coat	
Cellulose Acetate	10.5
PEG 4000 (SIGMA)	0.5
Titanium Dioxide	0.5
Anti-Abuse Naltrexone Pellets Weight	163.9
Abuse-Resistant Slow Release Morphine and Slow Release Naltrexone Dosage	
Morphine Sulfate Pellets	122.17
Enhancing Naltrexone HCl Pellets	127.98
Anti-Abuse Naltrexone HCl Pellets	163.9
Total Capsule Weight	**414.05**

[00147] **Manufacturing Process:** The Example 3 was prepared according to the formula provided in Table 3 using the procedures as disclosed under Example 1.

[00148] **Example 4:** A dosage form comprising tapentadol hydrochloride and naltrexone hydrochloride effective in enhancing the analgesic potency of tapentadol and attenuate its side effect was prepared according to the formula in Table 4.

TABLE 4

Slow Release Tapentadol 50 mg	
Tapentadol HCl	50
Eudragit RSPO	88
ETHOCEL (Ethocel® PR 100)	4.5
Stearyl Alcohol	35
Total	177.5
Naltrexone Pellets	
Naltrexone HCl	1
Eudragit RSPO+ Eudragit RLPO (6:1)	80
Stearic Acid	50
Total	131

Slow Release Tapentadol and Slow Release Naltrexone Dosage	
Tapentadol Pellets	177.5
Naltrexone Pellets	131
Total	308.5

[00149] **Manufacturing Process**: Tapentadol hydrochloride, Eudragit and ETHOCEL are blended together in a blender. To the well blended mix, milled stearyl alcohol is added and the contents were thoroughly mixed together and fed an extruder and later a pelletizer. The pellets are screened and sieved to obtain the required tapentadol pellets. In parallel, naltrexone hydrochloride pellets were prepared following a similar procedure. The final capsules comprising tapentadol and Naltrexone hydrochloride were prepared by filling the required quantity of tapentadol pellets and naltrexone hydrochloride pellets.

[00150] **Example 5**: In another mode of this invention, a representative dosage form comprising an opioid agonist such as morphine sulfate and an opioid antagonist such as naltrexone hydrochloride was prepared according to the formula in Table 5.

Table 5

Anti-Abuse Antagonist Core	mg/unit
Naltrexone Hydrochloride	50
Vegetable Oil	50
Seal Coat	
Opadry White Y-5-7068	2.5
Water	15
Non Releasable Coat	
Eudragit RS30D	13.2
Triethyl Citrate	2.5
Talc	5.2
Water	60
Anti-Abuse Antagonist Core Weight	123.4
Antagonist Layer	
Naltrexone Hydrochloride	2
Opadry Clear (YS-5-19010)	5
Water	15

Opioid Agonist Layer	
Morphine Sulfate	60
Hydroxymethyl Cellulose (Walocel, DOW)	110
MCC 301	135
Lactose	155
Magnesium Stearate	4
Colloidal Silicon Dioxide	4
Seal Coat	
Opadry White Y-5-7068	2.5
Water	15
Opioid Agonist Layer Weight	470.5
Final Tablet Weight	**593.9**

[00151] **Manufacturing Process:** The Example 5 was prepared according to standard methods known in the art. Specifically, anti-abuse core was prepared by mixing naltrexone hydrochloride and vegetable oil finely and compressing them into tablet core. The compressed core was seal coated with Opadry. The seal coated compressed tablet core was coated with a non-releasable coat prepared by mixing Eudragit RS30D, talc, triethyl citrate and water. The coated was adjusted to be over coated to prevent the release of Naltrexone. The over coated cores were seal coated with Opadry and water.

[00152] The cores prepared above were further coated with an enhancing layer comprising naltrexone HCl that would enhance the analgesic properties of morphine sulfate. The layering was done by spraying the above cores with the solution shown below in a coater using two spray guns at a solution application rate of 20 g/minute per gun and an outlet air temperature of 45'C. Application of the correct amount of drug to each tablet was verified by measuring the weight gain of a sample of 100 tablets and confirmed by UV analysis. The naltrexone hydrochloride layered anti-abuse naltrexone hydrochloride cores measured about 7 mm

[00153] A blend of morphine sulfate, hydroxymethyl cellulose (Walocel, DOW), MCC 301, lactose, magnesium stearate and colloidal silicon dioxide was prepared by thoroughly mixing them in a blender. The blend was loaded onto a tablet die with a 7 mm diameter. The naltrexone hydrochloride layered anti-abuse naltrexone HCl cores were inserted and compacted with additional blend to prepare anti-abuse tablets.

[00154] **Example 6;** Another example, an anti-abusive oxycodone hydrochloride and naltrexone hydrochloride was prepared according to the Table 6. The example is a granulated tablet prepared without a separate layer coating of opioid antagonist over the anti-abuse antagonist core as Example 5. The antagonist; naltrexone hydrochloride was mixed with the opioid agonist such as oxycodone hydrochloride to prepare granules that was compressed into tablets over the anti-abuse opioid antagonist core as per Table 6.

Table 6

Anti-Abuse Antagonist Core	mg/unit
Naltrexone Hydrochloride	50
Vegetable Oil	50
Seal Coat	
Opadry White Y-5-7068	2.5
Water	15
Non Releasable Coat	
Eudragit RS30D	13.2
Triethyl Citrate	2.5
Talc	5.2
Water	60
Anti-Abuse Antagonist Core Weight	**123.4**
Opioid Agonist-Antagonist Layer	
Oxycodone Hydrochloride	30
Naltrexone Hydrochloride	1
Povidone	6
Triacetin	2
Eudragit RS30D	12
Lactose	60
Talc	3
Magnesium Stearate	1.5
Stearyl Alcohol	15
Water	60
Seal Coat	
Opadry White Y-5-7068	2.5
Water	15
Opioid Agonist Layer Weight	193
Final Tablet Weight	**256.4**

[00155] **Manufacturing Process;** Eudragit and triacetin were mixed together to prepared a solution into which naltrexone hydrochloride was dissolved. The solution was applied over a mixture of oxycodone HCL, lactose and Povidone in a fluid bed granulator, milled in a mill, and stearyl alcohol melt was applied to this granulation. The granulation was cooled and mixed with magnesium stearate and talc. The granules were compressed into a jacked tablet over anti-abuse naltrexone hydrochloride core using tablet mould as in Example 4. The compressed and jacketed anti-abuse tablets comprising oxycodone HCl and naltrexone hydrochloride were coated with a seal coat optionally.

[00156] **Example 7:** In another example of this invention, a dosage form comprising hydromorphone hydrochloride and naltrexone hydrochloride were formulated according Table 7 as tablets in capsules that provide both enhanced analgesic property and anti-abusive.

Table 7

Ingredient	**Quantity mg/unit**
Hydromorphone HCl	15
Naltrexone HCl	0.5
Eudragit RSPO	65
Stearyl Alcohol	25
ETHOCEL	5
Total Opioid agonist-Antagonist Pellet Weight	110.5
Anti-abuse Naltrexone Pellets	
Naltrexone HCl	20
Lactose	95
Avicel microcrystalline cellulose	33
HPC	4.4
Non Releasable Coat	
Cellulose Acetate	10.5
PEG 4000 (SIGMA)	0.5
Titanium Dioxide	0.5
Anti-Abuse Naltrexone Pellets Weight	163.9
Final Tablet Weight	274.4

[00157] **Manufacturing Process:** Hydromorphone HCl, naltrexone HCl, Eudragit and ETHOCEL are blended together in a blender. To the well blended mix, milled stearyl alcohol is added and the contents were thoroughly mixed together and fed an extruder and later a

pelletizer. The pellets are screened and sieved to obtain the hydromorphone HCl pellets of required size.

[00158] In parallel, anti-abuse naltrexone HCl pellets were prepared following a similar procedure. The final capsules comprising hydromorphone HCL-naltrexone HCl and anti-abuse naltrexone HCl pellets were prepared by filling the required quantity of hydromorphone HCL-naltrexone HCl pellets and naltrexone pellets of desired quantity.

[00159] Hydromorphone HCl-naltrexone HCl pellets and Anti-Abuse naltrexone hydrochloride pellets were optionally color coated to disguise the pellets from potential abuser.

[00160] **Example 8**: In another Example of this invention, a dosage form comprising oxycodone HCL, enhancing naltrexone HCl and anti-abuse naltrexone HCl was prepared as jacked tablets according to the formula in Table 8.

