US 20190201344A1

(19) **United States**

(12) **Patent Application Publication**

HAYWARD et al.

(10) **Pub. No.: US 2019/0201344 A1**

(43) **Pub. Date: Jul. 4, 2019**

(54) **LONG ACTING OPIOID ANTAGONISTS**

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(21) Appl. No.: **16/235,021**

(22) Filed: **Dec. 28, 2018**

Related U.S. Application Data

(60) Provisional application No. 62/721,204, filed on Aug. 22, 2018, provisional application No. 62/610,998, filed on Dec. 28, 2017.

Publication Classification

(51) **Int. Cl.**

A61K 9/16 (2006.01)

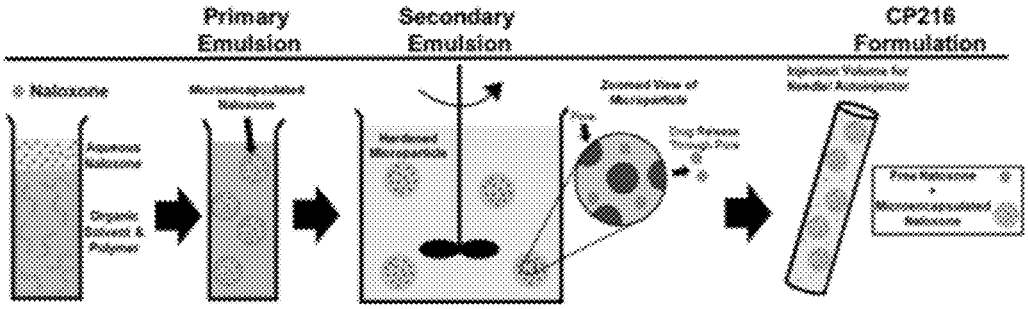
A61K 31/485 (2006.01)

(52) **U.S. Cl.**

CPC ***A61K 9/1647*** (2013.01); ***A61K 31/485*** (2013.01)

(57) **ABSTRACT**

Sustained release formulations of opioid antagonists containing both free and encapsulated opioid antagonist are described herein.



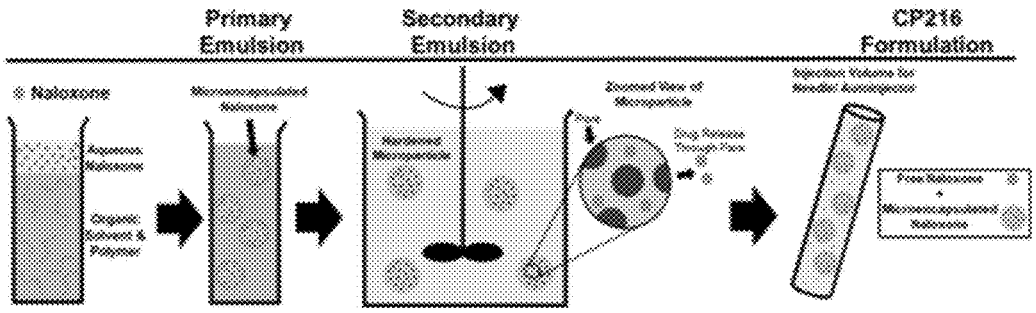

Primary
Emulsion
Secondary
Emulsion
CP216
Formulation
Naloxone

FIG. 1

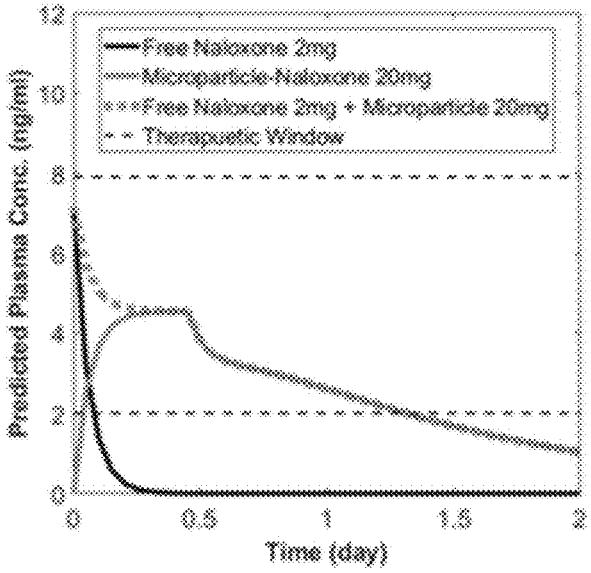

Free Naloxone 2mg
Microparticle-Naloxone 20mg
Free Naloxone 2mg + Microparticle 20mg
Therapeutic Window
Predicted Plasma Conc. (ng/ml)
12
10
8
6
4
2
0
0
0.5
1
1.5
2
Time (day)

FIG. 2

LONG ACTING OPIOID ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 62/721,204 filed Aug. 22, 2018, entitled "Extended Release Naloxone for Sustained Acute Opioid Overdose Reversal" and U.S. Provisional Application No. 62/610,998 filed Dec. 28, 2017 entitled "Extended Release Naloxone for Sustained Acute Opioid Overdose Reversal", the disclosures of which are incorporated herein by reference in their entireties.

GOVERNMENT INTERESTS

[0002] Not applicable

PARTIES TO A JOINT RESEARCH AGREEMENT

[0003] Not applicable

INCORPORATION OF MATERIAL ON COMPACT DISC

[0004] Not applicable

BACKGROUND

[0005] The proliferation of synthetic opioid availability and abuse, particularly the highly potent mu opioid receptor (MOR) agonist fentanyl and related analogues (10-1000 times more lethal than heroin), has led to an unprecedented rise in opioid overdoses and deaths in the United States. Because these drugs are readily absorbed via transdermal, and inhalation routes, there is an increasing direct threat to first responders and law enforcement for accidental overdose level exposure. The primary means of reversing an opioid overdose is the administration of a MOR antagonist, such as naloxone. However, the current generation of MOR antagonists on the market do not have the required properties to treat a fentanyl overdose.