Table 8

Oxycodone HCl layer	**Quantity mg/unit**
Oxycodone Hydrochloride	10
Naltrexone HCl	0.5
Eudragit RSPO	70
Stearyl Alcohol	28
ETHOCEL (Ethocel® PR 100)	6
Talc	3
Magnesium Stearate	1.25
Total	128.75
Anti-Abuse Antagonist Core	mg/unit
Naltrexone Hydrochloride	50
Vegetable Oil	50
Seal Coat	
Opadry White Y-5-7068	2.5
Water	15
Non Releasable Coat	
Eudragit RS30D	13.2
Triethyl Citrate	2.5
Talc	5.2
Water	60
Anti-Abuse Antagonist Core Weight	**123.4**
Total Anti Abuse Oxycodone tablet weight	**252.15**

[00161] **Manufacturing Process**: The Example 8 was prepared according to standard methods known in the art. Specifically, anti-abuse core was prepared by mixing naltrexone hydrochloride and vegetable oil finely and compressing them into tablet core. The compressed core was seal coated with Opadry. The seal coated compressed tablet core was coated with a non-releasable coat prepared by mixing Eudragit RS30D, talc, triethyl citrate and water. The coated was adjusted to be over coated to prevent the release of Naltrexone. The over coated cores were seal coated with Opadry and water.

[00162] Optionally, the cores prepared above were further coated with an enhancing layer comprising naltrexone HCl that would enhance the analgesic properties of morphine sulfate. The layering was done by spraying the above cores with the solution shown below in a coater using two spray guns at a solution application rate of 20 g/minute per gun and an outlet air temperature of 45'C. Application of the correct amount of drug to each tablet was verified by measuring the weight gain of a sample of 100 tablets and confirmed by UV analysis. The naltrexone HCl layered anti-abuse naltrexone HCl cores measured about 7 mm

[00163] Oxycodone hydrochloride, naltrexone HCl, Eudragit and ETHOCEL are blended together in a blender. To the well blended mix, milled stearyl alcohol is added and the contents were thoroughly mixed together and then blended with talc and magnesium stearate to provide a blend. The resulting blend is compressed into a tablet using a tablet press. The blend was loaded onto a tablet die with a 7 mm diameter. The naltrexone HCl layered anti-abuse naltrexone HCL cores were inserted and compacted with additional blend to prepare anti-abuse tablets.

[00164] **Example 9:** A dosage form comprising tramadol hydrochloride and naloxone hydrochloride was prepared according to the formula in Table 9.

Table 9

Ingredient	Quantity mg
Tramadol	50
Naloxone HCl	0.5
Povidone	5
Eudragit RS	10
Talc	2.5
Stearyl Alcohol	25
Magnesium Stearate	1.3
Lactose	70
Triacetin	2
Total	166.3
Anti-Abuse Antagonist Core	mg/unit
Naltrexone Hydrochloride	50
Vegetable Oil	50
Seal Coat	
Opadry White Y-5-7068	2.5
Water	15
Non Releasable Coat	
Eudragit RS30D	13.2
Triethyl Citrate	2.5
Talc	5.2
Water	60
Anti-Abuse Antagonist Core Weight	**123.4**
Final Anti-Abuse Opioid Agonist Tablet Weight	**289.7**

[00165] **Manufacturing Process**: The Example 9 was prepared according to the process given for Example 6

[00166] **Example 10**: A dosage form comprising hydrocodone bitartrarate and naltrexone HCl were prepared according to the formula in Table 10.

Table 10

Ingredient	Quantity mg
Hydrocodone Bitartrarate	30
Naltrexone HCl	0.5
Cetyl Alcohol + Stearyl Alcohol (1:1)	45
Hydroxyl Propyl Cellulose	14.5
Talc	5
Magnesium Stearate	3
Lactose	70
Water	35
Opadry	4.2
Water	15
Total Opioid Agonist-Antagonist pellet weight	172.2
Anti-abuse Naltrexone Pellets	
Naltrexone HCl	20
Lactose	95
Avicel microcrystalline cellulose	33
HPC	4.4
Non Releasable Coat	
Cellulose Acetate	10.5
PEG 4000 (SIGMA)	0.5
Titanium Dioxide	0.5
Anti-Abuse Naltrexone Pellets Weight	163.9
Final Capsule Weight	**336.1**

[00167] Hydrocodone bitartrarate, naltrexone hydrochloride HPC, and lactose are blended together in a blender. To the well blended mix, milled cetyl alcohol and stearyl alcohol is added and the contents were thoroughly mixed with talc and magnesium stearate and fed an extruder and later a pelletizer. The pellets are screened and sieved to obtain the required hydrocodone HCl pellets. The pellets were seal coated with Opadry. In parallel, Anti-abuse naltrexone pellets were prepared following a similar procedure. The final capsules comprising hydrocodone HCL and naltrexone HCl were prepared by filling the required quantity of hydrocodone HCl-naltrexone HCl pellets and anti-abuse naltrexone HCl pellets. The pellets may be color coded to disguise the identity from a potential abuser.

[00168] **Example 11**: Slow release tapentadol tablets were prepared according o the formula in Table 11. The slow release tapentadol was evaluated with three different doses of naltrexone hydrochloride in a clinical study.

TABLE 11

Slow Release Tapentadol 50 mg	
Core	**Quantity mg**
Tapentadol HCl	50
Polyvinyl Alcohol	1
Colloidal Silicon Dioxide (Abrosil® 200)	1
Sodium Stearyl Fumarate	1
Water*	Q.S
Core Weight	104
Coat	
Ethylcellulose (Ethocel® PR 100)	4.4
Polyvinylpyrrolidone (Kollidon® 90F)	2.21
Dibutyl Sebacate	1.8
Denatured Alcohol*	Q.S

Removed during processing

Manufacturing Process:

[00169] **Core Preparation;** Tapentadol HCl and colloidal silicon dioxide were mixed and passed through a 1.0 mm screen. Polyvinyl alcohol was dissolved in purified water. The mixed tapentadol HCl and colloidal silicon dioxide powder was granulated with the aqueous solution of polyvinyl alcohol in a fluidized bed granulator, Glatt GPCGl and then dried. After granulation, the granules were blended with sodium stearyl fumarate and then passed through a 1.0 mm screen. The blend was then compressed into tablet cores using a Manesty Betapress.

[00170] **Coating Preparation;** The ethyl alcohol and isopropanol in appropriate quantity were weighed and mixed together. Dibutyl sebacate and ethylcellulose were added to and dissolved in the ethyl alcohol and isopropyl alcohol midst of constant stirring with a propeller stirrer, Coframo RZR1 and polyvinylpyrrolidone was added. The solution was stirred until all components were dissolved. The solution was passed through a high pressure homogenizer.

[00171] The tablet cores were coated using the coating solution in a perforated coating pan, O'Hara Labcoat I11 36" Pan, Vector LCDS. The coating parameters are listed in Table 12.

Table 12

Coating Parameters	
Inlet Temperature:	48.5-49.5° C
Outlet Temperature:	38.5-39.5° C
Bed Temperature:	37.5-38.5° C
Spray Rate:	300g/minute
Atomizing Air/ Pattern:	25/25 psi
Distance gun/Bed:	6”
Distance between guns:	6”
Pan speed:	12rpm
Coating Amount Diameter:	
Thickness:	6 mm
Cup Height:	4.65 mm
Surface:	1.02 mm
Percentage:	112 mm#
Amount:	16 mg

[00172] **Example 12**: A dosage form comprising morphine sulfate and naltrexone hydrochloride was prepared to according the formal in Table 13.

Table 13

Morphine Micellar Formulation	
Ingredient	**Quantity grams**
Morphine Sulfate	20
Naltrexone Hydrochloride	1
Polyoxyethylene-9-Lauryl Ether	9
Glycerin	12
Phenol	10
Sodium Lauryl Sulfate	8
Sodium Glycocholate	6
Absolute Alcohol	40
Water	200
Total Solution Weight	306

[00173] **Manufacturing Process:** Morphine sulfate, naltrexone hydrochloride, polyoxyethylene-9-lauryl ether, glycerin, phenol, sodium lauryl sulfate, sodium glychocholate were all mixed in absolute alcohol with through shaking on automatic shaker and diluted with water to prepare 200 ml micellar solution.

[00174] **Example 13**: A dosage form comprising tapentadol hydrochloride and naltrexone hydrochloride was prepared to according the formal in Table 14.

Table 14

Morphine Micellar Formulation	
Ingredient	**Quantity grams**
Tapentadol Hydrochloride	50
Naltrexone Hydrochloride	1
Polyoxyethylene-9-Lauryl Ether	9
Glycerin	12
Phenol	10
Sodium Lauryl Sulfate	8
Sodium Glycocholate	6
Absolute Alcohol	40
Water	200
Total Solution Weight	306

[00175] **Manufacturing Process:** The formulation comprising tapentadol hydrochloride and naltrexone hydrochloride was prepared as per the formula in Table 14 according the process described under Example 12

[00176] **Administration:** A 10 ml metered dose dispenser was incorporated with one milliliter of formulation, along with a propellant such as 1,1,1,2-tetrafluoroethane. The solution was pipetted (1 mL) into glass vials and the vials were then charged with 10.8 g HFA 134a propellant per vial, with a Pamasol® 2008 automatic gas filling apparatus. The valves of the vials were designed to deliver 100 ! L of spray per actuation. The formulation in the glass vial including the propellant, was in is homogeneous. The aerosol formulation was incorporated into a dispenser equipped with a lining of excess naltrexone hydrochloride that is released only when the dispenser and the aerosol formulation was administered to the buccal mucosa of the subject by spraying, while resisting inhalation. Plasma levels of the drug were then measured.