[0006] Fentanyl is a small hydrophobic molecule that activates the MOR at an EC50 of ~1 nM. Naloxone is hydrophilic and requires 50-fold higher concentration to antagonize MOR. Fentanyl and related analogues' hydrophobicity "protect" these compounds from metabolic degradation due to sequestration in adipose tissue (half-life ~7-10 hrs.), while naloxone exhibits poor tissue uptake and has a very transient half-life (~1 hr.) due to rapid metabolic clearance. Taken together, this leads to a phenomenon known as "renarcotization" in which a patient treated with naloxone can overdose from residual fentanyl leaching from adipose tissue. As a result, there is a critical need to create new formulations of MOR antagonists that can combat a fentanyl overdose and provide the multi-hour antagonist activity required for safe and complete fentanyl clearance from circulation.

[0007] To date, the development of new and more effective MOR antagonists has been very limited. This is a direct result of the chemical composition this family of compounds share. Naloxone and other MOR antagonists undergo rapid excretion from the body because 1) their relative hydrophilicity precludes absorption by circulatory proteins or adipose tissue and 2) the metabolically labile 3' phenolic moiety that is rapidly metabolized by the UDP-Glucuronosyltransferase-2B7 enzyme to form Naloxone-3-glucuronide. This phenolic moiety is present in all currently available opioid antagonists (e.g., naloxone, naltrexone, and Nalmefene) and is crucial for their bioactivity. Nalmefene, a derivative of naltrexone used primarily in management of alcohol dependence (outside the US) and previously as an emergency opioid overdose antidote (REVEX™, discontinued in 2008), achieved the longest half-life of any antagonist developed to date. In a study comparing the ability of naloxone and nalmefene to reverse respiratory depression induced by fentanyl infusion in healthy adult volunteers, naloxone and nalmefene exhibited identical potency at the same dose, while the duration of action was about twice as long with nalmefene (108 vs. 55 min) (Glass et al. Anesth Analg. 1994 March; 78(3):536-41). Though significant, this increase in duration of action to antagonize fentanyl is not sufficient to remove renarcotization potential in an overdose situation.

[0008] Embodiments of the invention directly address this immediate need in the current opioid epidemic. The compositions described herein can be used to deliver naloxone as an injectable in-situ drug depot for extended release emergency treatment of opioid overdose by providing therapeutic plasma levels directly following injection and for a predetermined time interval thereafter. Specifically, the invention covers the reformulation of naloxone into a long acting injectable (LAI) that can provide sustained antagonist activity in vivo. The reformulation composition will be the first reformulation effort aimed at significantly increasing naloxone duration of action (12+ hrs.) without chemical modifications, but instead by utilizing proven microencapsulation and extended release technologies. The formulations of various embodiments contain both free naloxone and microencapsulated/extended release naloxone to provide immediate and sustained antagonist activity. This innovative design ensures that the formulations described herein will be able to combat both primary and secondary overdose (renarcotization) situations.

SUMMARY OF THE INVENTION

[0009] Various embodiments are directed to compositions containing free opioid antagonist and microparticles of encapsulated opioid antagonist. In some embodiments, the compositions may have a ratio of free opioid antagonist to encapsulated opioid antagonist of about 1:10 to about 1:50.

[0010] In certain embodiments, the free opioid antagonist may be about 0.4 milligrams (mg) to about 4 mg of opioid antagonist. The free opioid antagonist of various embodiments may be naloxone (17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, naltrexone (17-(cyclopropylmethyl)-4,5α-epoxy-3, 14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, nalmefene (6-desoxy-6-methylenenaltrexone) in free base, salt, or hydrate form, or any combination thereof.

[0011] In some embodiments, the encapsulated opioid antagonist may be about 10 mg to about 30 mg of encapsulated opioid antagonist. The encapsulated opioid antagonist of various embodiments may be naloxone (17-Allyl-4, 5α-epoxy-3,14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, naltrexone (17-(cyclopropylmethyl)-4,5α-epoxy-3, 14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, nalmefene (6-desoxy-6-methylenenaltrexone) in free base, salt, or hydrate form, or any combination thereof.

[0012] The microparticles may have a mean particle diameter of about 40 μm to about 60 μm, and in some embodiments, the microparticles may be composed of a biodegradable polymer such as PLGA, PLA, PGA, PBS, PHA, PCL, PHB, PHV, PHBV, PEG, PLEG, and copolymers thereof, or combinations thereof. In certain embodiments, the PLGA may be capped. In some embodiments, the PLGA may have a ratio of PLA to PGA of 50:50 by weight to about 60:40 by weight. In particular embodiments, the biodegradable polymer may include polymer units having molecular weights of about 5 kiloDalton (kDa) to about 150 kDa. In some embodiments, the opioid antagonist loading may be about 0.5 wt. % to about 50 wt. %.

[0013] Other embodiments are directed to a method for treating or preventing opioid overdose including the steps of administering to a subject in need of treatment a composition comprising free opioid antagonist and microparticles of encapsulated opioid antagonist. In some embodiments, the compositions may have a ratio of free opioid antagonist to encapsulated opioid antagonist of about 1:10 to about 1:50.

[0014] In certain embodiments, the free opioid antagonist may be about 0.4 milligrams (mg) to about 4 mg of opioid antagonist. The free opioid antagonist of various embodiments may be naloxone (17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, naltrexone (17-(cyclopropylmethyl)-4,5α-epoxy-3, 14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, nalmefene (6-desoxy-6-methylenenaltrexone) in free base, salt, or hydrate form, or any combination thereof.

[0015] In some embodiments, the encapsulated opioid antagonist may be about 10 mg to about 30 mg of encapsulated opioid antagonist. The encapsulated opioid antagonist of various embodiments may be naloxone (17-Allyl-4, 5α-epoxy-3,14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, naltrexone (17-(cyclopropylmethyl)-4,5α-epoxy-3, 14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, nalmefene (6-desoxy-6-methylenenaltrexone) in free base, salt, or hydrate form, or any combination thereof.

[0016] The microparticles may have a mean particle diameter of about 40 μm to about 60 μm, and in some embodiments, the microparticles may be composed of a biodegradable polymer such as PLGA, PLA, PGA, PBS, PHA, PCL, PHB, PHV, PHBV, PEG, PLEG, and copolymers thereof, or combinations thereof. In certain embodiments, the PLGA may be capped. In some embodiments, the PLGA may have a ratio of PLA to PGA of 50:50 by weight to about 60:40 by weight. In particular embodiments, the biodegradable polymer may include polymer units having molecular weights of about 5 kiloDalton (kDa) to about 150 kDa. In some embodiments, the opioid antagonist loading may be about 0.5 wt. % to about 50 wt. %.

[0017] In particular embodiments, administration may result in a plasma concentration in the subject of greater than about 2 ng/ml for up to about 7 days, and in various embodiments, administration may be carried out by depo injection, intramuscular injection, subcutaneous injection, oral, sublingual, and intranasal administration.

DESCRIPTION OF THE DRAWINGS

[0018] For a fuller understanding of the nature and advantages of the invention, reference should be made to the following detailed description taken in connection with the accompanying drawings, in which:

[0019] FIG. **1** is a diagram showing the process for making encapsulated naloxone. 2

[0020] FIG. **2** is a graph showing simulated release of naloxone formulated to contain both free naloxone and microparticle-encapsulated naloxone (red dotted line above) that achieves immediate and sustained MOR antagonist activity in vivo. Such a formulation provides relief from primary and potential secondary overdose events.

DETAILED DESCRIPTION

[0021] Various aspects now will be described more fully hereinafter. Such aspects may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey its scope to those skilled in the art.

[0022] Where a range of values is provided, it is intended that each intervening value between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the disclosure. For example, if a range of 1 μm to 8 μm is stated, 2 μm, 3 μm, 4 μm, 5 μm, 6 μm, and 7 μm are also intended to be explicitly disclosed, as well as the range of values greater than or equal to 1 μm and the range of values less than or equal to 8 μm and non-integers such as 2.5 μm, 4.33 μm, 5.25 μm, 6.75 μm, and the like.

[0023] All percentages, parts and ratios are based upon the total weight of the topical compositions and all measurements made are at about 25° C., unless otherwise specified.

[0024] The singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a "polymer" includes a single polymer as well as two or more of the same or different polymers; reference to an "excipient" includes a single excipient as well as two or more of the same or different excipients, and the like.

[0025] The word "about" when immediately preceding a numerical value means a range of plus or minus 10% of that value, e.g, "about 50" means 45 to 55, "about 25,000" means 22,500 to 27,500, etc, unless the context of the disclosure indicates otherwise, or is inconsistent with such an interpretation. For example, in a list of numerical values such as "about 49, about 50, about 55, "about 50" means a range extending to less than half the interval(s) between the preceding and subsequent values, e.g, more than 49.5 to less than 52.5. Furthermore, the phrases "less than about" a value or "greater than about" a value should be understood in view of the definition of the term "about" provided herein.

[0026] The terms "administer," "administering," or "administration" as used herein refer to either directly administering a compound (also referred to as an agent of interest) or pharmaceutically acceptable salt of the compound (agent of interest) or a composition to a subject.

[0027] The term "carrier" as used herein encompasses carriers, excipients, and diluents, meaning a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material involved in carrying or transporting a pharmaceutical, cosmetic or other agent across a tissue layer such as the stratum corneum or stratum spinosum.

[0028] The terms "effective amount" and "therapeutically effective amount" are used interchangeably in this disclosure and refer to an amount of a compound that, when adminis-

tered to a subject, is capable of reducing a symptom of a disorder in a subject or enhance the texture, appearance, color, sensation, or hydration of the intended tissue treatment area. The actual amount which comprises the "effective amount" or "therapeutically effective amount" will vary depending on a number of conditions including, but not limited to, the severity of the disorder, the size and health of the patient, and the route of administration. A skilled medical practitioner can readily determine the appropriate amount using methods known in the medical arts.

[0029] The phrase "pharmaceutically acceptable" or "cosmetically acceptable" is employed herein to refer to those agents of interest/compounds, salts, compositions, dosage forms, etc, which are—within the scope of sound medical judgment—suitable for use in contact with the tissues of human beings and/or other mammals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. In some aspects, pharmaceutically acceptable means approved by a regulatory agency of the federal or a state government, or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals (e.g., animals), and more particularly, in humans.

[0030] The term "salts" as used herein embraces pharmaceutically acceptable salts commonly used to form alkali metal salts of free acids and to form addition salts of free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. The term "salts" also includes solvates of addition salts, such as hydrates, as well as polymorphs of addition salts. Suitable pharmaceutically acceptable acid addition salts can be prepared from an inorganic acid or from an organic acid. Non-limiting examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Appropriate organic acids can be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, and heterocyclyl containing carboxylic acids and sulfonic acids, for example formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, 3-hydroxybutyric, galactaric and galacturonic acid.