DISSOLUION STUDIES

[00177] The pharmaceutical composition prepared according Example 2 was evaluated in a dissolution study in a USP Type II paddle apparatus at 100 rpm at 37”C in 900 ml SGF/SIF combination and the results are in Table 15 and Figure 1;

Table 15

Dissolution Profile of Morphine Sulfate, Example 2

Hours	Percent of Morphine
0	0
2	8
4	22
6	34
8	48
12	70
16	78
18	83
20	84

[00178] The pharmaceutical composition prepared according Example 7 was evaluated in a dissolution study in a USP Type II paddle apparatus at 100 rpm at 37"C in 900 ml SIF and the results are in Table 16 and in Figure 2;

Table 16

Dissolution Profile of Hydromorphone, Example 7

Hours	Percent
0	0
1	12
2	22
4	41
6	55
8	65
12	85
16	88
20	92

CLINICAL TRIALS

[00179] The objects of the present inventions were established using four well controlled human clinical trials. The trials established 1) a method for treating pain in a subject by administering to the human subject an optimal or suboptimal amount of at least one active agent prone to abuse and at least one antagonist of the active agent effective to enhance the analgesic potency of the active agent, as well as a method for treating pain with active agent such as tapentadol and attenuating an adverse side effect of tapentadol in a human subject by

administering to the human subject an analgesic or sub-analgesic amount of tapentadol and an amount of naltrexone hydrochloride effective to attenuate the adverse side effects and 2) a method for treating pain in a human subject by administering to the human subject an optimal or suboptimal amount of slow release opioid agonist such as tapentadol and an amount of an opioid antagonist such as naltrexone effective to enhance the analgesic potency of tapentadol, as well as 3) a method for treating pain in a human subject by administering to the human subject an optimal or suboptimal amount of slow release opioid agonist and an amount of an opioid antagonist and a second drug, effective to enhance the analgesic potency of opioid agonist and further attenuating an adverse side effect of opioid agonist in a human subject by administering to the human subject an analgesic or sub-analgesic amount of opioid agonist, a second drug and an amount of an opioid antagonist effective to attenuate the adverse side effects.

tudy 1; Treatment of Humans with Tapentadol Hydrochloride and Naltrexone Hydrochloride

[00180] In order to establish the invention, human subjects/patients with pain, tapentadol was administered alone or in combination with various amounts (doses) of an opioid antagonist, naltrexone hydrochloride both as co-administration and fixed dose forms. Opioid antagonists, such as naltrexone, are also referred to herein as "excitatory opioid receptor antagonists". The effects of the combination of tapentadol and an opioid antagonist (e.g., naltrexone) on analgesia or analgesic potency were measured. The effects of naltrexone on tapentadol side effects in humans (e.g., dizziness, nausea, sedation, etc.) were also measured.

[00181] In this randomized, double-blind, active-controlled and placebo-controlled, parallel-group study, study, one objective was to determine whether an opioid antagonist such as naltrexone hydrochloride (hereafter referred to as naltrexone or NTX) enhances the analgesic properties of slow release tapentadol hydrochloride (hereafter referred to as tapentadol or ST) in human subjects/patients with pain following dental surgery. Another objective was to evaluate whether an opioid antagonist such as NTX attenuated (e.g., reduced, blocked or prevented) tapentadol adverse side effects in humans. The dosages, prepared according to the Example 1 and Example 4 are used in the study.

[00182] Three hundred sixty six (366) subjects were actually entered in the study and among them 307 completed the study. A positive control (ST) and a negative control (placebo) were used and the human subjects were randomized into one of the following six treatment groups: The numbers of subjects were actually assigned to the six treatment groups are as shown in Table 17.

Table 17

GROUP	DRUGS	No. of Subjects (N)
Group 1	Placebo with Placebo	51
Group 2	Example 1 ST (100 mg) with Placebo	49
Group 3	ST (100 mg) with NTX (0.01 mg)	53
Group 4	ST (100 mg) with NTX (0.1 mg)	50
Group 5	ST (100 mg) with NTX (1 mg):	52
Group 6	Example 4 (ST (50 mg) with NTX (1 mg) X 2:	52
Group 7	Example 1 (ST (50 mg) with NTX (1mg) X 2:	53

[00183] A positive control (ST, Group 2) was used to determine the sensitivity of the clinical end points. A negative control (placebo, Group 1) was used to establish the frequency and magnitude of changes in clinical end points that may occur in the absence of an active treatment. A single oral dose of study medication was administered when the subject experienced moderate to severe pain following the surgical extraction of three or four third molars. Patients in Group 6 and Group 7 were administered with two tablets.

[00184] **Inclusion Criteria**: (1) male or female subjects of any race and at least sixteen years of age (a subject under eighteen years old participated only if emancipated or if a parent (or guardian) gave written informed consent); (2) able to speak and understand English and provide meaningful written informed consent; (3) outpatients in generally good health (in particular, the subject must have had no history of liver or kidney disease); (4) three or four third molars to be extracted (at least one tooth must be mandibular bony impacted) and the subject was considered to have had surgery significant enough to warrant an opioid analgesic; (5) an initial categorical pain intensity score of at least moderate on a scale of none, mild, moderate or severe, and the subject willing and able to complete the subject evaluations; (6) able to remain at the study site for at least eight hours following the dose of study drug; and (7) if female, postmenopausal, or physically incapable of childbearing, or practicing an acceptable method of birth control (IUD or hormones or diaphragm and spermicide or abstinence), and if

practicing an acceptable method of birth control, must also have maintained a normal menstrual pattern for the three months prior to study entry and have had a negative urine pregnancy test performed within seven days before surgery.

[00185] **Exclusion Criteria**: (1) pregnant or breast-feeding; (2) have a history of hepatic or renal disease; (3) have a history of seizures, however, subjects with a history of juvenile febrile seizures could be included if there was no seizure history within the past ten years; (4) have a medical or psychiatric condition that compromises the subject's ability to give informed consent or appropriately complete the study evaluations; (5) have a known allergy or significant reaction to opioids, tapentadol, tramadol or naltrexone; (6) have a history of chronic opioid use or opioid abuse within six months prior to study; (7) have used an anticonvulsant drug or tricyclic antidepressant drugs (including serotonin reuptake inhibitors and doses of St. John's Wort exceeding 1,000 mg per day) within four weeks prior to study entry; (8) currently taking a monoamine oxidase inhibitor (MAOI) or have taken a MAOI within two weeks prior to study entry; (9) consumed alcohol twelve hours prior to surgery and consumed alcohol or caffeine-containing products during the eight-hour observation period; (10) have taken any of the following drugs from at least four hours prior to dosing until the end of the study: analgesics, including aspirin, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDS) and opioids (or opioid combinations); minor tranquilizers; muscle relaxants and antihistamines, as well as long-acting analgesics (e.g., long-acting NSAIDs) from twelve hours prior to dosing until completion of study observations; (11) have previously participated in this study; and (12) have been a participant in a study of an investigational drug or device within thirty days prior to this study.

[00186] **Randomization**: Randomization was used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) were evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment was used to reduce potential bias during data collection and evaluation of clinical end points. Prior to randomization, the following was accomplished: (1) informed consent; (2) medical history and demographics; (3) inclusion and exclusion criteria; and (4) prior and concomitant medication.

[00187] Subjects were assigned to treatment groups based on a computer generated randomization schedule prepared prior to the study. The randomization was balanced by using permuted blocks. Study drug for each subject was packaged and labeled according to this randomization code. In order to achieve balance among treatment groups with respect to starting pain, subjects with moderate starting pain were assigned medication with the lowest available number (next sequential treatment number in ascending order). Subjects with severe starting pain were assigned medication with the highest available number.

[00188] **Medication**: Following compliance with all Inclusion/Exclusion Criteria, all subjects with moderate to severe pain received one dose of study medication. Subjects received two capsules to take by mouth, one tapentadol, or placebo, the other naltrexone or placebo. Study medication was packaged per subject in study drug containers. Study medication was packaged in single-dose bottles identified by subject number and each contained 2 capsules. The label identified the study as PROTOCOL TA. Each bottle had a two-way drug disclosure label attached that listed the following information: subject number; cautionary statement; and general instructions. The labels bore the instructions: "Take contents when pain is moderate or severe." The tear-off portion of the label was removed prior to dispensing the study drug and attached unopened to the Label Page Case Report Form.

[00189] Any medications which a subject had taken in the twenty-four hours prior to surgery (including vitamins, thyroid or other prophylactic medication) had to be reported at the baseline visit on the concomitant medications Case Report Form. If the administration of any concomitant therapy became necessary due to treatment-emergent adverse events, it had to be reported on the appropriate Case Report Form. The medical monitor was notified in advance of (or as soon as possible after) any instances in which prohibited therapies according to the Exclusion Criteria were administered.