[0031] The term "patient" and "subject" are interchangeable and may be taken to mean any living organism which may be treated with compounds of the present invention. As such, the terms "patient" and "subject" may include, but is not limited to, any non-human mammal, primate or human. In some embodiments, the "patient" or "subject" is a mammal, such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, or humans. In some embodiments, the patient or subject is an adult, child or infant. In some embodiments, the patient or subject is a human.

[0032] The term "prevent" as used herein shall mean stopping or reducing the severity of symptoms related to opioid ingestion or overdose.

[0033] The term "treating" is used herein, for instance, in reference to methods of treating a skin disorder or a systemic condition, and generally includes the administration of a compound or composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition or enhance the texture, appearance, color, sensation, or hydration of the intended tissue treatment area of the tissue surface in a subject relative to a subject not receiving the compound or composition. This can include reversing, reducing, or arresting the symptoms, clinical signs, and underlying pathology of a condition in a manner to improve or stabilize a subject's condition.

[0034] By hereby reserving the right to proviso out or exclude any individual members of any such group, including any sub-ranges or combinations of sub-ranges within the group, that can be claimed according to a range or in any similar manner, less than the full measure of this disclosure can be claimed for any reason. Further, by hereby reserving the right to proviso out or exclude any individual substituents, analogs, compounds, ligands, structures, or groups thereof, or any members of a claimed group, less than the full measure of this disclosure can be claimed for any reason. Throughout this disclosure, various patents, patent applications and publications are referenced. The disclosures of these patents, patent applications and publications in their entireties are incorporated into this disclosure by reference in order to more fully describe the state of the art as known to those skilled therein as of the date of this disclosure. This disclosure will govern in the instance that there is any inconsistency between the patents, patent applications and publications cited and this disclosure.

[0035] For convenience, certain terms employed in the specification, examples and claims are collected here. Unless defined otherwise, all technical and scientific terms used in this disclosure have the same meanings as commonly understood by one of ordinary skill in the art to 5 which this disclosure belongs.

[0036] Various embodiments of the invention are directed to pharmaceutical compositions for sustained release of opioid antagonists such as, for example, naloxone, naltrexone, or nalmefene, over a period of up to about 7 days and, in some embodiments, about 10 hours to about 7 days or about 12 hours to about 7 days, about 10 hours to about 7 days, about 12 hours to about 5 days, about 10 hours to about 4 days, about 12 hours to about 4 days, about 10 hours to about 72 hours, about 12 hours to about 48 hours, or any range or individual time encompassed by these examples. Such compositions may contain a mixture of free opioid antagonists and encapsulated opioid antagonists such that a plasma concentration of greater than about 2 ng/ml of opioid antagonist is maintained for up to about 7 days, up to about 5 days, up to about 4 days, up to about 72 hours, about 1 hour to about 24 hours, about 2 hours to about 24 hours, about 5 hours to about 24 hours, about 2 hours to about 12 hours, about 5 to about 12 hours, about 5 to about 24 hours, about 5 hours to about 48 hours, about 5 hours to about 36 hours. For example, the plasma concentration may be about 2 ng/ml to about 10 ng/ml, about 2 ng/ml to about 8 ng/ml, about 2 ng/ml to about 5 ng/ml, or any plasma concentration or range encompassed by these example ranges. In particular embodiments, the formulation may include about 0.4 to about 4 mg of free opioid antagonists and about 10 mg to about 30 mg of encapsulated opioid antagonists. Further embodiments are directed to methods for treating opioid overdose by administering to a patient in need of treatment a formulation of opioid antagonists containing free opioid antagonists and encapsulated opioid antagonists.

[0037] The term "free opioid antagonists" refers to opioid antagonists in free base, salt, or hydrate form that is not encapsulated nor covalently associated with an excipient. For example, "free opioid antagonists" can refer to naloxone (17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form (e.g. naloxone, naloxone HCl ("Narcan"), naloxone HCl dehydrate, or other naloxone salts) or naltrexone (17-(cyclopropylmethyl)-4,5α-epoxy-3, 14-dihydroxymorphinan-6-one) that is not encapsulated in a microparticle or nanoparticle.

[0038] The term "encapsulated opioid antagonist" refers to opioid antagonist, in free base, salt, or hydrate form, that is encapsulated in a microparticle or nanoparticle. Embodiments are not limited to particular types of microparticles or nanoparticles. For example, in certain embodiments, an active agent may be encapsulated in microparticles made from biodegradable polymers, such as polylactides (PLA), poly glycolides (PGA), and poly(lactide-co-glycolide) (PLGA) polymers. In some embodiments, the microparticles may also include derivatives of PLA or PGA, such as poly butylene succinate (PBS), polyhydroxyalkanoate (PHA), polycaprolactone acid lactone (PCL), polyhydroxybutyrate (PHB), glycolic amyl (PHV), PHB and PHV copolymer (PHBV), and poly lactic acid (PLA)-polyethylene glycol (PEG) copolymers (PLEG). PLA/PGA/PLGA degrade in the body by simple hydrolysis of the ester backbone to non-harmful and non-toxic compounds. The in vivo degradation products are either excreted by the kidneys or eliminated as carbon dioxide and water through well-known biochemical pathways. Typically, the active agent can be entrapped in solid microparticles in which release of the agent is achieved by either bioerosion of the microparticles or diffusion out of the microparticle.

[0039] For purposes of this disclosure reference to a single biodegradable is meant to encompass the other biodegradable polymers. For example, the term "PLGA microparticle" as used herein below is meant as example biodegradable polymer, and is meant to encompass microparticle composed of PLGA as well as microparticles composed of PLA, PGA, PBS, PHA, PCL, PHB, PHV, PHBV, PEG, PLEG, and copolymers thereof.

[0040] The molecular weight of the biodegradable polymer units that make up the microparticles can affect the rate of degradation of the microparticle and subsequent release of the drug. For example, microparticles composed of polymer units having low molecular weights generally degrade faster and release the drug at an earlier period when compared to microparticles composed of polymer with high molecular weight polymer units. In various embodiments, the microparticles may be composed of polymer units having molecular weights of from about 5 kiloDalton (kDa) to about 150 kDa, about 5 kDa to about 125 kDa, about 10 kDa to about 100 kDa, about 15 kDa to about 75 kDa, or about 20 kDa to about 50 kDa, or any individual molecular weight or range encompassed by these example ranges. Specific examples include about 5 kDa, about 10 kDa, about 15 kDa, about 20 kDa, about 25 kDa, about 30 kDa, about 40 kDa, about 50 kDa, about 60 kDa, about 75 kDa, about 100 kDa, about 150 kDa, and ranges between any of these example values.

[0041] In some embodiments, the ratio of biodegradable polymer components, for example, PLA to PGA, in the microparticles can be about 1:99 to about 99:1 by weight, about 10:90 to about 90:10 by weight, about 30:70 to about 70:30 by weight, about 40:60 to about 60:40 by weight, about 50:50 by weight, or about 30:70 to about 40:60 by weight. Specific examples of ratio of PLA to PGA include about 30:70 by weight, about 40:60 by weight, 50:50 by weight, about 60:40 by weight, about 70:30 by weight, about 75:25 by weight, and ranges between any two of these values. Microparticles having a higher concentration of lactide units degrade more slowly allowing for delayed release of the active agent.

[0042] Microparticles of encapsulated opioid antagonist can have a mean particle diameter (MPD) of about 0.5 micrometers (μm) to about 90 μm, about 1 μm to about 75 μm, about 2 μm to about 70 μm or any range or individual value encompassed by these example ranges. In particular 7 embodiments, the mean particle diameter of the microparticles may be about 30 μm to about 70 μm, about 35 μm to about 65 μm, about 40 μm to about 60 μm, or any individual diameter or range encompassing these example ranges. In various embodiments, the microparticles may have a monomodal particle size distribution in which a single maximum discernable on a particle size distribution curve (weight percent or population on the ordinate or Y-axis, and particle size/diameter on the abscissa or X-axis). In some embodiments, the microparticles may have a monodisperse particle size distribution, meaning all of the particles have substantially the same mass.

[0043] In various embodiments, the microparticles may have an opioid antagonist loading of about 0.5 wt. % to about 50 wt. %, about 1 wt. % to about 40 wt. %, about 10 wt. % to about 35 wt. %, about 15 wt. % to about 25 wt. %, or any range or individual value encompassed by these ranges. "Drug (e.g., opioid antagonist) loading" as used herein is defined as the weight of drug in the final microparticle formulation divided by the weight of microparticles in the final formulation (units of % w/w; e.g. weight naloxone/weight PLGA).

[0044] The biodegradable polymer components of the microparticles, for example, PLGA, may be capped or uncapped. The term "uncapped PLGA" indicates that the PLGA of the microparticles described or its underlying components, PLA and PGA, have not been functionalized. Thus, "uncapped PLGA" or "uncapped microparticles" contain carboxyl (—COOH) end groups at polymer component termini. The term "capped PLGA" or "capped microparticles" indicates that the PLGA of the microparticles described or its underlying components, PLA and PGA, have been functionalized. For example, the carboxyl end groups of "capped PLGA" have undergone a chemical reaction, i.e. functionalization, to produce, for example, ester end groups (—COOR). Without wishing to be bound by theory, capped PLGA may be less charged and, therefore, less likely to produce ionic interactions with free opioid antagonists. The use of capped PLGA in microparticles may reduce or eliminate any delay in immediate release of opioid antagonist upon administration of the formulations of embodiments of the invention.

[0045] The microparticle encapsulation of opioid antagonists can be performed by any means. For example, as illustrated in FIG. **1**, PLGA polymers of known molecular weights can be dissolved in organic solvents, such as halogenated hydrocarbons such as methylene chloride, chloroform, and carbon tetrachloride; aromatic hydrocarbons such as toluene and xylene; or mixtures or combinations thereof. The opioid antagonists may be dissolved in an aqueous

solvent, such as polyvinyl alcohol, polyvinyl pyrrolidone, carboxymethyl cellulose, lecithin, and gelatin, and the PLGA solution and the anticancer agent solution can be mixed and sonicated to form a uniform distribution of the opioid antagonists and the PLGA polymer. Homogenization is subsequently performed to form the polymer particle emulsion. The resulting polymer emulsion is stirred until the organic solvent is evaporated, resulting in precipitation of polymer particles that encapsulate the opioid antagonists. The size of the microparticles may be controlled by varying homogenization speed during emulsification.

[0046] The ratio of free opioid antagonist to encapsulated antagonist in the formulations of embodiments, may range from about 100:1 to about 1:100, and in certain embodiments, the ratio of free opioid antagonist to encapsulated antagonist may be about 1:1 to about 1:80, about 1:5 to about 1:60, about 1:10 to about 1:50, or any range or individual ratio encompassed by these example ranges. In some embodiments, the formulation may include about 0.4 to about 4 mg of free opioid antagonists and about 10 mg to about 30 mg of encapsulated opioid antagonists. Thus, microparticles may make up about 50 wt. % to about 95 wt. % of the formulation, or about 60 wt. % to about 90 wt. %, about 75 wt. % to about 90 wt. % of the total formulation or any range or individual value encompassed by these example ranges.