[00190] **Pain Assessment Method**: A pain assessment was performed pre-treatment. Following the dental surgery and, the subject's pain level was assessed by a trained observer. The subject reported the initial pain intensity by both (1) verbalizing one pain category (0=none, 1=mild, 2=moderate or 3=severe), and (2) using a Visual Analog Scale (VAS) of 0-100 mm where 0=no pain and 100=worst pain imaginable, by placing a single slash on the scale. The decision to medicate was based only on the categorical response. When the

categorical pain level was moderate or severe, the subject then took the dose of study medication.

[00191] A pain assessment was also performed post-treatment. Following dosing, pain intensity and pain relief was recorded at the following times: 30 minutes, 60 minutes and hourly thereafter up to Hour 12 after dosing. All efficacy assessments were recorded by the subject in a diary in response to questioning by the trained observer. The observer questioned the subject for all observations and provided instruction as needed. Pain intensity was measured in response to the question, "How much pain do you have now?" with (1) subject response choices of none, mild, moderate and severe on a categorical scale, and (2) a mark on a 100-mm VAS. The pain relief relative to baseline was assessed in response to the question, "How much pain relief do you have now compared to when you took the medicine?" with subject response choices of none, a little, some, a lot, and complete. For the pain relief assessment, the subject was given a stopwatch and asked to stop it when any meaningful pain relief was felt.

[00192] Adverse events were assessed by non-directed questioning and recorded for the eight hours following dosing. A symptom checklist was also used for the most common adverse side effects of tapentadol in humans (e.g., dizziness, drowsiness, nausea, vomiting, headache, pruritus). These assessments were self-recorded by the subject in a diary at 30 minutes, 60 minutes and hourly thereafter up to Hour 8 after dosing

[00193] At the end of eight hours, or at the termination of hourly observations if sooner than eight hours, a global assessment was made by the subject and the observer in response to the question, "How do you rate the pain relief?" with response choices of excellent, very good, good, fair or poor. Assessment of adverse events continued for at least one hour following rescue medication. Subjects not completing at least the Hour 1 observation period were considered not evaluable for efficacy and were replaced.

[00194] The study was completed after twelve hours of evaluation or upon receipt of rescue medication. Subjects could discontinue the study at any time.

[00195] Subjects who did not get adequate pain relief were provided a final set of pain observations. The subject was then given a rescue medication and discontinued from study.

[00196] Efficacy Evaluations were performed using primary and secondary efficacy parameters. The primary efficacy parameters included: (1) 4-hour Total Pain Relief Scores

(TOTPAR) (described below); (2) 4-hour Sum of Pain Intensity Differences (SPID), (categorical and VAS) (described below); (3) time to onset of meaningful pain relief within 8 hours; and (4) percent of subjects remedicating within 8 hours. The secondary efficacy parameters included: (1) 6 and 8 hour Total Pain Relief Scores (TOTPAR); (2) 6 and 8 hour Sum of Pain Intensity Difference (SPID), (Categorical and VAS); (3) hourly pain relief scores; (4) hourly pain intensity difference scores (categorical and VAS); (5) remedication time within 8 hours; and (6) global evaluations.

[00197] Safety Evaluations included: (1) Adverse Events (AE); and (2) symptom checklist. All adverse events occurring during the study had to be recorded on the case report forms. An adverse event was defined as any untoward medical occurrence connected with the subject being treated during the study, whether or not it was considered related to the study. All serious or unexpected adverse events, whether or not they were considered related to the study medication, had to be reported by telephone to the medical monitor immediately (no later than twenty-four hours after the investigator's receipt of the information) according to Ethical and Regulatory Requirements. The symptom checklist was used, as described above, to record the most common adverse side effects of tapentadol in humans.

[00198] In this study, standard measurements and determinations were utilized. For example, pain intensity was evaluated using both a categorical scale and a VAS, which are standard measurement instruments in analgesic studies. A global assessment of pain relief using a categorical scale and measurements of time to rescue medication are both standard measurements. The safety measures (history, adverse events, and concomitant medications) were also standard determinations.

[00199] Data Analysis: For the data analysis, computed parameters were as follows. The extent to which pain intensity changed over the test period was measured by the Total Pain Relief Score (TOTPAR) and the Sum of Pain Intensity Differences (SPID). TOTPAR was defined as the sum of Pain Relief Scores (PAR) (0=none, 1=a little, 2=some, 3=a lot, 4=complete) over the 4, 6 and 8-hour observation period. The Pain Intensity Difference (PID) at each time point was calculated as the difference between the Pain Intensity Score at Hour 0 and that score at the observation point (0=none, 1=mild, 2=moderate, 3=severe). SPID was defined as the sum of PIDs over the 4, 6 and 8-hour observation period. VAS-PID and VAS-SPID were defined similarly for the VAS scores. Missing values and evaluations performed

after rescue medication were imputed by the Last Observation Carried Forward procedure (LOCF).

[00200] The primary analysis population was the Intent-To-Treat (ITT) population, which comprised all subjects who were randomized. All efficacy analyses were conducted on the ITT population. In addition, efficacy analyses were also conducted on the evaluable population which comprised subjects who were randomized, had pain or relief assessments after dosing, and stayed on the study for at least one hour.

[00201] One-way analysis of variance (ANOVA) was performed on TOTPAR, SPID and VAS-SPID. Each combination treatment was compared with the tapentadol alone treatment with Fisher's least significant difference test (LSD), using Hochberg's (Biometrik 75: 800 (1988)) procedure to control the family-wise type 1 error. For all pair wise comparisons, the error mean square from the overall analysis of variance with all treatments were used as the estimate of error variance. Similar techniques were used for pain relief, PID and VAS-PID.

[00202] Time to remedication (or rescue medication) was analyzed using the Kaplan-Meier estimate to compute the survival distribution function. The distribution was compared among groups using the Log Rank Test. A subject was considered censored at eight hours if remedication had not occurred. Pair wise comparisons were made using the LIFETEST methodology. Hochberg's procedure was used to control the family-wise type 1 error. Time to Onset of Meaningful Relief (determined by the stopwatch) was similarly analyzed. Subjects who did not achieve meaningful relief or take rescue medications were considered treatment failures and were assigned a value of 8 hours or the time when the rescue medication was taken. In all the above analyses baseline pain intensity could be used as a stratification factor. The distribution of Starting Pain Intensity, Global Evaluations and Adverse Side Effects were displayed. The sample size was estimated from historical data and from practical considerations rather than from calculation of expected measured differences.

[00203] Efficacy analyses were conducted on 2 populations: the ITT population and the evaluable population (Table 18). The ITT population comprised all subjects who were randomized, took study drug, and had post randomization data. The evaluable population comprised of only the ITT subjects who had pain or relief assessments after dosing and did not take rescue medication within the first hour following dosing.

[00204] **Study 2**; Treatment of humans with crushed Oxycodone hydrochloride and intact Oxycodone hydrochloride dosage forms.

[00205] In order to assess the extent of abuse resistant design, a clinical study in ten human volunteers was conducted using a method most commonly used to abuse the an active agent prone to abuse; to crush the tablet or capsule containing abuse prone active agent and consuming it with water or alcohol. The objective of this study was to quantify the absorption of oxycodone in human volunteers after physically crushing both an abuse resistant dosage form prepared according of this invention and a reference drug was Oxycontin.

[00206] Drugs: 1) Reference Drug- Oxycontin 10 mg, 2) Investigation drug-Abuse Resistant Oxycodone Hydrochloride 10 mg Example 8.

[00207] The studies were open, single dose or steady state, randomized, two-way crossover design and included two treatment phases, which in turn included two regimen, with water and alcohol for, reference drug and investigational drug. Each phase was separated by washout period of at least a 7 day wash-out period between each administration. Subjects were randomized to receive one of the above two regimens as randomly assigned by Latin Square and each subject crossed to each regimen according to the randomization sequence until all subjects have received all two regimens (with one week separating each regimen). Blood samples, taken 48 hours after dosing were centrifuged within 2 hours of collection and the plasma were separated and frozen at –10° C or lower until assayed. HPLC Analysis was carried out using stand techniques known to the person skilled in art. The plasma concentration of oxycodone for investigational drug was significantly lower that it was for Oxycontin. The AUC (Area under curve) differences were statistically significant and the results are listed in Table 18 below.

Table 18

	Water			
AUC ! g min mL^{-1}	0-60 min		0-120 min	
Dosage 10 mg Oxycodone	Crushed	Intact	Crushed	Intact
Reference Drug (Oxycontin 10 mg)	14.1	19.2	32.5	37.3
Test formulation (Example 9)	4.2	14.8	10.5	41.1
	Alcohol			
	0-60 min		0-120 min	
	Crushed	Intact	Crushed	Intact
Reference Drug (Oxycontin 10 mg)	12.3	17.1	27.4	33.5
Test formulation (Example 9)	3.5	13.4	9.9	35.5

RESULTS

[00208] Table 19 illustrates comparison of key side effects associated with tapentadol at different doses of the opioid antagonist.