[0047] The pharmaceutical compositions disclosed herein provide for sustained release of opioid antagonist for a time period of about 12 hours to about 36 hours or about 48 hours. "Sustained release" refers to the process in which the opioid antagonist is released gradually over a period of time. As illustrated in FIG. **2**, In the context of the formulations of the invention, free opioid antagonist may provide an initial burst of opioid antagonist released immediately up on administration of the formulation. The microparticles or nanoparticles may allow for sustained release of opioid antagonist after the initial burst has dissipated and/or the effect of the opioid antagonist has worn off. Thus, the formulations of embodiments may provide an initial dose of opioid antagonist that is sufficient to reverse an opioid overdose. Release of opioid antagonist from the microparticles in the formulation may continue to block opioid receptors as residual opioid, e.g., fentanyl, is leached from adipose tissue reducing the likelihood of renarcotization.

[0048] Further embodiments include compositions containing opioid antagonists dissolved in oils producing a sustained release formulation. In such embodiments, the opioid antagonists may ionically associate with the oils without forming microparticles or nanoparticles. Without wishing to be bound by theory, this ionic association may delay release of the opioid antagonist after administration as the oil is broken down releasing additional opioid antagonist over time. The oil used in such embodiments is not limited, for example, the oil may be vegetable oil, olive oil, grapeseed oil, tea tree oil, almond oil, avocado oil, sesame oil, evening primrose oil, sunflower oil, kukui nut oil, jojoba oil, walnut oil, peanut oil, pecan oil, macadamia nut oil, coconut oil, and the like and combinations thereof. The amount of opioid antagonist in such embodiments may be from about 2 mg to about 30 mg, or any range or individual amount encompassed by this range, and the oil may make up the remaining volume of the composition. In some embodiments, the opioid antagonist may be a free base form of the opioid antagonist, for example, naloxone free base or naltrexone free base, which may render the opioid antagonist more hydrophobic and more soluble in the oil than salt forms of the opioid antagonists.

[0049] The sustained release pharmaceutical compositions disclosed herein may further contain a hydrogel. The hydrogel may help to hold the microparticles in the composition without clumping, maintain the integrity of the microparticles by buffering the pH, and aid in administration of the composition. Non-limiting examples of hydrogels include methyl cellulose (MC), ethyl cellulose (EC), ethyl methyl cellulose (EMC), hydroxyethyl cellulose (HEC), hydroxylpropyl cellulose (HPC), hydroxymethyl cellulose (HMC), hydroxypropylmethyl cellulose (HPMC), ethylhydroxyethyl cellulose (EHEC), hydroxyethylmethy cellulose (HEMC), methylhydroxyethyl cellulose (MHEC), methylhydroxypropylcellulose (MHPC), and hydroxyethylcarboxymethyl cellulose (HECMC).

[0050] Other materials that can be used to form a hydrogel include modified alginates. Alginate is a carbohydrate polymer isolated from seaweed that can be crosslinked to form a hydrogel by exposure to a divalent cation, such as calcium. Additionally, polysaccharides that gel by exposure to monovalent cations, including bacterial polysaccharides, such as gellan gum, and plant polysaccharides, such as carrageenans, may be crosslinked to form a hydrogel, using methods known in the art. Tragacanth, pectin, guar gum, xanthan gum, and polyacrylamide may also be used as hydrogels.

[0051] In some embodiments, the formulations discussed above may have an inherent viscosity of about 300 cP or less, about 200 cP or less, about 100 cP or less or about 50 cP or less. Combinations of viscosity reducing agents may be used to achieve the desired viscosity. For example, polyethylene glycol polymers, surfactants, organic solvents, aqueous solvents and combinations thereof are suitable for use as viscosity reducing agents. The amount of viscosity reducing agent present in the sustained release composition can range from about 5 wt % to about 40 wt % of the total weight of the sustained release composition.

[0052] The pharmaceutical compositions of the invention are typically used in the form of a drug reservoir such as injectable microparticles, passive transdermal/transmucosal drug delivery or electrotransport drug delivery systems. It will be appreciated by those skilled in the art that the inventive formulations described herein can be combined with suitable carriers to prepare alternative drug dosage forms (e.g., oral capsule, topical ointment, rectal and/or vaginal suppositories, buccal patches, or an aerosol spray).

[0053] It is also known in the art that the active ingredients can be contained in such formulations with pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. The means and methods for administration are known in the art and an artisan can refer to various pharmacologic references for guidance. For example, Modern Pharmaceutics, Banker & Rhodes, Marcel Dekker, Inc. (1979); and Goodman & Gilman's The Pharmaceutical Basis of Therapeutics, 6th Edition, MacMillan Publishing Co., New York (1980) can be consulted.

[0054] Pharmaceutical compositions disclosed herein can include suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers

such as, e.g., polyethylene glycols. In some embodiments, the pharmaceutical excipient may include, without limitation, binders, coating, disintegrants, fillers, diluents, flavors, colors, lubricants, glidants, preservatives, sorbents, sweeteners, conjugated linoleic acid (CLA), gelatin, beeswax, purified water, glycerol, any type of oil, including, without limitation, fish oil or soybean oil, or the like.

[0055] In some embodiments, the pharmaceutical composition may include one or more disintegrant component, such as croscarmellose sodium, carmellose calcium, crospovidone, alginic acid, sodium alginate, potassium alginate, calcium alginate, an ion exchange resin, an effervescent system based on food acids and an alkaline carbonate component, clay, talc, starch, pregelatinized starch, sodium starch glycolate, cellulose floc, carboxymethylcellulose, hydroxypropylcellulose, calcium silicate, a metal carbonate, sodium bicarbonate, calcium citrate, or calcium phosphate.