Table 19 - Adverse Effect Profile

Patient Group	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
Ex. #	Placebo	Example 11	Example 11	Example 11	Example 11	Example 4	Example 1
Drug Dosage	Placebo+ Placebo	ST 100 mg+ Placebo	ST 100 mg+ NTX 0.01 mg	ST 100 mg+ NTX 0.1 mg	ST 100 mg+ NTX 1 mg	ST 100 mg+ NTX 2 mg	ST 100 mg+ NTX 2 mg
Dosage type	Co-Admin	Co-Admin	Co-Admin	Co-Admin	Co-Admin	Fixed Dose	Fixed Dose
No. of Patients	51	49	53	50	52	52	52
Nausea	18.00%	31.00%	21.00%	28.00%	38.00%	28.00%	29.00%
Vomiting	4.00%	13.00%	10.00%	12.00%	15.00%	9.00%	10.00%
Dizziness	19.00%	22.00%	11.00%	17.00%	19.00%	18.00%	20.00%
Head Ache	51.00%	48.00%	41.00%	43.00%	49.00%	43.00%	44.00%

[00209] FIG 1 illustrates the dissolution profile of Example 2 evaluated in a dissolution study in a USP Type II paddle apparatus at 100 rpm at 37°C in 900 ml of SGF/SIF combination;

[00210] FIG 2 illustrates the dissolution profile of Example 7 was evaluated in a dissolution study in a USP Type II paddle apparatus at 100 rpm at 37°C in 900 ml SIF.

[00211] FIG. 3 illustrates the 4-hour Total Pain Relief Scores (TOTPAR) for Group 1: Placebo with Placebo, Group 2: ST (Example 2) (100 mg) with Placebo, Group 3: ST (Example 2) (100 mg) with NTX (0.01 mg), Group 4: ST (Example 2) (100 mg) with NTX (0.1 mg), Group 5: ST (Example 2) (100 mg) with NTX (1 mg), Group 6: Example 4 and Group 7, Example 1.

[00212] FIG. 4 illustrates the hourly pain relief scores from 0-12, 0-8 and 0-4 hours for Group 1: Placebo with Placebo, Group 2: ST (Example 2) (100 mg) with Placebo, Group 3: ST (Example 2) (100 mg) with NTX (0.01 mg), Group 4: ST (Example 2) (100 mg) with NTX (0.1 mg), Group 5: ST (Example 2) (100 mg) with NTX (1 mg Group 6: Example 4 and Group 7, Example 1.

[00213] FIG. 5 illustrates Changes in the " mean pain relief scores at four hours and at eight hours and twelve hours for Group 1: Placebo with Placebo, Group 2: ST (Example 2) (100 mg) with Placebo, Group 3: ST (Example 2) (100 mg) with NTX (0.01 mg), Group 4: ST (Example 2) (100 mg) with NTX (0.1 mg), Group 5: ST (Example 2) (100 mg) with NTX (1 mg) Group 6: Example 4 and Group 7, Example 1

We Claim:

1. A dosage form comprising at least one active agent prone to abuse, and at least one antagonist of the active agent effective to enhance the therapeutic potency of the active agent and reduce the abuse of the active agent.

2. A dosage form comprising at least one active agent prone to abuse, and at least one antagonist of the active agent; wherein the antagonist bioavailability is sufficient to enhance the therapeutic potency of the active agent and is sufficient to reduce the abuse of the active agent.

3. A dosage form comprising at least one active agent prone to abuse and at least one antagonist of the active agent, wherein the dosage form provides effective therapeutic relief for at least about 12 hours, or at least about 24 hours, when administered to a human patient.

4. A dosage form of any previous claim, wherein the active agent is alfentanil, allylprodine, alphaprodine, amfepramone, amphetamine, amphetaminil, anileridine, apocodeine, benzylmorphine, bezitramide, buprenorphine, butorphanol, D-norpseudoephedrine, clonitazene, cocaine, codeine, cyclorphan, cyprenorphine, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimephetamol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, dronabinol, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, fencamfamine, fenethylline, fenproporex, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, hydroxymethylmorphinan, ketobemidone, levacetylmethadol(LAAM)), levomethadone, levorphanol, levophenacylmorphane, lofentanil, mazindol, mefenorex, meperidine, meptazinol, metazocine, methylmorphine, metamphetamine, methadone, methylphenidate, 3methyprylon, modafinil, morphine, myrophine, nabilone, nalbuphene, narceine, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pernoline, pentazocine, pethidine, phenadoxone, phenomorphane, phenazocine, phenoperidine, piminodine, pholcodeine, phenmetrazine, phentermine, pipradrol, piritramide, profadol, proheptazine, promedol,

properidine, propoxyphene, sufentanil, axomadol, tapentadol, and tramadol, a pharmaceutically acceptable salt of any of the foregoing or a mixture thereof.

5. A dosage form of any previous claim, wherein the antagonist is naloxone, naltrexone, nalmefene, nalide, nalmexone, nalorphine, naluphine, haloperidol, promethazine, fluphenazine, perphenazine, levomepromazine, thioridazine, perazine, chlorpromazine, chlorprothixine, zuclopentixol, flupentixol, prothipendyl, zotepine, benperidol, pipamperone, melperone and bromperidol or a mixture thereof.

6. A dosage form of claim 5, wherein the active agent is tapentadol.

7. A dosage form of claim 5, wherein the active agent is morphine.

8. A dosage form of claim 5, wherein the active agent is oxycodone.

9. A dosage form of claim 5, wherein the active agent is hydromorphone.

10. A dosage form of claim 5, wherein the active agent is tramadol.

11. A dosage form of claim 5, wherein the active agent is hydrocodone.

12. A dosage form of claim 1, 2, or 3, comprising at least one active agent prone to abuse, and at least one antagonist of the active agent, effective to enhance the therapeutic potency of the active agent and reduce the abuse of the active agent, wherein the dosage forms administered in physically abused form shows a mean AUC, that is significantly less than that from a physically abused dosage form administered without an antagonist of the active agent.

13. A dosage form of claim 12, wherein the active agent is oxycodone.

14. A dosage form of claim 1, 2, or 3, comprising of at least one opioid agonist, and at least one opioid antagonist, effective to enhance the analgesic potency of the opioid agonist and reduce the abuse of the opioid agonist.

15. A dosage form of claim 1, 2, or 3, comprising at least one opioid agonist and at least one opioid antagonist; wherein the antagonist bioavailability is sufficient to enhance the analgesic potency of the opioid agonist and is sufficient to reduce the abuse of the opioid agonist.

16. A dosage form of claim 1, 2, or 3, comprising at least one opioid agonist and at least one opioid antagonist, wherein the dosage form provides effective pain relief for at least

about 12 hours, or at least about 24 hours, when administered to a human patient.

17. A dosage form of claim 16, comprising at least one opioid agonist and at least one opioid antagonist, wherein the dosage form provides effective pain relief for at least about 24 hours, when administered to a human patient.

18. A dosage form of claim 14, 15, 16, or 17, wherein the route of administration is oral, sublingual, buccal, transdermal, intranasal, suppository or intramuscular.

19. A dosage form of claim 14, 15, 16, or 17, wherein the dosage form is a tablet, capsule, tablet-in-capsule, powder, thin film or suspension

20. A dosage form of claim 1, 2, or 3, comprising at least one opioid agonist and at least one opioid antagonist, wherein the dosage form, upon oral administration, results in an adverse event profile which is better than the adverse event profile resulting from the administration of a dosage form without an opioid antagonist.

21. A dosage form of claim 1, 2, or 3, comprising at least one opioid agonist and at least one opioid antagonist, wherein the dosage form, upon oral administration, results in fewer occurrences of dizziness or vertigo than would result from the administration of a dosage form without an opioid antagonist.

22. A dosage form of claim 1, 2, or 3, comprising at least one opioid agonist and at least one opioid antagonist, wherein the dosage form, upon oral administration, results in fewer occurrences of nausea than would result from the administration of a dosage form without an opioid antagonist.

23. A dosage form of claim 1, 2, or 3, comprising at least one opioid agonist and at least one opioid antagonist, wherein the dosage form, upon oral administration, results in fewer occurrences of vomiting than would result from the administration of a dosage form without an opioid antagonist.

24. A dosage form of claim 1, 2, or 3, comprising at least one opioid agonist and at least one opioid antagonist, wherein the dosage form, upon oral administration, results in fewer occurrences of headache than would result from the administration of a dosage form without an opioid antagonist.

25. A dosage form of claim 1, 2, or 3, comprising at least one opioid agonist and at least one opioid antagonist, wherein the dosage exhibits a dissolution profile, when measured

in a USP Type II paddle apparatus at 100 rpm at 37"C in 900 ml SGF/SIF combination, such that from about 0% to about 10% of opioid agonist was released after two hours, from about 5% to about 25% of opioid agonist was released after 4 hours, from about 25% to about 50% of opioid agonist was released after 8 hours, from about 50% to about 70 % of opioid agonist was released after 12 hours, not less than 70 % of opioid agonist was released after 16 hours, and at least about 80 % of opioid agonist was released after 20 hours.

26. A dosage form of claim 25, wherein he opioid agonist is morphine

27. A dosage form of claim 25, wherein he opioid agonist is hydrocodone

28. The dosage form of any preceding claim, wherein the composition is in micellar form.

29. The dosage form of claim 28, wherein the composition comprises an alkali metal alkyl sulfate, a polyoxyethylene ether or pharmaceutically acceptable salts thereof.

30. A method for treating pain in a patient comprising administering to a patient an oral dosage form of claim 1, 2, or 3, comprising at least one opioid agonist and at least one opioid antagonist, effective to enhance the analgesic potency of opioid agonist and reduce the abuse of opioid agonist.

31. The method of claim 30, wherein the opioid agonist is tapentadol.

32. The method of claim 30 or 31, wherein the dosage form provides effective pain relief for at least about 12 hours, when administered to a human patient.

33. The method of claim 32, wherein the dosage form provides effective pain relief for at at least about 24 hours, when administered to a human patient.

34. A method for enhancing the rate of absorption of at least one agent prone to abuse in a patient comprising administering an oral dosage form of claim 1, 2, or 3, comprising said the active agent in conjunction with at least one antagonist of the active agent.

35. A method for reducing the effect of at least one agent prone to abuse in a mammal comprising by combining an oral dosage form of claim 1, 2, or 3, comprising said the active agent in conjunction with at least one antagonist of the active agent.

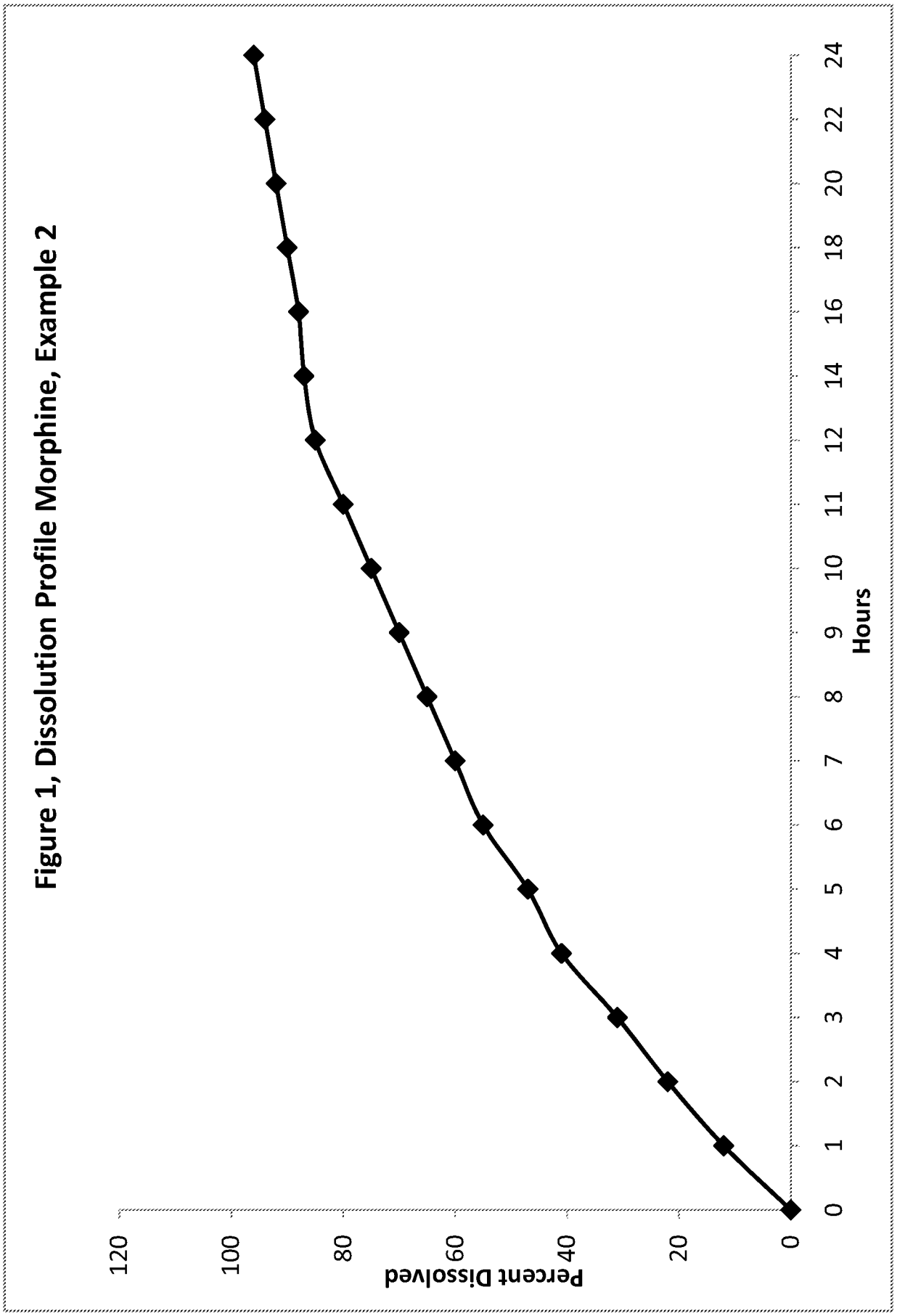


Figure 1, Dissolution Profile Morphine, Example 2
Percent Dissolved
0
20
40
60
80
100
120
Hours
0
1
2
3
4
5
6
7
8
9
10
11
12
14
16
18
20
22
24

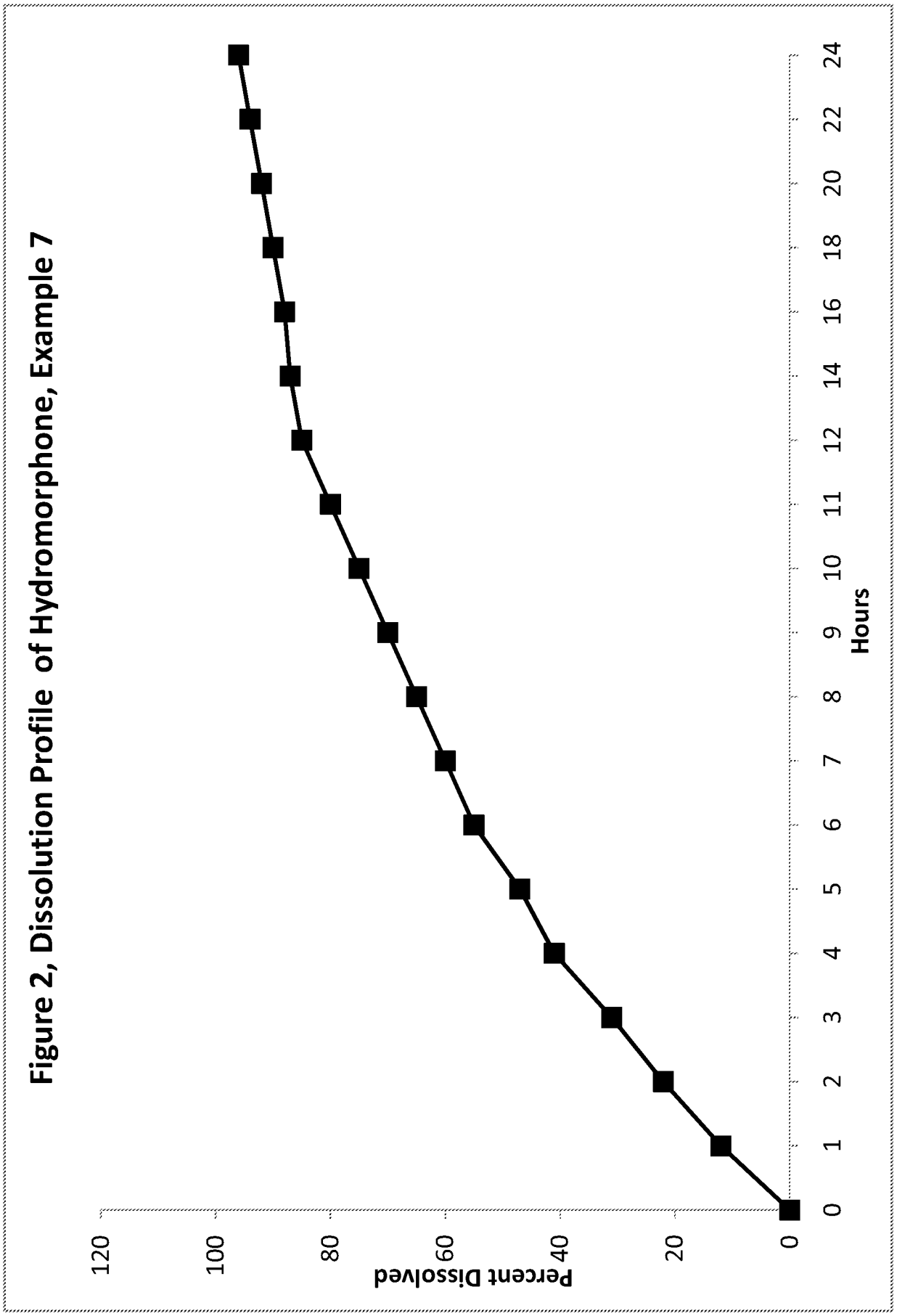


Figure 2, Dissolution Profile of Hydromorphone, Example 7
Percent Dissolved
0
20
40
60
80
100
120
Hours
0
1
2
3
4
5
6
7
8
9
10
11
12
14
16
18
20
22
24