[0056] In some embodiments, the pharmaceutical composition may include one or more diluent component, such as mannitol, lactose, sucrose, maltodextrin, sorbitol, xylitol, powdered cellulose, microcrystalline cellulose, carboxymethyl-cellulose, carboxyethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, methylhydroxyethylcellulose, starch, sodium starch glycolate, pregelatinized starch, a calcium phosphate, a metal carbonate, a metal oxide, or a metal aluminosilicate.

[0057] In some embodiments, the pharmaceutical composition may include one or more optional lubricant component, such as stearic acid, metallic stearate, sodium stearyl fumarate, fatty acid, fatty alcohol, fatty acid ester, glyceryl behenate, mineral oil, vegetable oil, paraffin, leucine, silica, silicic acid, talc, propylene glycol fatty acid ester, polyethoxylated castor oil, polyethylene glycol, polypropylene glycol, polyalkylene glycol, polyoxyethylene-glycerol fatty ester, polyoxyethylene fatty alcohol ether, polyethoxylated sterol, polyethoxylated castor oil, polyethoxylated vegetable oil, or sodium chloride.

[0058] Disclosed herein are methods for treating opioid overdose in a subject. In various embodiments, such methods may include the step of administering a therapeutically effective amount of a formulation disclosed herein. In various embodiments, the subject may be experiencing opioid overdose or symptoms related thereto, such as, for example, vomiting, dilated pupils, extreme sleepiness, or the inability to wake up, intermittent loss of consciousness, slowed or irregular breathing, respiratory arrest (absence of breathing), cold, clammy skin, or bluish skin around the lips or under the fingernails, and the like and combinations thereof.

[0059] The term "subject" includes animals which can be treated using the methods of the invention. Examples of animals include mammals, such as mice, rabbits, rats, horses, goats, dogs, cats, pigs, cattle, sheep, and primates (e.g. chimpanzees, gorillas, and humans).

[0060] Certain embodiments are directed to veterinary formulations and methods for administration of the compositions of the invention to animals such as dogs, cats, pigs, and horses. Animals trained for use in law enforcement, particularly "drug detection dogs," are often used to find illicit drugs including opioids. As such, these animals inadvertently inhale amounts of opioids sufficient to cause overdose. Thus, embodiments are directed to veterinary compositions, as described above, for sustained release of opioid antagonists such as, for example, naloxone, naltrexone, or nalmefene, over a period of up to about 7 days, and in some embodiments, up to about 12 or up to about 24 hours. Such compositions can be administered by any means described below either prophylactically, i.e. before the animal is exposed to, or potential exposed to opioids, mitigate the effects of opioids on the animal or after the animal is exposed to opioids to limit adverse effects of the exposure.

[0061] Administration of any of the compositions described above either formulated for humans or animals can be systemic, parenteral, intranasal, topical, or oral. For example, administration can be, but is not limited to, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, oral, buccal, ocular routes, or intravaginally, by inhalation, by depot injections, or by implants. In particular embodiments, administering can be carried out by injection including, for example, depot injection, intramuscular injection, or subcutaneous injection, and the like, or by oral, sublingual, or intranasal administration, and the like. The selection of the specific route of administration and the dose regimen is to be adjusted or titrated by the clinician according to methods known to the clinician in order to obtain the optimal clinical response. The amount of compounds to be administered is that amount which is therapeutically effective. The dosage to be administered will depend on the characteristics of the subject being treated, e.g., the particular animal or human being treated, age, weight, health, types of concurrent treatment, if any, and frequency of treatments, and can be easily determined by one of skill in the art (e.g., by the clinician). Administration can be carried out by a clinician, or in other embodiments can be carried out by a first responder, emergency medical technician (EMT), bystander, friend, or family member with access to the compositions of embodiments in a deliverable form, for example, a prefilled syringe or kit.

[0062] In certain embodiments, the formulations of embodiments may be administered by a syringe. The sustained release composition is formulated so that the composition can be readily implanted (e.g., by injection) into the desired location to form a mass that can remain in place for the period suitable for controlled release of the opioid antagonist. The mechanical and rheological properties suitable for injectable depot compositions are known in the art. Typically, the polymer of the depot vehicle with particulates are present in an appropriate amount of solvent such that the depot composition can be so implanted.

[0063] For oral administration, the pharmaceutical composition can be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by adding a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, but are not limited to, fillers such as sugars, including, but not limited to, lactose, sucrose, mannitol, and sorbitol; cellulose preparations such as, but not limited to, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as, but not limited to, the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0064] For oral administration, the hydrogel formulation is preferably encapsulated by a retardant coating, e.g., a bio-

erodible polymer. Upon dissolution or erosion of the encapsulating material, the hydrogel core becomes exposed and the drug contained within the gel can be released for enteric adsorption. Bioerodible coating materials may be selected from a variety of natural and synthetic polymers, depending on the agent to be coated and the desired release characteristics. Exemplary coating materials include gelatins, carnauba wax, shellacs, ethylcellulose, cellulose acetate phthalate or cellulose acetate butyrate. Release of the agent is controlled by adjusting the thickness and dissolution rate of the polymeric coat.

[0065] Dragee cores can be provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active doses.

[0066] Pharmaceutical preparations which can be used orally include, but are not limited to, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as, e.g., lactose, binders such as, e.g., starches, and/or lubricants such as, e.g., talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration.

[0067] For intranasal administration, the compositions for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0068] The compositions of the present invention can also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

[0069] In transdermal administration, the compositions of the present invention, for example, can be applied to a plaster, or can be applied by transdermal, therapeutic systems that are consequently supplied to the organism. In some embodiments, the formulation can be delivered using microneedle apparatuses.

[0070] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

[0071] The invention also provides kits for carrying out the therapeutic regimens of the invention. Such kits comprise in one or more containers having therapeutically or prophylactically effective amounts of the sustained release compositions in pharmaceutically acceptable form. The sustained release compositions in a vial of a kit of the invention may be in the form of a pharmaceutically acceptable solution, e.g., in combination with sterile saline, dextrose solution, or buffered solution, or other pharmaceutically acceptable sterile fluid. Alternatively, the complex may be lyophilized or desiccated; in this instance, the kit optionally further comprises in a container a pharmaceutically acceptable solution (e.g., saline, dextrose solution, etc.), preferably sterile, to reconstitute the complex to form a solution for injection purposes.

[0072] In another embodiment, a kit of the invention further comprises a needle or syringe, preferably packaged in sterile form, for injecting the complex, and/or a packaged alcohol pad. Instructions are optionally included for administration of sustained release compositions by a clinician, first responder, emergency medical technician (EMT), bystander, friend, family member or the patient. Such kits may contain one or more vials of a sustained release opioid antagonist formulation that is manually loaded into a syringe before administering or autoinjectors that are pre-loaded with the formulation in an appropriate amount for administration.

EXAMPLES

[0073] Although the present invention has been described in considerable detail with reference to certain preferred embodiments thereof, other versions are possible. Therefore, the spirit and scope of the appended claims should not be limited to the description and the preferred versions contained within this specification. Various aspects of the present invention will be illustrated with reference to the following non-limiting examples.

Example 1

[0074] A simulation was carried out for formulations containing 2 mg free naloxone, 20 mg microencapsulated naloxone, and 2 mg free and 20 mg microencapsulated naloxone. Predicted PK data using human PK data for naloxone HCl as a baseline is provided in FIG. **2**. These data suggest that a formulation that provides at least 2 ng/ml plasma concentration of naloxone for a time period of at least 12 hours to 24 hours can be achieved by combining free naloxone and microencapsulated naloxone.

1. A composition comprising free opioid antagonist and microparticles of encapsulated opioid antagonist.

2. The composition of claim **1**, having a ratio of free opioid antagonist to encapsulated opioid antagonist of about 1:10 to about 1:50.

3. The composition of claim **1**, wherein the free opioid antagonist comprises about 0.4 milligrams (mg) to about 4 mg of opioid antagonist.

4. The composition of claim **1**, wherein the free opioid antagonist is selected from the groups consisting of naloxone (17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, naltrexone (17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, nalmefene (6-desoxy-6-methylenenaltrexone) in free base, salt, or hydrate form, and combinations thereof.

5. The composition of claim **1**, wherein the encapsulated opioid antagonist comprises about 10 mg to about 30 mg of encapsulated opioid antagonist.

6. The composition of claim **1**, wherein the encapsulated opioid antagonist is selected from the groups consisting of naloxone (17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, naltrexone (17-(cyclopropylmethyl)-4,5α-epoxy-3, 14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, nalmefene (6-desoxy-6-methylenenaltrexone) in free base, salt, or hydrate form, and combinations thereof.

7. The composition of claim **1**, wherein the microparticles have a mean particle diameter of about 40 μm to about 60 μm.

8. The composition of claim **1**, wherein the microparticles comprise a biodegradable polymer selected from the group consisting of PLGA, PLA, PGA, PBS, PHA, PCL, PHB, PHV, PHBV, PEG, PLEG, and copolymers thereof.

9. The composition of claim **8**, wherein the PLGA is capped.

10. The composition of claim **8**, wherein the PLGA comprises a ratio of PLA to PGA of 50:50 by weight to about 60:40 by weight.

11. The composition of claim **8**, wherein the biodegradable polymer comprises polymer units having molecular weights of about 5 kiloDalton (kDa) to about 150 kDa.

12. The composition of claim **1**, wherein opioid antagonist loading is about 0.5 wt. % to about 50 wt. %.

13. A method for treating or preventing opioid overdose comprising administering to a subject in need of treatment a composition comprising free opioid antagonist and microparticles of encapsulated opioid antagonist.

14. The method of claim **13**, having a ratio of free opioid antagonist to encapsulated opioid antagonist of about 1:10 to about 1:50.

15. The method of claim **13**, wherein the free opioid antagonist comprises about 0.4 milligrams (mg) to about 4 mg of opioid antagonist.

16. The method of claim **13**, wherein the free opioid antagonist is selected from the groups consisting of naloxone (17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, naltrexone (17-(cyclopropylmethyl)-4,5α-epoxy-3, 14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, nalmefene (6-desoxy-6-methylenenaltrexone) in free base, salt, or hydrate form, and combinations thereof.

17. The method of claim **13**, wherein the encapsulated opioid antagonist comprises about 10 mg to about 30 mg of encapsulated opioid antagonist.

18. The method of claim **13**, wherein the encapsulated opioid antagonist is selected from the groups consisting of naloxone (17-Allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, naltrexone (17-(cyclopropylmethyl)-4,5α-epoxy-3, 14-dihydroxymorphinan-6-one) in free base, salt, or hydrate form, nalmefene (6-desoxy-6-methylenenaltrexone) in free base, salt, or hydrate form, and combinations thereof.

19. The method of claim **13**, wherein administration results in a plasma concentration in the subject of greater than about 2 ng/ml for up to about 7 days.

20. The method of claim **13**, wherein administration is selected from the group consisting of depo injection, intramuscular injection, subcutaneous injection, oral, sublingual, and intranasal administration.

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