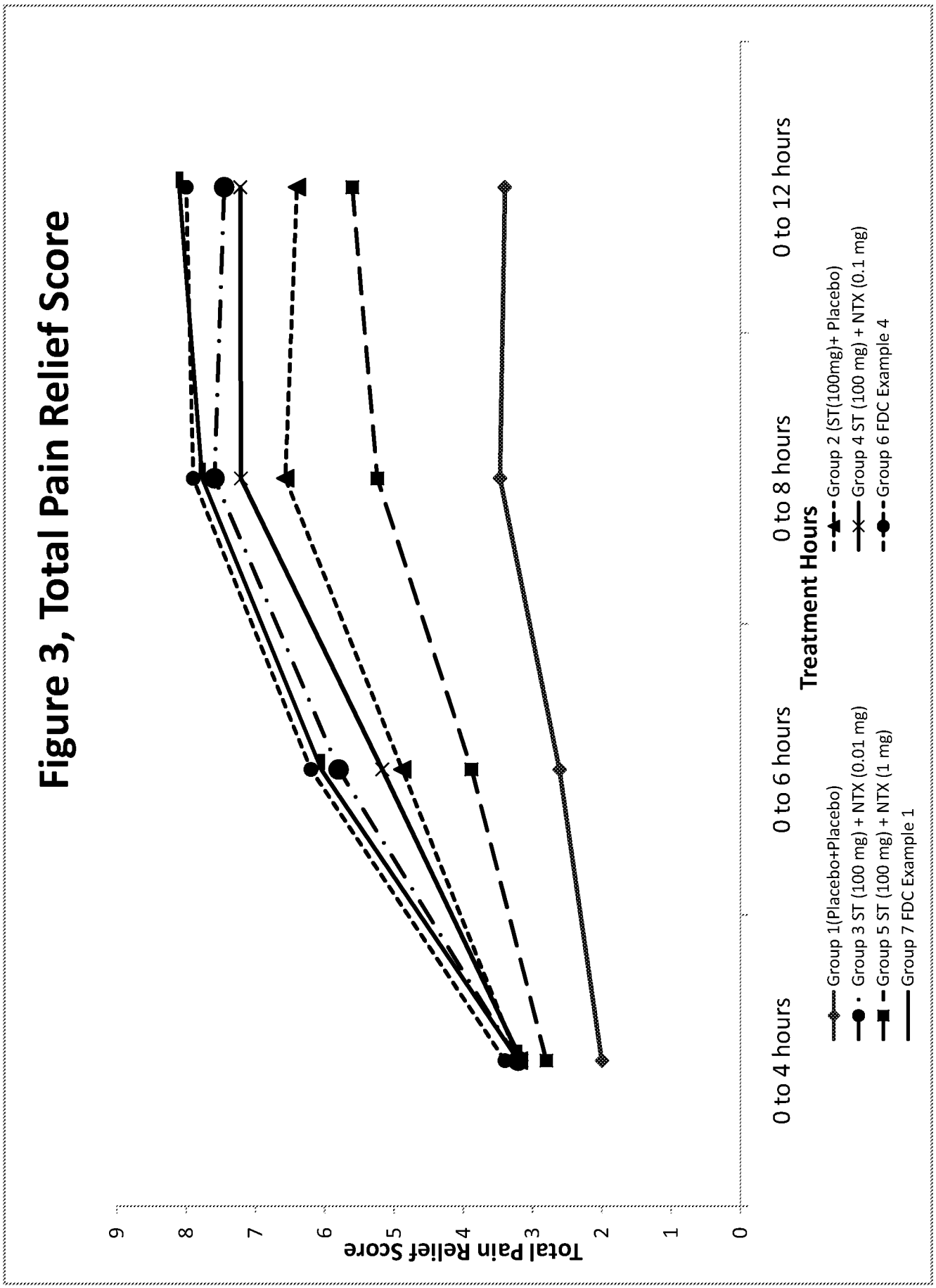
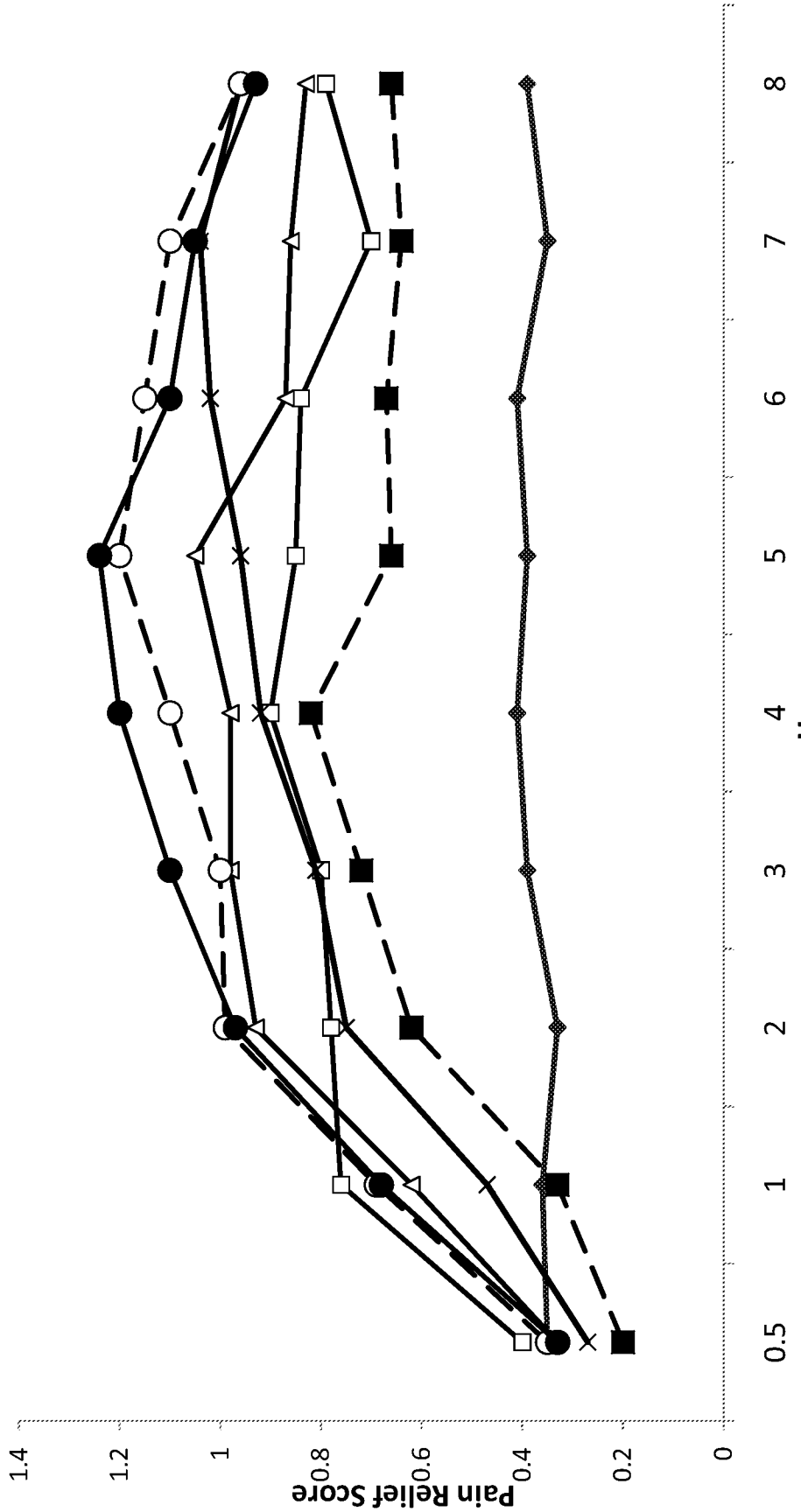


Figure 3, Total Pain Relief Score
Total Pain Relief Score
0
1
2
3
4
5
6
7
8
9
0 to 4 hours
0 to 6 hours
0 to 8 hours
0 to 12 hours
Treatment Hours
Group 1(Placebo+Placebo)
Group 2 (ST(100mg)+ Placebo)
Group 3 ST (100 mg) + NTX (0.01 mg)
Group 4 ST (100 mg) + NTX (0.1 mg)
Group 5 ST (100 mg) + NTX (1 mg)
Group 6 FDC Example 4
Group 7 FDC Example 1

Figure 4, Mean Pain Relief Scores



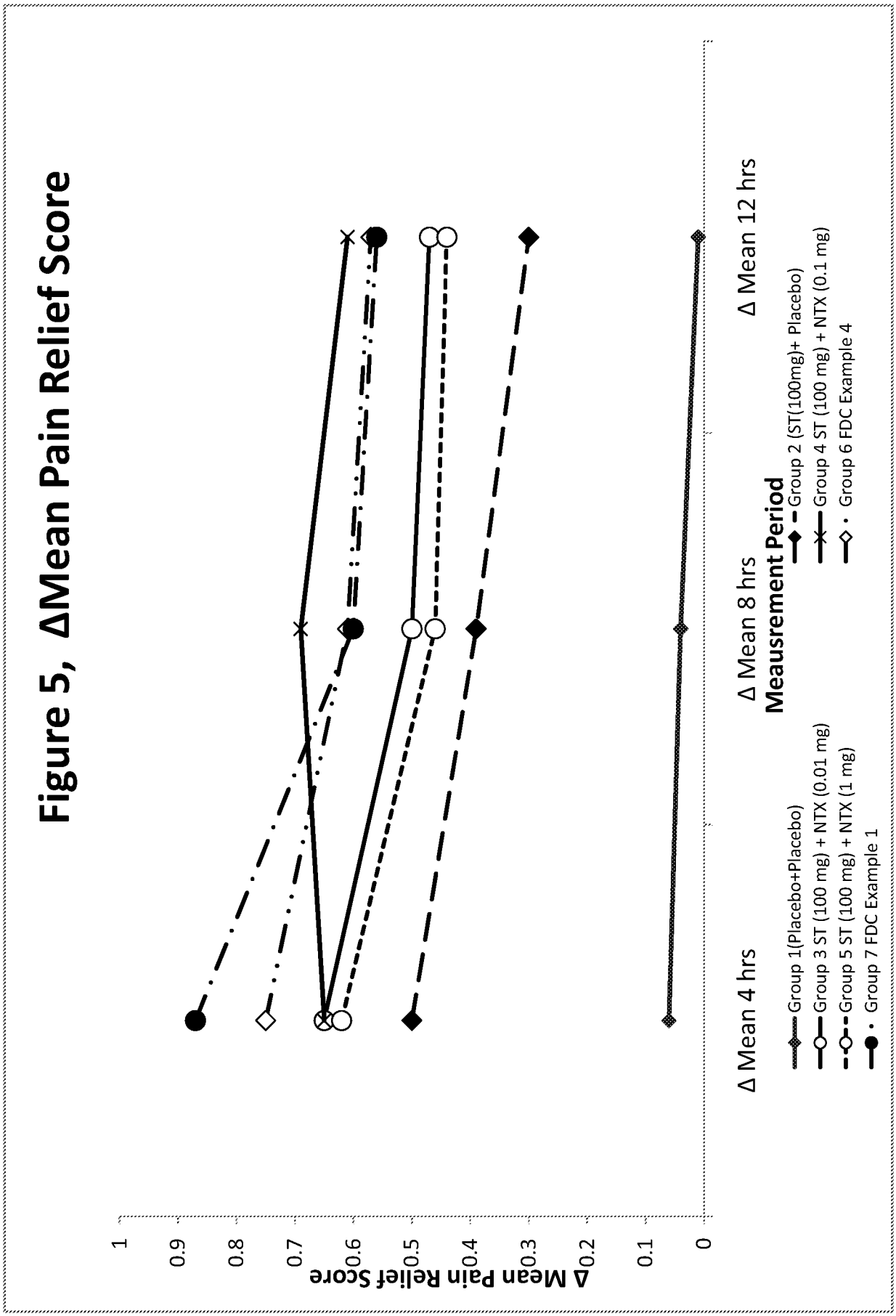


Figure 5, ΔMean Pain Relief Score
Δ Mean Pain Relief Score
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Δ Mean 4 hrs
Δ Mean 8 hrs
Δ Mean 12 hrs
Meausrement Period
Group 1(Placebo+Placebo)
Group 2 (ST(100mg)+ Placebo)
Group 3 ST (100 mg) + NTX (0.01 mg)
Group 4 ST (100 mg) + NTX (0.1 mg)
Group 5 ST (100 mg) + NTX (1 mg)
Group 6 FDC Example 4
Group 7 FDC Example 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/036955

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

A61K 31/485 (2006.01) ***A61P 25/04*** (2006.01)
A61K 31/135 (2006.01) ***A61P 25/30*** (2006.01)

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)

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Medline, EPODOC, WPI: tapentadol, oxycodone, morphine, hydromorphone, tramadol, hydrocodone, naltrexone, naloxone, abuse, etc.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2003/013525 A1 (EUROCELTIQUE S.A.) 20 February 2003	7-11
X	US 6228863 B1 (PALERMO, P.J. et al) 8 May 2001	7-11
X	US 2003/0191147 A1 (SHERMAN, B. et al) 9 October 2003	7, 8, 10 and 11
X	WO 2007/088489 A2 (HARROGATE HOLDINGS [GB]) 9 August 2007	7-11

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 July 2010	26 JUL 2010 26 JUL 2010

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Leri F, et al., "Ultra-low-dose naltrexone reduces the rewarding potency of oxycodone and relapse vulnerability in rats", Pharmacol. Biochem. Behav. 2005 Oct; 82(2): 252-62.	8
X	US 2004/0110781 A1 (HARMON, T.M. et al) 10 June 2004	7-11
X	WO 2005/032555 A2 (EUROCELTIQUE S.A.) 14 April 2005	11
X	US 2007/0185146 A1 (FLEISCHER, W. et al) 9 August 2007.	7-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/036955

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-5 and 12- 35;
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The claims do not comply with Article 6. See Supplemental Box I.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
See Supplemental Box II.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Supplemental Box II

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box III

There are different inventions based on the following features that distinguish the claims from each other:

- Claims 6-11 (in part). It is considered that dosage forms comprising at least one of the opioid agonists, tapentadol, morphine, oxycodone, hydromorphone, tramadol or hydrocodone, in combination with an amount of the opioid antagonists of claim 5, effective to enhance the therapeutic potency of the agonist and reduce the abuse of the agonist, or to provide effective therapeutic relief for at least 12 hours, comprises a first distinguishing feature.

- Claims 1-5 and 12-35 (in full) and claims 6-11 (in part). It is considered that dosage forms comprising at least one pharmaceutically active agent other than tapentadol, morphine, oxycodone, hydromorphone, tramadol or hydrocodone, in combination with an amount of an antagonist to that active agent, namely naloxone, naltrexone and nalmefene, exemplified at page 4, and the structurally similar antagonists of claim 5, namely nalmexone, nalorphine and naluphine, effective to enhance the therapeutic potency of the agonist and reduce the abuse of the agonist, or to provide effective therapeutic relief for at least 12 hours comprises numerous distinguishing features constituting many different inventions.

Unity of invention is only fulfilled when there is at least one "special technical feature" present in the claims. This is a feature that both:

- provides a technical relationship among all the claims; and,
- makes a contribution over the prior art.

In the above groups of claims, the identified distinguishing features may have the potential to make a contribution over the prior art but are not common to all the claims and therefore cannot provide the required technical relationship. The only feature common to all of the claims and which provides a technical relationship among them is a dosage form comprising at least one pharmaceutically active agent in combination with an amount of an antagonist to that active agent, effective to enhance the therapeutic potency of the active agent and reduce the abuse of the active agent, or to provide effective therapeutic relief for at least 12 hours. However this feature does not make a contribution over the prior art because it is disclosed in:
D1, WO 2003/013525 A1 (EURO-CELTIC SA);
D2, US 6228863 B1 (PALERMO, P. J. et al); and
D3, US 2003/0191147 A1 (SHERMAN, B. et al).
Therefore in the light of each of these documents there is no special technical feature present in the claims and the requirements for unity of invention are consequently not satisfied a posteriori.

Restriction of search.

Consequently the search has been carried out for claims 6-11 (in part) which are directed to Invention 1, that is, dosage forms comprising at least one of the opioid agonists, tapentadol, morphine, oxycodone, hydromorphone, tramadol or hydrocodone, in combination with an amount of an opioid antagonist namely naloxone, naltrexone, nalmefene, exemplified at page 4, and the structurally similar antagonists of claim 5, namely nalide, nalmexone, nalorphine and naluphine, in an amount effective to enhance the therapeutic potency of the defined agonist and reduce the abuse of that agonist, or to provide effective therapeutic relief for at least 12 hours

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2010/036955

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	2003013525	AU	2002323032	CA	2457361	CO	5640086
		EP	1414451	HR	20040125	HU	0401191
		IS	7142	JP	2009185046	MA	27265
		MX	PA04001210	NO	20040968	NZ	530971
		PL	367427	RU	2004106619	US	2003073714
		ZA	200400893				
US	6228863	AU	20899/99	BR	9813826	CA	2314896
		CN	1284879	EP	1041988	HU	0100310
		NO	20003278	NZ	505192	NZ	523964
		PL	341309	US	2002004509	US	6627635
		US	2005192309	WO	9932120		
US	20030191147	NONE					
WO	2007088489	EP	1981502	US	2007185145		
US	2004110781	AU	2003298841	WO	2004052346		
WO	2005032555	AU	2004277898	AU	2009201097	CA	2539027
		EP	1663229	MX	PA06003392	US	2006194826
US	2007185146	CA	2569743	CN	1984658	EP	1604666
		EP	1765349	EP	1961421	WO	2005120507

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX