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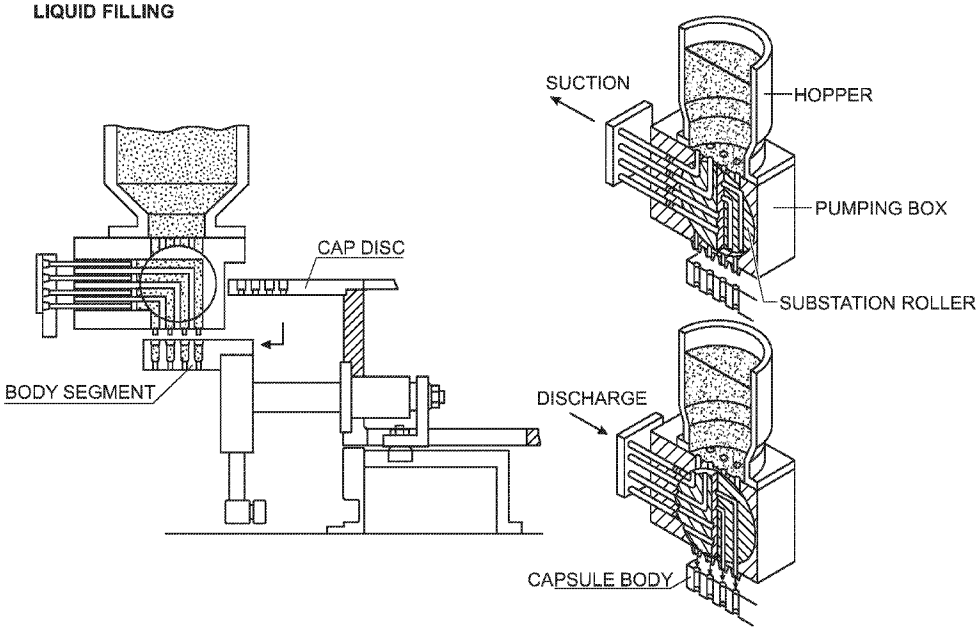
(54) **Titre : FORME POSOLOGIQUE REMPLIE DE LIQUIDE ANTI-ABUS A LIBERATION IMMEDIATE**
(54) **Title: IMMEDIATE RELEASE ABUSE DETERRENT LIQUID FILL DOSAGE FORM**



(57) **Abrégé/Abstract:**
The present disclosure relates to an oral, immediate release, abuse deterrent liquid filled capsule containing polyethylene glycol and at feast one active pharmaceutical ingredient susceptible to abuse. The dosage form is abuse deterrent to parenteral administration. The present disclosure also relates to processes of preparing the dosage form.

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(54) Title: IMMEDIATE RELEASE ABUSE DETERRENT LIQUID FILL DOSAGE FORM

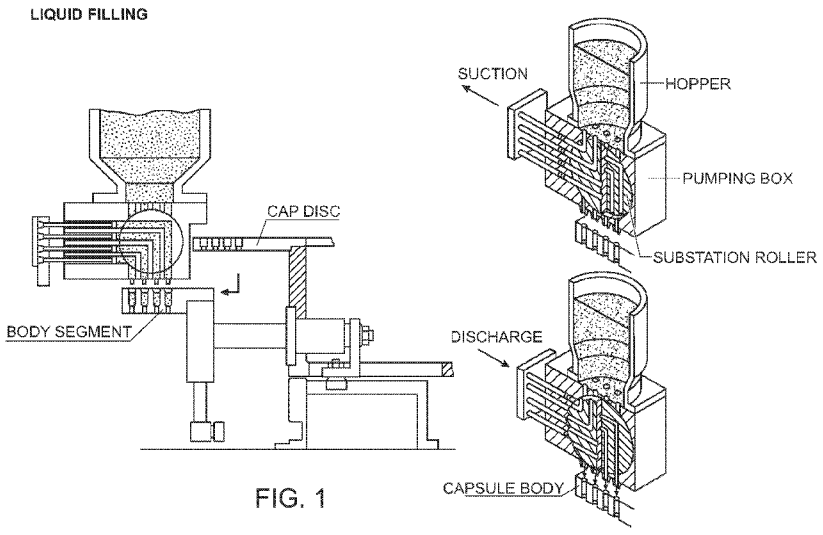

FIG. 1

(57) Abstract: The present disclosure relates to an oral, immediate release, abuse deterrent liquid filled capsule containing polyethylene glycol and at feast one active pharmaceutical ingredient susceptible to abuse. The dosage form is abuse deterrent to parenteral administration. The present disclosure also relates to processes of preparing the dosage form.

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IMMEDIATE RELEASE ABUSE DETERRENT LIQUID FILL DOSAGE FORM

[0001]

Field of the Technology

[0002] The present disclosure relates to an oral immediate release, abuse deterrent dosage form. The dosage form contains polyethylene glycol (PEG) to reduce abuse by non-oral administration routes, e.g. intranasal and/or intravenous. The composition of PEG is designed to allow for immediate release of the active ingredient while deterring abuse and maintaining stability of the dosage form at elevated temperatures.

Background

[0003] FDA-approved drugs are provided in many different forms based on the type of active substance, the indication treated and the preferred route of administration. These forms include enteral formulations (e.g., tablets, capsules or pills), parenteral formulations (e.g., injectable formulations such as intravenous, subcutaneous, intramuscular and intraarticular), liquid formulations (e.g., elixirs), lyophilized formulations and topical formulations. A majority of the FDA-approved drugs are currently available in enteral form, as either a tablet or capsule.

[0004] Several formulations have been investigated for deterring abuse, either by oral ingestion of the drug with alcohol, or by non-oral administration routes such as intranasal and/or intravenous administration. For example, U.S. 2014/0010873 (assigned to Egalet Ltd.) is directed to an abuse-deterrent pharmaceutical composition including at least one polyethylene oxide and at least one plasticizer. The polyethylene oxide has an average molecular weight of at least 1,000,000 Daltons, and the pharmaceutical composition includes at least 5 percent w/w of the at least one plasticizer. The pharmaceutical composition is designed to prevent immediate release of the at least one active drug substance after physical tampering. U.S. 2009/0123386 (assigned to MW Encap Limited) is directed to an abuse deterrent capsule including at least one

modifier selected to prevent abuse. The modifier may have a high melting point or be insoluble in aqueous solvents or ethanol. For example, the high melting point excipient may be Poloxamer 188 or PEG 8000. U.S. 2010/0204259 (assigned to Egalet A/S) is directed to immediate release pharmaceutical compositions that are resistant to abuse by intake of alcohol. The release of the drug substance from the immediate release composition is decreased when the composition is exposed to a dissolution medium that includes ethanol. The compositions may be formulated to include at least one polyglycol and at least one effervescent agent.

Summary

[0005] The present disclosure relates to an immediate release, abuse deterrent capsule including an active substance susceptible to abuse, a first polyethylene glycol (PEG) having an average molecular weight between about 30,000 Daltons and about 40,000 Daltons; and a second PEG having an average molecular weight between about 3000 Daltons and about 4000 Daltons. The ratio of the first PEG to the second PEG is less than about 1:4 w/w.

[0006] In some embodiments, the first PEG and the second PEG together are at least about 60 wt% of the dosage form. In some embodiments, the active substance is hydrocodone bitartrate. In other embodiments, the active substance is oxycodone hydrochloride (HCl). In some embodiments the capsule includes a grey dye including FD&C Blue #1, FD&C Yellow #6, and FD&C Red #40. In certain embodiments, the dye reduces abuse by providing a visual deterrent to injecting. In certain embodiments, about 60%, 70% 75%, 80%, 85% or about 90% or more of the capsule fill contents are soluble in both water and/or alcohol, e.g., ethanol. In certain embodiments, the ratio of the first PEG to the second PEG is between about 1:7 w/w and about 1:11 w/w. In some embodiments, the first PEG has an average molecular weight of about 35,000 Daltons and the second PEG has an average molecular weight of about 3350 Daltons. In some embodiments, the capsule includes at least about 2.5 wt% of the active substance. The capsule may be prepared by filling a capsule body with a heated homogenized suspension including the active substance, the first PEG and the second PEG.

[0007] The present disclosure also relates to an immediate release, abuse deterrent capsule including an active substance susceptible to abuse and polyethylene glycol with a weighted average molecular weight between about 6200 Daltons and about 7800 Daltons. In certain embodiments, the capsule includes at least about 60 wt% of PEG. In some embodiments,

the active substance is hydrocodone bitartrate. In other embodiments, the active substance is oxycodone HCl.

[0008] The present disclosure also relates to an immediate release, abuse deterrent capsule including an active substance susceptible to abuse, a first PEG having a melting point greater than or equal to about 60 °C, and a second PEG having a melting point less than or equal to about 57 °C. The contents of the capsule can be solid at 40 °C / 75% relative humidity. In some embodiments, at least 90% of the active ingredient can be released from the capsule within 30 minutes following administration or via dissolution testing. In other embodiments, at least 75% of the active ingredients can be released from the capsule within 45 minutes following administration or via dissolution testing. In some embodiments, the first PEG and the second PEG together are at least about 60 wt% of the capsule. In particular embodiments, the active substance is hydrocodone bitartrate. In other embodiments, the active substance is oxycodone HCl.

[0009] The present disclosure also relates to a process for the production of an immediate release, abuse deterrent capsule including at least one active substance susceptible to abuse including preparing a homogenized suspension of the at least one active substance susceptible to abuse, a first PEG having an average molecular weight between about 30,000 Daltons and about 40,000 Daltons, and a second PEG having an average molecular weight between about 3000 Daltons and about 4000 Daltons. The process can further include filling the homogenized suspension into a capsule body to produce an encapsulated dosage form. The ratio of the first PEG to the second PEG can be less than about 1:4 w/w, e.g., between about 1:7 w/w and about 1:11 w/w.

[0010] In certain embodiments of the aforementioned process, the first PEG and the second PEG together can be at least about 60 wt% of the capsule. In particular embodiments, the active substance is hydrocodone bitartrate. In other embodiments, the active substance is oxycodone HCl. In certain embodiments the capsule can be formed by joining a capsule body with a capsule cap.

[0011] The present disclosure also relates to a method of treating pain including administering to a subject in need thereof a therapeutically effective amount of any of the aforementioned capsules.

Brief Description of the Drawings

[0012] The foregoing and other advantages provided by the present disclosure will be more fully understood from the following description of exemplary embodiments when read together with the accompanying drawings, in which:

[0013] Figure 1 shows cross sections of a capsule filling machine including the body segment, the cap disc, the hopper, the pumping box, the substation roller, and capsule bodies.

[0014] Figure 2A shows solutions of grey dye before filtering. Figure 2B shows solutions of grey dye after filtering.

[0015] Figure 3 shows a summary of an exemplary manufacturing process for formulations of the present disclosure.

[0016] Figure 4 shows unfiltered solutions of the dosage forms in 190 proof ethanol after shaking at 250 rpm for 3 hours.

[0017] Figure 5 shows syringe-filtered solutions of the dosage forms in 190 proof ethanol after shaking at 250 rpm for 3 hours.

Detailed Description

[0018] Abuse of prescription drugs, particularly opioids, is a serious and growing public health concern. To address this concern, new formulations are being developed that contain abuse-deterrent properties. Abuse deterrent properties include properties that make product manipulation more difficult or make abuse of the manipulated product less attractive or rewarding.

[0019] Recently the FDA issued a draft guidance for industry related to formulations having abuse deterrent properties. *Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling*, U.S. Department of Health and Human Services, FDA, CDER, January 2013. These guidelines separate abuse deterrent formulations into six categories, including: physical/chemical barriers, agonist/antagonist combinations, aversion, delivery system, prodrug, or a combination of the aforementioned. As described by the FDA guidance, the categories are:

[0020] Physical/Chemical barriers – Physical barriers can prevent chewing, pulverizing, cutting, grating, or grinding. Chemical barriers can resist extraction of the opioid using common solvents like water, alcohol, or other organic solvents. Physical and chemical barriers can change the physical form of an oral drug rendering it less amenable to abuse.

[0021] Agonist/Antagonist combinations – An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse. The antagonist can be sequestered and released only upon manipulation of the product. For example, a drug product may be formulated such that the substance that acts as an antagonist is not clinically active when the product is swallowed but becomes active if the product is crushed and injected or snorted.

[0022] Aversion – Substances can be combined to produce an unpleasant effect if the dosage form is manipulated prior to ingestion or a higher dosage than directed is used.

[0023] Delivery System (including depot injectable formulations and implants) – Certain drug release designs or the method of drug delivery can offer resistance to abuse. For example, a sustained-release depot injectable formulation that is administered intramuscularly or a subcutaneous implant can be more difficult to manipulate.

[0024] Prodrug – A prodrug that lacks opioid activity until transformed in the gastrointestinal tract can be unattractive for intravenous injection or intranasal routes of abuse.

[0025] Combination – Two or more of the above methods can be combined to deter abuse.

[0026] An opioid analgesic submitted for abuse deterrent formulation (ADF) labeling must show conformance to one or more of these categories. The present disclosure relates to an abuse deterrent dosage form for oral administration, which provides immediate release of an active pharmaceutical substance and conforms to one or more of these categories. In one embodiment, the abuse deterrent dosage form of the present disclosure conforms to at least one of the six FDA categories. In another embodiment, the abuse deterrent dosage form of the present disclosure conforms to at least two of the six FDA categories. In another embodiment, the abuse deterrent dosage form of the present disclosure conforms to at least three of the six FDA categories. In another embodiment, the abuse deterrent dosage form of the present disclosure conforms to at least four of the six FDA categories. In another embodiment, the abuse deterrent dosage form of the present disclosure conforms to at least five of the six FDA categories.

[0027] For example, an abuse deterrent dosage form of the present disclosure can reduce abuse by the incorporation of at least one physical barrier. The physical barrier is designed to prevent abuse based on chewing, pulverizing, cutting, grating or grinding. Preferably, the physical barrier prevents or reduces the effectiveness of these methods. As used herein, the phrase "abuse deterrent" means that the active substance cannot readily be separated from the formulation in a form suitable for abuse by such means as, for example, grinding. The abuse deterrent form of the present disclosure cannot be easily ground, extracted from, or both. Abuse deterrent measures render it difficult to transform the dosage form into a residue or extract for non-oral administration, such as intranasal or intravenous.

[0028] In one embodiment, the present disclosure relates to an oral, immediate release, abuse deterrent dosage form including an active substance susceptible to abuse, a first PEG having an average molecular weight between about 30,000 Daltons and about 40,000 Daltons, and a second PEG having an average molecular weight between about 3000 Daltons and about 4000 Daltons. The ratio of the first PEG to the second PEG can be less than about 1:4 w/w. The wt% of active substance in the formulation may also vary depending on the active substance of the dosage form. In some embodiments, the dosage form includes at least about 0.1 wt%, 0.2 wt%, 0.3 wt%, 0.4 wt%, 0.5 wt%, 0.6 wt%, 0.7 wt%, 0.8 wt%, 0.9 wt%, 1.0 wt%, 1.1 wt%, 1.2 wt%, 1.3 wt%, 1.4 wt%, 1.5 wt %, 2 wt%, 2.5 wt%, 3 wt%, 4 wt%, 5 wt%, 6 wt%, 7 wt%, 7.5 wt%, 8 wt%, 9 wt%, 10 wt%, 11 wt%, 12 wt%, 13 wt%, 14 wt%, 15 wt%, 16 wt%, 17 wt%, 18 wt%, 19 wt%, 20 wt%, 21 wt%, 22 wt%, 23 wt%, 24 wt%, 25 wt%, 26 wt%, 27 wt%, 28 wt%, 29 wt%, 30 wt%, 31 wt%, 32 wt%, 33 wt%, 34 wt%, 35 wt%, 36 wt%, 37 wt%, 38 wt%, 39 wt%, 40 wt%, 41 wt%, 42 wt%, 43 wt%, 44 wt%, 45 wt%, 46 wt%, 47 wt%, 48 wt%, 49 wt%, 50 wt%, 51 wt%, 52 wt%, 53 wt%, 54 wt%, 55 wt%, 56 wt%, 57 wt%, 58 wt%, 59 wt%, 60 wt%, 65 wt%, 69 wt%, 70 wt%, 75 wt%, 80 wt%, 85 wt%, 88 wt%, 90 wt%, or 95 wt% of the active substance. Any of these values may be used to define a range for the wt% of the active substance depending on the application. For example, the amount of active substance in the dosage form may range from about 0.10 wt% to about 60 wt%. Particularly, the amount of active substance in the dosage form may range from about 0.1 wt% to about 1.5 wt%, from about 5 wt% to about 30 wt%, from about 15 wt% to about 20 wt%, from about 15 wt% to about 30 wt%, from about 40 wt% to about 60 wt%, from about 40 wt% to about 50 wt%, or from about 42 wt% to about 46 wt%.

[0029] For example, the dosage form may be a 100 mg capsule including about 5 mg, about 10 mg, about 15 mg, about 20 mg, or about 30 mg of active substance (e.g., oxycodone HCl). In other embodiments, the dosage form may be a 150 mg capsule including about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, or about 45 mg of active substance (e.g., oxycodone HCl). In other embodiments, the dosage form may be a 200 mg capsule including about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, or about 60 mg of active substance (e.g., oxycodone HCl). In other embodiments, the dosage form may be a 700 mg capsule including about 2.5 mg, about 5 mg, about 7.5 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 45 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg or about 100 mg of an active substance (e.g., hydrocodone bitartrate).

[0030] As used herein, the term "active" or "active substance" or "active substance susceptible to abuse" or "API" means any opioid or opioid related compound subject to potential abuse. The active substance may include, without limitation, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levophenacylmorphan, levorphanol, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbulphine, narceine, nicomorphine, norpipanone, opium, oxycodone, papvretum, pentazocine, phenadoxone, phenazocine, phenomorphan, phenoperidine, piminodine, propiram, propoxyphene, sufentanil, tilidine, tapentadol, and tramadol, and pharmaceutically acceptable salts and mixtures thereof. For example, in some embodiments the active can be oxycodone HCl or hydrocodone bitartrate. In the dosage forms of the present disclosure, the active substance is not oxymorphone.

[0031] In particular, the active substance can be hydrocodone bitartrate or oxycodone HCl. The dosage form of the present disclosure can be rendered abuse deterrent by incorporating PEG in the dosage form. The PEG can deter abuse by preventing at least 50%, or at least 75%, of the capsule weight from being ground to a particle size below 500 μm, such as after 30 seconds of

milling at 10,000 RPM. PEG can also prevent extraction of the active substance from the dosage form using an alcohol. Abusers can use the partial solubility characteristics of dosage form excipients to extract the active substance using alcohol and subsequently burn off the alcohol to form a purer residue containing the active substance. The inclusion of PEG in the formulation can prevent or reduce extraction because PEG can melt and form a wax before the alcohol can be completely evaporated or flashed off, an abuser may not be able to obtain a residue containing the active substance. Addition of a dye to the dosage form can also result in a colored solution after extraction of the active substance, deterring intravenous injection. By selecting the appropriate average molecular weight and quantity of PEG present within a dosage form, the characteristics of the dosage form can be manipulated in a way to create a wide array of abuse deterrent capsules having immediate release profiles.

[0032] Inclusion of PEG in the dosage form can result in the inability of the dosage form, e.g., capsule, to be abused by pulverizing and snorting, pulverizing and injecting, or combinations thereof. For example, the abuse deterrent dosage form of the present disclosure may be incapable of being significantly pulverized by physical or mechanical force due at least in part to the waxy characteristics of the PEG.

[0033] One of the most common means of abuse of an orally administered opioid analgesic involves the manipulation of the oral dosage form in order to cause rapid delivery to the bloodstream via nasal insufflation. In order for insufflation to be used as an effective means of abuse, the original dosage form must be manipulated so as to decrease the particle size of the ingested drug to about 500 μm or less. A particle size of about 500 μm or less is necessary for effective intranasal absorption to occur. By limiting the quantity of particles under about 500 μm that an abuser can obtain by reasonable methods, one can render insufflation ineffective as a means of abuse. Thus one way to prevent abuse by nasal insufflation is by capturing the active substance susceptible to abuse in a matrix which is resistant to being physically broken down to produce particles smaller than about 500 μm.

[0034] The dosage form of the present disclosure can inhibit manipulation by grinding or pulverizing using common equipment, such as a coffee grinder. For example, the formulation can deter abuse by limiting the particle size to which the formulation may be ground. The formulation prevents the dosage form, or at least substantial portions of the dosage from, from

being ground in particles having a particle size of about 500 μm or less that may pass through the mucus membranes of the nasal cavity. The dosage form can also significantly limit the extraction of the active substance by common solvents (e.g., cold water or distilled aqueous ethanol) from the formulation. For example, the formulation deters abuse by limiting the ability of persons to extract the active substance from the formulation (either intentionally or unintentionally), such that the active substance cannot easily be concentrated for parenteral administration. The abuse deterrent dosage form may also include, but does not require, the incorporation of other deterrents such as antagonists or irritants.

[0035] For example, in one embodiment, the abuse deterrent can work as follows. If the dosage form is extracted with alcohol or an aqueous solution, the PEG and/or dye will also be extracted and cannot easily be separated from the active substance, preventing the preparation of pure drug for intravenous administration. Extraction with a solution would result in a grey/black liquid containing the PEG, dye and active substance. The inclusion of PEG in the formulation can prevent or reduce extraction because PEG can melt and form a wax before the alcohol can be completely evaporated or flashed off, an abuser may not be able to obtain a residue containing the active substance. These properties can allow for an oral drug delivery system that satisfies at least one of the categories in the FDA guidance (e.g., "physical and chemical barriers can change the physical form of an oral drug rendering it less amenable to abuse").

[0036] The PEG can be capable of allowing immediate release of the active substance, providing abuse deterrence, and/or ensuring the formation of a solid dosage form that is stable at elevated temperatures, for example 40 °C. In some embodiments, the PEG provides all three. The dosage form of the present disclosure can accomplish the above capabilities by using a mixture of PEG molecules of at least two different average molecular weights. For example, the dosage form may include a first PEG having an average molecular weight between about 30,000 Daltons and 40,000 Daltons, and a second PEG having an average molecular weight about 3000 Daltons and 4000 Daltons.

[0037] In some embodiments, the first PEG has an average molecular weight of about 20, 000, 21,000, 22,000, 23,000, 24,000, 25,000, 26,000, 27,000, 28,000, 29,000, 30,000, 30,500, 31,000, 31,500, 32,000, 32,500, 33,000, 33,500, 34,000, 34,500, 35,000, 35,500, 36,000, 36,500, 37,000, 37,500, 38,000, 38,500, 39,000, 39,500 or 40,000 Daltons. Any of these values may be

used to define a range for the average molecular weight of the first PEG. For example, the first PEG can have an average molecular weight between about 31,000 Daltons and about 39,000 Daltons, between about 32,000 Daltons and about 38,000 Daltons, between about 33,000 Daltons and about 37,000 Daltons, between about 34,000 Daltons and about 36,000 Daltons, between about 30,000 Daltons and about 32,000 Daltons, between about 32,000 Daltons and about 34,000 Daltons, between about 36,000 Daltons and about 38,000 Daltons, or between about 38,000 Daltons and about 40,000 Daltons.

[0038] In some embodiments, the second PEG can have an average molecular weight of 3000, 3050, 3100, 3150, 3200, 3250, 3300, 3350, 3400, 3450, 3500, 3550, 3600, 3650, 3700, 3750, 3800, 3850, 3900, 3950 or 4000 Daltons. Any of these values may be used to define a range for the average molecular weight of the second PEG. For example, the second PEG can have an average molecular weight between about 3100 Daltons and about 3900 Daltons, between about 3200 Daltons and about 3800 Daltons, between about 3300 Daltons and about 3700 Daltons, between about 3400 Daltons and about 3600 Daltons, between about 3000 Daltons and 3200 Daltons, between about 3200 Daltons and about 3400 Daltons, between about 3600 Daltons and about 3800 Daltons, or between about 3800 Daltons and about 4000 Daltons.

[0039] In some embodiments, the ratio of the first PEG to the second PEG can be about 3:1, 2:1, 1:1, 1:2, 1:3. 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:11, 1:12, 1:13, 1:14, 1:15, 1:16, 1:17, 1:18, 1:19 or 1:20. Any of these values may be used to define a range for the ratio of the first PEG to the second PEG. For example, in some embodiments, the ratio of the first PEG to the second PEG can be between about 1:2 w/w and about 2:1 w/w, between about 1:3 w/w and about 1:1 w/w, between about 1:2 w/w and about 1:1 w/w, between about 1:1 w/w and about 2:1 w/w, between about 1:1 w/w and about 3:1 w/w, between about 1:4 w/w and about 1:10 w/w, between about 1:7 w/w/ and about 1:11 w/w, or between about 1:8 w/w and about 1:10 w/w. In other embodiments, the ratio of the first PEG to the second PEG can be less than about 3:1, 2:1, 1:1, 1:2, 1:3. 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:11, 1:12, 1:13, 1:14, 1:15, 1:16, 1:17, 1:18, 1:19 or 1:20. For example, a ratio of 1:10 is less than a ratio of 1:9.

[0040] The total wt% of PEG in the dosage form may vary depending on the active substance, stability, and release profile. In some embodiments, the first PEG and the second PEG together are at least about 5 wt%, 10 wt%, 15 wt%, 20 wt%, 25 wt%, 30 wt%, 35 wt%, 36

wt%, 37 wt%, 38 wt%, 39 wt%, 40 wt%, 41 wt%, 42 wt%, 43 wt%, 44 wt%, 45 wt%, 46 wt%, 47 wt%, 48 wt%, 49 wt%, 50 wt%, 51 wt%, 52 wt%, 53 wt%, 54 wt%, 55 wt%, 56 wt%, 57 wt%, 58 wt%, 59 wt%, 60 wt%, 61 wt%, 62 wt%, 63 wt%, 64 wt%, 65 wt%, 66 wt%, 67 wt%, 68 wt%, 69 wt%, 69.7 wt%, 70 wt%, 71 wt%, 72 wt%, 73 wt%, 74 wt%, 75 wt%, 76 wt%, 77 wt%, 78 wt%, 79 wt%, 80 wt%, 85 wt%, 88 wt%, 90 wt%, or 95 wt% of the dosage form.

[0041] In one embodiment, the formulation includes a disintegrant. A disintegrant promotes disintegration of the capsule, and dissolution of the active substance, after administration and upon contact with water. The disintegrant may be selected from sodium starch glycolate, cross-linked polyvinylpyrrolidone (e.g. crospovidone), cross-linked sodium carboxymethylcellulose (e.g. croscarmellose sodium) sodium bicarbonate/citric acid, alginic acid or combinations thereof. In particular embodiments, the disintegrant is selected from sodium starch glycolate, crospovidone and croscarmellose. The dosage form may contain about 1 wt%, 2 wt%, 3 wt%, 4 wt%, 5 wt%, 6 wt%, 7 wt%, 8 wt%, 9 wt%, 10 wt%, 11 wt%, 12 wt%, 13 wt%, 14 wt%, 15 wt%, 16 wt%, 17 wt%, 18 wt%, 19 wt% or 20 wt% of disintegrant. Any of these values may be used to define a range for the wt% of disintegrant. For example, the dosage form may contain between about 1.0 wt% and about 20 wt% of disintegrant. Particularly, the formulation may contain between about 1.0 wt% and about 10 wt% disintegrant or between about 5 wt% and about 8 wt% disintegrant. In certain embodiments, the dosage form includes 5 wt% sodium starch glycolate, 8 wt% sodium starch glycolate, 5 wt% crospovidone, or 5 wt% croscarmellose sodium. In another embodiment, the dosage form of the present disclosure excludes a disintegrant.

[0042] In some embodiments, the formulation includes a dye. A dye can be useful in deterring abuse by discouraging the abuser from intravenous injection. For example, extraction of the dye along with the active ingredient would result in a colored solution that would discourage the abuser from intravenous injection. Thus, in certain embodiments, the dye reduces abuse by extracting and injecting. The dye may be selected from known dyes suitable for use in pharmaceutical formulations or approved by the FDA for such use. For example, the dye may be FD&C Blue No. 2 or a 50/50 wt% solution of FD&C Blue No. 2 in PEG. In another embodiment, the dye may be a grey dye including FD&C Blue #1, FD&C Yellow #6, and FD&C Red #40. The dye may be in a 90% PEG 3350 blend. In certain embodiments, 14 mg of dye

blend can be used in each capsule or about 1.4 mg of concentrated dye. In certain embodiments a grey dye is used since it is visually deterring and non-transparent. The dosage form may include about 0.10 wt%, 0.20 wt%, 0.30 wt%, 0.40 wt%, 0.50 wt%, 1 wt%, 2 wt%, 3 wt%, 4 wt%, 5 wt%, 6 wt%, 7 wt%, 8 wt%, 9 wt%, 10 wt%, 11 wt%, 12 wt%, 13 wt%, 14 wt%, 15 wt%, 16 wt%, 17 wt%, 18 wt%, 19 wt%, or 20 wt% dye. Any of these values may be used to define a range for the wt% of the dye. For example, the dosage form may contain between about 0.10 wt% and about 15 wt% dye. Particularly, the dosage form may contain between about 0.20 wt% and about 1.5 wt% dye, about 0.50 wt% and about 1.0 wt% dye , or about 7 to about 14 wt% dye. In certain embodiments, the dosage form may include about 1 mg, 1.4 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg or 30 mg of dye. In another embodiment, the dosage form of the present disclosure excludes a dye.

[0043] In some embodiments, the dosage form includes a first dye and a second dye, wherein the first dye has a high solubility in aqueous solution that is higher than the solubility of the second dye in aqueous solution. For example, in some embodiments the first dye has a solubility in aqueous solution of about 1 g, 5 g, 10 g, 30 g, 50 g, 100 g or 500 g in 1 L of aqueous solution and the second dye has a solubility in aqueous solution of about 1 mg, 5 mg, 10 mg, 30 mg, 50 mg, 100 mg, 500 mg, 1 g, or 10 g in 1 L of aqueous solution. In some embodiments, the second dye has a high solubility in non-aqueous solution that is greater than the solubility of the first dye in non-aqueous solution. For example, in some embodiments, the first dye has a solubility in non-aqueous solution of about 1 mg, 5 mg, 10 mg, 30 mg, 50 mg, 100 mg, 500 mg, 1 g, or 10 g in 1 L of non-aqueous solution, and the second dye has a solubility in non-aqueous solution of about 1 g, 5 g, 10 g, 30 g, 50 g, 100 g or 500 g in 1 L of non-aqueous solution. In some embodiments, the color of the first dye is substantially the same as the color of the second dye. In other embodiments, the color of the first dye is substantially different from the color of the second dye. For the purposes of the present disclosure, a dye is considered to be soluble in a solvent if about 1 g of the dye can be dissolved in about 10-30 mL of the solvent. For example, a dye is considered to be water soluble if about 1 g of the dye can be dissolved in 10-30 mL of water.

[0044] In another embodiment, the dosage form includes a preservative or antioxidant. The preservative or antioxidant can reduce or limit the degradation or deterioration of the abuse deterrent dosage form. For example, the components of the oral drug delivery system (e.g., active substances, PEG) may undergo degradation (e.g., oxidative reduction, chain cleavage) due to oxidation. Preventing degradation can help maintain the abuse deterrent properties of the formulation. For instance, the molecular weight of PEG in the formulation affects the resistance to grinding, for example, with a coffee grinder. The addition of a preservative or antioxidant in the formulation that reduces or eliminates the degradation of the molecular weight of PEG may be useful in maintaining the abuse deterrence properties of the dosage form. In addition to maintaining abuse deterrence, the addition of a preservative or antioxidant in the dosage form may be necessary to prevent premature degradation of the active substance over the shelf life of the dosage form.

[0045] The preservative or antioxidant may be selected from preservatives or antioxidants known to one skilled in the art for use in pharmaceutical formulations, such as citric acid, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), erythorbic acid, hypophosphorous acid, lactobionic acid, monothioglycerol, potassium metabisulfite, propyl gallate, racemethionine, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite, sodium sulfite, sodium thiosulfate, stannous chloride, sulfur dioxide and tocopherols. The formulation, or dosage form, may contain between about 0.1 wt% and about 2.0 wt%, or about 0.25 wt% and about 0.75 wt% of preservative or antioxidant. In another embodiment, the dosage form of the present disclosure excludes a preservative or antioxidant.

[0046] In some embodiments, the dosage form includes one or more excipients that form a gel in the presence of an alcohol. The alcohol gelling/thickening agent reduces or limits the potential for abuse by preventing extraction of the active substance from the dosage form. For example, when introduced to an alcohol solution, the components of the dosage form (e.g., active substances, PEG) may become trapped in a gel/viscous liquid which prevents extraction and subsequent alcohol evaporation to produce a pure active substance. In one embodiment, the alcohol gelling/thickening agent does not form a gel in the presence of water. The dosage form can contain up to about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%,

15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39% or about 40%. These values can be used to define a range, such as about 0.1 wt% to about 40 wt% alcoholic gelling/thickening agent. In another embodiment, the dosage form of the present disclosure does not contain an alcohol gelling/thickening agent.

[0047] The alcohol gelling/thickening agent may be a gelling or thickening agent known to one skilled in the art for use in pharmaceutical formulations, such as acacia, alginic acid, bentonite, calcium acetate, carbomers, carboxymethylcellulose, ethylcellulose, gelatin, hydroxyethylcellulose, hydroxypropyl cellulose, magnesium aluminum silicate, methylcellulose, poloxamers, polyvinyl alcohol, polyvinyl acetate, polyvinylpyrrolidone, sodium alginate, sorbitol derivatives, tragacanth, or xanthan gum.

[0048] The dosage form may additionally include at least one additive independently selected from surfactants, bulking agents, lubricants, flavorings or combination thereof.

[0049] The abuse deterrent dosage form of the present disclosure is capable of immediate release of the active substance. The dosage form may be manufactured to provide a composition exhibiting an immediate release profile of at least one active substance. As used herein, "immediate release" refers to a dosage form that releases the active substance or a pharmaceutically acceptable salt thereof, e.g., oxycodone HCl or hydrocodone bitartrate, substantially completely into the gastrointestinal tract of the user within a period of less than an hour, and often less than about 45 minutes or 30 minutes from ingestion. In one embodiment, the amount of active substance released from the dosage form, e.g., oxycodone HCl or hydrocodone bitartrate, by exposure to deaerated water within 45 minutes is greater than or equal to 75%. In another embodiment, the amount of active substance released from the dosage form, e.g., hydrocodone bitartrate, by exposure to a 0.1 N hydrochloric acid solution within 30 minutes is greater than or equal to 90%. In other embodiment, the amount of active substance released from the dosage form, e.g., oxycodone HCl, within 45 minutes is greater than or equal to 75%.

[0050] In one embodiment, the dosage form of the present disclosure releases greater than or equal to about 75% of the active substance within 45 minutes after administration or via dissolution testing. Particularly, the dosage form releases greater than or equal to about 80%,

about 85%, about 90%, or about 95% of the active substance within 45 minutes after administration or via dissolution testing.

[0051] In other embodiments, the dosage form of the present disclosure releases greater than or equal to about 90% of the active substance within 30 minutes after administration or via dissolution testing. Particularly, the dosage form releases greater than or equal to about 92%, about 94%, about 96%, or about 98% of the active substance within 30 minutes after administration or via dissolution testing.

[0052] The present disclosure also relates to an oral, immediate release, abuse deterrent dosage form including an active substance susceptible to abuse and PEG with a weighted average molecular weight between about 6200 Daltons and about 7800 Daltons. In one embodiment, dosage forms containing an average molecular weight of PEG in this particular range have several desirable characteristics including immediate release of the active substance, stability at high temperature conditions (e.g., 40 °C with 75% relative humidity), relatively low viscosity at elevated temperatures (e.g., a viscosity less than or equal to 2000 cP at 75 °C), and/or a relatively high particle size after grinding (e.g., greater than or equal to 50% of the particles having a diameter greater than or equal to 500 μm after grinding, such as for 30 seconds at 10,000 RPM). Dosage forms including PEG with an average molecular weight between about 6200 Daltons and about 7800 Daltons may be prepared by combining two or more PEGs with different molecular weights. For example, any of the PEGs described herein (e.g., PEG 3350 and PEG 35000) may be combined to prepare a dosage form including PEG with an average molecular weight range between about 6200 Daltons and about 7800 Daltons.

[0053] In particular embodiments, the dosage form includes PEG, or two or more PEGs, with an average molecular weight of about 5000, 5015, 5100, 5200, 5300, 5400, 5500, 5600, 5700, 5800, 5900, 6000, 6100, 6200, 6300, 6400, 6500, 6515, 6600, 6700, 6800, 6900, 7000, 7100, 7200, 7300, 7400, 7500, 7600, 7700, 7800, 7900, 8000, 8100, 8200, 8300, 8400, 8500, 8600, 8700, 8800, 8900, 9000, 9100, 9200, 9300, 9400, 9500, 9600, 9700, 9800, 9900, 10,000, 10,100, 10,200, 10,300, 10,400, 10,500, 10,600, 10,700, 10,800, 10,900, 11,000, 11,100, 11,200, 11,300, 11,400, 11,500, 11,600, 11,675, or 11,700 Daltons. Any of these values may be used to define a range of average molecular weights for PEG, or PEGs, depending on the application. For example, in some embodiments, the dosage form includes PEG, or PEGs, with an average

molecular weight between about 6200 Daltons and about 6515 Daltons, between about 6515 Daltons and about 6800 Daltons, or between about 6200 Daltons and about 6800 Daltons.

[0054] In other embodiments, the present disclosure relates to an oral, immediate release, abuse deterrent dosage form including an active substance susceptible to abuse, a first PEG having a melting point greater than or equal to about 60 °C, and a second PEG having a melting point less than or equal to about 57 °C. The dosage form can be a solid at 40 °C / 75% relative humidity, and at least 90% of the active ingredient can be released from the dosage form within 30 minutes following administration or via dissolution testing. The dosage form can be a solid at 40 °C / 75% relative humidity, and at least 75% of the active ingredient can be released from the dosage form within 45 minutes following administration or via dissolution testing.

[0055] The melting point of PEG can be positively correlated with molecular weight, i.e. higher molecular weight PEGs have higher melting points. For example, PEGs with an average molecular weight up to 400 Daltons can be considered nonvolatile liquids at room temperature. PEG 600, for example, has a melting range of about 17 to 22 °C, and may be liquid at room temperature but waxy at lower temperatures. PEGs with an average molecular weight of 800 to 2000 Daltons can be considered waxy materials at room temperature with a relatively low melting range. For example, PEG 1500 has a melting point of about 42-46 °C. PEGs with an average molecular weight above 3000 can be considered solids. For example, PEG 3350 has a melting point of about 53-57 °C, and PEG 35,000 has a melting point of about 60-65 °C. By combining a PEG with a relatively low melting point (e.g., PEG 3350) with a PEG with a relatively high melting point (e.g., PEG 35,000) a dosage form with several desirable properties can be formed, including immediate release of an active substance, stability at high temperatures (e.g., 40° C with 75% relative humidity), relatively low viscosity at elevated temperatures (e.g., less than or equal to 2000 cP at 75 °C), and/or a relatively high particle size after grinding (e.g., greater than or equal to 50% of the particles having a diameter greater than or equal to 500 µm) and/or the incorporation of a chemical barrier which makes it difficult to separate the active substance from the rest of the formulation.

[0056] In some embodiments, the dosage form includes a first PEG having a melting temperature greater than or equal to about 52 °C, 53 °C, 54 °C, 55 °C, 56 °C, 57 °C, 58 °C, 59 °C, 60 °C, 61 °C, 62 °C, 63 °C, 64 °C, 65 °C, 66 °C, 67 °C, 68 °C, 69 °C, or 70 °C. Any of these

values may be used to define a range of melting temperatures for the first PEG depending on the application. For example, the dosage form may include a first PEG having a melting temperature from about 52 °C to about 60 °C, from about 55 °C to about 60 °C, from about 53 °C to about 57 °C, from about 53 °C to about 56 °C, from about 55 °C to about 58 °C, from about 60 °C to about 65 °C, or from about 60 °C to about 70 °C.

[0057] In some embodiments, the dosage form includes a second PEG having a melting temperature less than or equal to about 5 °C, 10 °C, 15 °C, 16 °C, 17 °C, 18 °C, 19 °C, 20 °C, 21 °C, 22 °C, 23 °C, 24 °C, 25 °C, 25 °C, 27 °C, 28 °C, 29 °C, 30 °C, 31 °C, 32 °C, 33 °C, 34 °C, 35 °C, 36 °C, 37 °C, 38 °C, 39 °C, 40 °C, 41 °C, 42 °C, 43 °C, 44 °C, 45 °C, 46 °C, 47 °C, 48 °C, 49 °C, 50 °C, 51 °C, 52 °C, 53 °C, 54 °C, 55 °C, 55 °C, 56 °C, or about 57 °C. Any of these values may be used to define a range of melting temperatures for the second PEG depending on the application. For example, the dosage form may include a second PEG having a melting temperature between about 17 °C and about 22 °C, between about 42 °C and about 46 °C, between about 53 °C and about 57 °C, or between about 42 °C and about 57 °C.

[0058] In some embodiments, the dosage form includes a first PEG and a second PEG, wherein the first PEG and the second PEG combined have a melting temperature of about 42 °C, 43 °C, 44 °C, 45 °C, 46 °C, 47 °C, 48 °C, 49 °C, 50 °C, 51 °C, 52 °C, 53 °C, 54 °C, 55 °C, 56 °C, 57 °C, 58 °C, 59 °C, 60 °C, 61 °C, 62 °C, 63 °C, 64 °C, 65 °C, 66 °C, 67 °C, 68 °C, 69 °C, 70 °C. Any of these values may be used to define a range of melting temperatures for the combined first and second PEG depending on the application. For example, the first PEG and the second PEG combined may have a melting temperature between about 53 °C and about 65 °C.

[0059] In other embodiments, the present disclosure relates to an oral, immediate release, abuse deterrent dosage form including an active substance susceptible to abuse, a first PEG having a melting point greater than or equal to about 60 °C and a second PEG having a viscosity at 100 °C less than or equal to about 110 cSt. The dosage form can be a solid at 40 °C / 75% relative humidity, and at least 75% of the active ingredient can be released from the dosage form within 45 minutes following administration or via dissolution testing or at least 90% of the active ingredient can be released from the dosage form within 30 minutes following administration or via dissolution testing.

[0060] In some embodiments, the dosage form includes a second PEG having a viscosity at 100 °C of less than or equal to about 500 cSt, 450 cSt, 400 cSt, 350 cSt, 300 cSt, 250 cSt, 200 cSt, 190 cSt, 180 cSt, 170 cSt, 160 cSt, 158 cSt, 150 cSt, 140 cSt, 130 cSt, 123 cSt, 120 cSt, 110 cSt, 105 cSt, 100 cSt, 99 cSt, 93 cSt, 90 cSt, 87 cSt, 80 cSt, 76 cSt, 75 cSt, 73 cSt, 70 cSt, 67 cSt, 60 cSt, 50 cSt, 49 cSt, 48 cSt, 47 cSt, 46 cSt, 45 cSt, 44 cSt, 43 cSt, 42 cSt, 41 cSt, 40 cSt, 39 cSt, 38 cSt, 37 cSt 36 cSt, 35 cSt, 34 cSt, 33 cSt, 32 cSt, 31 cSt, 30 cSt, 29 cSt, 28 cSt, 27 cSt, 26 cSt, 25 cSt, 24 cSt, 23 cSt, 22 cSt, 21 cSt, 20 cSt, 19 cSt, 18 cSt, 17 cSt, 16 cSt, 15 cSt, 14 cSt, 13 cSt, 12 cSt, 11 cSt, 10 cSt, 9 cSt, 8 cSt, 7 cSt, 6 cSt, 5 cSt, or about 4 cSt. Any of these values may be used to define a range of viscosities for the second PEG depending on the application. For example, the dosage form may include a second PEG having a viscosity between about 4.0 cSt and about 49.0 cSt, between about 16.0 cSt and about 49.0 cSt, between about 25.0 cSt and about 32.0 cSt, or between about 76 cSt and about 110 cSt.

[0061] In some embodiments, the formulation of the present disclosure can have a viscosity at 100 °C of about 40 cSt, 41 cSt, 42 cSt, 43 cSt, 44 cSt, 45 cSt, 46 cSt, 47 cSt, 48 cSt, 49 cSt, 50 cSt, 51 cSt, 52 cSt, 53 cSt, 54 cSt, 55 cSt, 56 cSt, 57 cSt, 58 cSt, 59 cSt, 60 cSt, 61 cSt, 62 cSt, 63 cSt, 64 cSt, 65 cSt, 66 cSt, 67 cSt, 68 cSt, 69 cSt, 70 cSt, 71 cSt, 72 cSt, 73 cSt, 74 cSt, 75 cSt, 76 cSt, 77cSt, 78 cSt, 80 cSt, 90 cSt, 100 cSt, 110 cSt, 120 cSt, 130 cSt, 140 cSt, 150 cSt, 158 cSt, 160 cSt, 170 cSt, 180 cSt, 190 cSt, 200 cSt, 250 cSt, 300 cSt, 350 cSt, 400 cSt, 450 cSt 500 cSt, 600 cSt, 700 cSt, 800 cSt, 900 cSt, 1000 cSt, 1100 cSt, 1200 cSt, 1300 cSt, 1400 cSt, 1500 cSt, 1600 cSt, 1700 cSt, 1800 cSt, 1900 cSt, or about 2000 cSt. Any of these values may be used to define a range of viscosities for the formulation of the present disclosure depending on the application. For example, the formulation of the present disclosure may have a viscosity between about 500 cSt and about 2000 cSt, or between about 800 cSt and about 1900 cSt. In some embodiments, the formulation or dosage form is a solid at room temperature and/or at 100 °C and has not measureable viscosity.

[0062] In another embodiment, the present disclosure relates to a process for the production of an oral, immediate release, abuse deterrent dosage form including preparing a homogenized suspension of at least one active substance susceptible to abuse, a first PEG, and a second PEG. For example, the first PEG can have an average molecular weight between about 30,000 Daltons and about 40,000 Daltons, and the second PEG can have an average molecular weight between

about 3000 Daltons and about 4000 Daltons. The ratio of the first PEG to the second PEG can be less than about 1:4 w/w. The process can further include dispensing or filling a homogenized suspension into a capsule to produce the dosage form. In some embodiments, the capsule can be formed by joining a capsule body with a capsule cap. The first PEG and the second PEG together may be any wt% of the dosage form as described herein, for example at least about 60 wt% of the dosage form. In some embodiments of the processes described herein, the active substance is hydrocodone bitartrate. In other embodiments, the active substance is oxycodone HCl. In certain embodiments, the abuse deterrent dosage forms of the present disclosure are capsules.

[0063] The abuse deterrent dosage forms of the present disclosure may be produced by liquid filled encapsulation. Liquid filled encapsulation is a process in which active pharmaceutical ingredients are suspended or emulsified in a carrier matrix and filled into capsules. The capsules are usually made of hard gelatin or hydroxypropyl methylcellulose. One of the advantages of this dosage form is that it requires fewer excipients and processing steps than other traditional compressed solid dosage forms. The internal solid phase API (e.g., oxycodone HCl or hydrocodone bitartrate) can be suspended in a PEG external fluid phase. In one embodiment, PEGs with average molecular weights greater than about 1500 Daltons are ideal for liquid filled capsules because they are thermoplastics that melt at temperatures below the melting point of the hard gelatin capsule (<70 °C) and are solids at room temperature. If the filling material is liquid at room temperature, a banding process can be used. This process adds a gelatin band around the point where the capsule body and cap join to create a unified capsule body to prevent leakage. In some embodiments, the formulation of the present disclosure can include a band.

[0064] In one embodiment, the liquid fill process can begin by dispensing excipients (e.g., PEG and stabilizers/preservatives) and API according to theoretical percent weights of the final capsule fill weight. Following this step, the PEG powders or flakes and dyes are pre-melted before they are added to a homogenizing mixing kettle which can maintain the PEG above its melting point via jacketing on the kettle. When the PEG is completely fluid, the API and other non-melting stabilizers and/or preservatives can be mixed in to form a homogenized suspension. This can occur with the aid of mechanical agitation by way of several internal stirring arms. Once a homogenized suspension is attained (in some embodiments newer kettles can be

equipped with NIR probes to indicate when this happens), the suspension can be pumped through jacketed hoses (to maintain the internal kettle temperature to prevent solidification in the hose) to a hopper on the capsule filling machine. An illustration of a capsule filling machine is provided in Figure 1.

[0065] The capsule filling hopper can also be jacketed to heat the suspension to prevent solidification. The capsule filling machine can contain a separate hopper which operators fill with hard gelatin capsules. The hopper can feed into a rectifying drum which can align all capsules in the same direction. Once aligned, the capsules can sit vertically in a cap disk which can allow for separation of the body and cap via vacuum. To fill the capsule, a positive displacement piston pump can be used to draw the product in from the jacketed hopper and dispense the suspension into the capsule body through a set of changeable nozzles. Fill weight adjustment can be achieved by varying the piston stroke of the pump. These changes can be made throughout the process due to frequent in-process capsule weight checks.

[0066] Once the capsule body is filled, the capsule body and cap can be joined via pusher pins which raise the capsule body upwards and into the capsule cap, which are held in place above the capsule body by a joining block. The pusher pins can then push the unified capsule out of the cap disk and discharge them from the machine. The capsules can then be allowed to cool at room temperature on trays and can be each weight checked via a capsule weigh checking machine. Following this, the capsules can then be placed into a final output drum. Automatic capsule filling machines can have the ability to produce 500 to 150,000 capsules an hour with a very high degree of accuracy.

[0067] In some embodiments, the present disclosure relates to a dosage form as described herein prepared by filling a capsule body with a heated homogenized suspension including an active substance, a first PEG and a second PEG. In some embodiments, the homogenized suspension including an active substance, a first PEG, and a second PEG melts at a temperature of about 42 °C, 43 °C, 44 °C, 45 °C, 46 °C, 47 °C, 48 °C, 49 °C, 50 °C, 51 °C, 52 °C, 53 °C, 54 °C, 55 °C, 56 °C, 57 °C, 58 °C, 59 °C, 60 °C, 61 °C, 62 °C, 63 °C, 64 °C, 65 °C, 66 °C, 67 °C, 68 °C, 69 °C, 70 °C, 71 °C, 72 °C, 73 °C, 74 °C, or 75 °C. Any of these values may be used to define a range of melting temperatures for the homogenized suspension. For example, in certain embodiments, the homogenized suspension has a melting temperature between about 53 °C and

about 65 °C. In particular embodiments, the homogenized suspension including an active substance, a first PEG and a second PEG melts at temperatures below 77 °C, i.e., the melting point of the hard gelatin capsule. In another embodiment, the present disclosure relates to a method of treating pain including administering to an individual in need thereof a therapeutically effective amount of a dosage form as described herein. The dosage form can be used for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. The dosage form can provide rapid onset of analgesia for the treatment of moderate to severe pain. The dosage form, e.g., a hard gelatin capsule, can be administered orally every 4-6 hours as needed.

[0068] When an amount, concentration, or other value or parameter is given as either a range, preferred range, or a list of upper preferable values and lower preferable values, this is to be understood as specifically disclosing all ranges formed from any pair of any upper range limit or preferred value and any lower range limit or preferred value, regardless of whether ranges are separately disclosed. Where a range of numerical values is recited herein, unless otherwise stated, the range is intended to include the endpoints thereof, and all integers and fractions within the range. It is not intended that the scope of the invention be limited to the specific values recited when defining a range.

[0069] The present invention is further defined in the following Examples. It should be understood that these Examples, while indicating preferred embodiments of the invention, are given by way of illustration only.

Examples

Example 1

[0070] Initial testing and evaluation experiments for the immediate release ADF liquid filled capsule were based on suspending an API in PEG and filling it to weight into a hard gelatin capsule which then solidifies into a wax at room temperature. Some of these experiments used acetaminophen (APAP) as a tracer drug in place of C-II narcotics. Oxycodone HCl and APAP are both soluble in reaerated water. The USP monograph for pooled hydrocodone bitartrate and acetaminophen tablets specifies 80% (Q) +10% release of both drugs in 30 minutes in 0.1N HCl,

indicating both are capable of immediate release. As a result, APAP was expected to be a viable alternative for experimentation.

[0071] A formulation was prepared containing 30 mg APAP and a 50:50 ratio of PEG 3350:1500 g/mol and 0.50% FD&C dye in size 3 white opaque capsules. Three capsule fill weights were evaluated: 100 mg, 150 mg, and 200 mg. These formulations were tested for dissolution. The USP criteria for immediate release of oxycodone HCl is 500 mL purified water as media, Q=70% at 45 minutes, Specification = 75% (Q+5%), apparatus 2 (paddles), 50 rpm. All capsule weights proved to release immediately, with the 150 mg and 200 mg formulations releasing completely at 20 minutes. 100 mg capsule fill would be preferred to decrease material costs. Table 1 below list the dissociation data of size 3 capsules containing 30 mg APAP, a 50:50 ratio of PEG 3350:1500 g/mol, and 0.5% FD&C dye.

Table 1

Batch	Capsule fill	20 Minutes	Average	45 Minutes	Average
18-1	100 mg	78.18	78.07	86.25	86.19
18-2		78.66		88.23	
18-3		77.37		84.11	
Batch	**Capsule fill**	**20 Minutes**	**Average**	**45 Minutes**	**Average**
19-1	150 mg	92.76	95.48	96.95	95.17
19-2		98.55		100.69	
19-3		95.13		87.86	
Batch	**Capsule fill**	**20 Minutes**	**Average**	**45 Minutes**	**Average**
20-1	200 mg	92.74	91.82	96.68	96.59
20-2		88.16		96.59	
20-3		94.57		96.50	

[0072] These dosage forms contain water- and ethanol-soluble FD&C dyes, e.g., 0.5% FD&C dye, to deter extraction of the API and intravenous injection of the solution. Further rendering of the drug solution would be required to separate the pure API from the PEG and FD&C dyes.

[0073] PEG 1450 (NF grade available from Dow Chemical Company) can be used in place of PEG 1500 in the oxycodone HCl dosage forms. Additional exemplary oxycodone HCl dosage forms are shown in Table 2 below. 1% citric acid may be used in the dosage forms as an API stabilizer.

Table 2

Dosage	Oxycodone HCl (mg)	PEG 3350 (mg)	PEG 1450 (mg)	FD&C Dye (mg)	Citric Acid (mg)	Total Capsule Fill (mg or %)
5	5	44.25	44.25	0.5	1	100
15	15	34.25	34.25	0.5	1	100
30	30	19.25	19.25	0.5	1	100
Dosage	Oxycodone HCl (%)	PEG 3350 (%)	PEG 1450 (%)	FD&C Dye (%)	Citric Acid (%)	Total Capsule Fill (mg or %)
5	5	41-47	41-47	0.25-0.75	0.5-2	100
15	15	31-37	31-37	0.25-0.75	0.5-2	100
30	30	16-22	16-22	0.25-0.75	0.5-2	100

Example 2 – Immediate Release ADF Liquid Fill Capsules including PEG 35000

[0074] The dissolution rate, ADF properties and melt temperatures of additional immediate release ADF oxycodone HCl liquid fill capsule formulations containing varying amounts of PEG 1450 and PEG 35000 were evaluated. Acetaminophen (APAP) was used as a tracer drug for oxycodone HCl. The formulations are shown in Table 3 below. The target amount of APAP was 30 mg per capsule, and the target fill weight was 100 mg (batch number 92) or 200 mg (batch numbers 93-94). The capsules contained 30% w/w (batch number 92) or 15% w/w (batch numbers 93-94) APAP. Size 3 opaque hard gelatin capsules were used.

[0075] Dissolution was tested using the following criteria: Q = not less than 70% dissolved at 45 minutes, and the specification = Q+5% (75%) dissolved at 45 minutes. As shown in Table 3, the average dissolution for the three formulations ranged from 87% to 98%. Accordingly, all of the formulations met the specification of at least 75% dissolution at 45 minutes.

[0076] As mentioned above, it is generally accepted that any particle greater than 500 μm in diameter cannot be sufficiently absorbed by the blood vessels in the nasal mucosa. Thus, in one embodiment, a formulation is considered to deter intranasal abuse if $\geq$ 75% of the particles are $\geq$ 500 μm in diameter after grinding. As shown in Table 3, the percentage of particles $\geq$ 500 μm in diameter after grinding ranged from 90% to 92%. Thus all of the oxycodone formulations met the standard of $\geq$ 75% of the particles being $\geq$ 500 μm in diameter after grinding.

Table 3: Dissolution and Particle Size after Grinding for Oxycodone HCl Formulations Including PEG 35000 and PEG 1450.

Batch Number	Excipients			Dissolution		Grinding / Particle Size	
	% PEG 35000	% PEG 1450	% of Overall Fill	% @ 45 min**	Average	% ≥ 500µm	% < 500µm
92-1	100	0	70	100	87	92	8
92-2				83			
92-3				77			
93-1	82	18	85	91	90	91	9
93-2				90			
93-3				88			
94-1	59	41		98	98	90	10
94-2				99			
94-3				95			

[0077] The oxycodone HCl formulations were also analyzed to determine melting temperature. The capsules were held at 40 °C / 75% relative humidity for 72 hours. As shown in Table 4 below, the batch number 92 and 93 formulations containing 100% and 82% PEG 35000, respectively, were solid at these conditions, while the batch number 94 formulation containing 59% PEG 35000 had a much softer fill.

Table 4: Melt study of Oxycodone HCl formulations.

Batch Number	% PEG 1450	% PEG 35000	% of Overall Fill	Designation*	Notes
92	0	100	70	1	No evidence of melt
93	18	82	85	1	No evidence of melt
94	41	59		2	Much softer fill
*- 1 (one) = Solid, 5 (five) = Thick Liquid					

[0078] The dissolution, particle size after grinding, and color extraction of two additional formulations of oxycodone HCl (batch numbers 11 and 12) containing varying percentages of

PEG 35000 and PEG 1450 were determined as described above. The formulations also contained 1% citric acid and 14% Grey Dye. Both formulations used a size 3 opaque hard gelatin capsule with a target fill weight of 100 mg. APAP was used as a tracer drug for oxycodone HCl. The target amount of APAP was 5 mg (5% w/w) for batch number 11 and 30 mg (30% w/w) for batch number 12. For dissolution, Q = Not less than 70% dissolved at 45 minutes, and the specification = Q+5% (75%) dissolved at 45 minutes. As a reference, an acceptable particle size after grinding is ≥ 75% particles ≥ 500 μm in diameter. As a reference, an acceptable color scale designation after extraction of the dye is ≥ 4 on a scale of 1 to 5, with 5 being the highest level of color.

[0079] As shown in Table 5 below, both oxycodone HCl formulations met the criteria for dissolution rate, particle size after grinding, and color extraction.

Table 5: Dissolution, Particle Size after Grinding, and Color Extraction of Oxycodone HCl Formulations containing PEG 35000 and PEG 1450.

Oxycodone HCl Formulation									
Batch Number	Excipients					Dissolution	Grinding / Particle Size		Extraction
	% PEG 35000	% PEG 1450	% Citric Acid	% Grey Dye	% of Overall Fill	Avg. % @ 45 min	% ≥ 500 μm	% < 500 μm	Color Scale Designation
11-1	48	32	1	14	95	106	90	10	5
11-2									
11-3									
12-1	33	22			70	96	89	11	5
12-2									
12-3									

[0080] In one embodiment, hot melt fill capsules are sufficiently viscous at elevated temperatures to allow for flow of the fill into the capsules. Accordingly, additional oxycodone

HCl formulations containing PEG 35000 and either PEG 3350 or PEG 1450 were evaluated by measuring viscosity at 75 °C at 50 rpm. Formulations were weighed out according to total wt % of a 15g batch. Each formulation was poured into a viscosity testing crucible and placed in an 80 °C water bath to melt. Once fully melted, the formulations were mixed using a stainless steel spatula and transferred to a Brookfield DV-II+ Pro Viscometer (VIS29 NCD: Upon Use) utilizing Spindle: S27 (Small Sample Adapter). The viscometer was equipped with a water jacketed crucible platform. Once the melt temperature reached 75 °C, a viscosity reading was taken in centipoise (cP). Based on manufacturer specifications, an acceptable viscosity for the purposes of this study is ≤ 1000 cP. The particle size after grinding and stability at 40 °C / 75% relative humidity (RH) was also determined. For the grinding analysis, an acceptable particle size after grinding was considered to be ≥ 75% particles ≥ 500 µm in diameter. All formulations were size 3 opaque hard gelatin capsules.

[0081] As shown in Table 6 below, batch number 100 containing 11% PEG 35000 and 44% PEG 1450 had a viscosity of 1288 cP at 75 °C / 50 rpm, above the manufacturer specification of ≤ 1000 cP. Accordingly, viscosity was not measured for the formulations containing higher percentages of PEG 35000 (i.e. batch numbers 97-99). In addition, batch number 100 was not sufficiently stable for storage, since this formulation was a very viscous liquid at the stability test conditions of 40 °C / 75% RH.

[0082] Although batch number 101 containing 5.5% PEG 35000 and 49.5% PEG 1450 had an acceptable viscosity (705 cP) at 75 °C / 50 rpm, the stability tests revealed that this formulation was a very viscous liquid at 40 °C / 75% RH, and thus was not stable for storage. Because the formulations containing 11% PEG 35000 (batch number 100) and 5.5% PEG 35000 (batch number 101) were not sufficiently stable for storage, stability of batch number 103 containing 7.7% PEG 35000 was not determined.

[0083] Formulations containing PEG 35000 and PEG 3350 were also evaluated. As shown in Table 6 below, the formulation containing 6.97% PEG 35000 and 62.7% PEG 3350 (batch number 104) and the formulation containing 7.7% PEG 35000 and 69.3% PEG 3350 (batch number 105) met all of the criteria for particle size after grinding, viscosity, and stability.

Table 6: Particle size, Viscosity, and Stability for Oxycodone HCl Formulations Containing PEG 35000.

Batch	Excipients							Grinding / Particle Size		Visc-osity (cP)	Stability at 40C/75 %RH
	% PEG 35000	% PEG 3350	% PEG 1450	Peg Ratio	% Grey Dye	% API	Capsule Target Weight (mg)	% ≥ 500 µm ***	% < 500 µm		
97	27.5	0	27.4	50:50	14	30	100	83.0	17.0	NA	Softened Wax, non-liquid
98	22		33	40:60				91.4	8.6	NA	Softened Wax, non-liquid
99	16.5		38.5	30:70				90.1	9.9	NA	Semi-solid
100	11		44	20:80				95.7	4.3	1288	Very viscous liquid
101	5.5		49.5	10:90				99.6	0.4	705	Very viscous liquid
103	7.7		69.3	10:90	7	15	200	NA	NA	298	NA
102	5.5	49.5	0	10:90	14	30	100	78.8	21.2	1045	Softened Wax, non-liquid
104	6.97	62.7		10:90	9.33	20	150	79.9	20.1	745	Softened Wax, non-liquid
105	7.7	69.3		10:90	7	15	200	77.5	22.5	620	Softened Wax, non-liquid
106	15.4	61.6		20:80	7	15	200	85.1	14.9	1375	NA

Example 3 - Evaluation of Dyes

[0084] Numerous dyes were evaluated for their potential to deter intravenous abuse. Varying concentrations of FD&C Blue #2, green (FD&C Blue #2 and FD&C Yellow #5), FD&C Yellow #5, FD&C Red #40, and grey dye (FD&C Blue#1, FD&C Yellow #6, FD&C Red #40) were evaluated by dissolving them in a 95% ethanol 5% purified water (190 proof) solution and passing the solution through a syringe filter. After syringe filtering the dye solutions were visually evaluated for color intensity and rated on a scale of 0 to 5, with 0 indicating no color and 5 indicating dark, significant color. As shown in the Table 7 below, the blue and green dyes exhibited the highest color intensity at low concentrations, e.g. 0.25% w/w. Solutions of grey dye before and after filtering are shown in Figures 2A and 2B, respectively. The grey dye was particularly striking and less appealing. An acceptable color scale designation after extraction of the dye is ≥ 4 on a scale of 1 to 5, with 5 being the highest level of color.

Table 7: Evaluation of Various Dyes at Varying Concentrations in 190 Proof Alcohol

Batch	Dye Color	Dye (% w/w)	Dye (mg)	Color Number*
66	Blue	0.25	1.75	4
67	Blue	0.50	3.50	5
68	Blue	0.75	5.25	5
69	Blue	1.00	7.00	5
70	Green	0.25	1.75	4
71	Green	0.50	3.50	4
72	Green	0.75	5.25	4
73	Green	1.00	7.00	4
74	Yellow	0.25	1.75	3
75	Yellow	0.50	3.50	4
76	Yellow	0.75	5.25	5
77	Yellow	1.00	7.00	5
78	Red	0.11	0.75	2
79	Red	0.21	1.50	3
80	Red	0.43	3.00	4
81	Red	0.63	4.44	5
82	Grey	0.25	1.75	2
83	Grey	0.50	3.50	2
84	Grey	0.75	5.25	4
85	Grey	1.00	7.00	4
86	Grey	2.00	14.00	5

[0085] In one embodiment, the dye can be grey. Grey can be chosen because it is darker than the others and can be effective at a lower relative concentration. Grey dye can allow for the most visually deterring form with the least amount of dye present in the formulation.

Example 4 - Immediate Release ADF Oxycodone HCl Liquid Fill Capsules

[0086] Abusers of opioid products often adulterate the product to promote more rapid release of the active ingredient. The products can be chewed and swallowed, crushed and inhaled, or extracted in water or alcohol (either crushed or intact) to produce a solution that can be used for intravenous administration or dried for insufflation of a purified product. Adulteration of the products can enable a more rapid delivery of active than can be achieved by ingestion of the intact product. This rapid onset, high exposure is associated with euphoria, drug liking, and greater abuse potential.

[0087] Current abuse-deterrent formulations have limitations. Insufflation is a common route of abuse for oxycodone HCl products. To be attractive for insufflation, crushing a product should yield particles of less than 500 μm to allow uptake of the active substance though the nasal mucosa. Therefore, abuse deterrent formulations can be made to discourage crushing or breaking of tablets to yield particles less than 500 μm. Test methods using flat platens to crush the product as a criterion for abuse deterrence is not meaningful. All C-II narcotic drug products tested can be cut with an edged surface (e.g., scissors or a razor blade) and therefore can potentially be abused, with forces that are substantially lower than what has been reported using the breaking strength test or equivalent (e.g., >500 N). Flattening the tablets using forces greater than 500 N (with traditional "tablet breaking force" definitions) does not address abuse deterrence potential in the tested C-II narcotic drug products.

[0088] Grinding can be a better evaluation of the relative resistance of marketed products to abuse. The formulation of the present disclosure compares favorably against Roxicodone® with respect to a decrease in the percentage of particles produced after grinding that are smaller than 500 μm. Statistically different results emerge between the formulation of the present disclosure and Roxicodone® in the degree of resistance to grinding, with the formulation of the present disclosure yielding less than 50% of particles smaller than 500 μm, compared with approximately 77% of particles less than 500 μm for Roxicodone®. Better resistance to grinding

can be due to differences in the manufacturing processes and/or the excipients employed for the two products.

[0089] The formulation of the present disclosure can be resistant to abuse by nasal insufflation or extraction due to, in part, the waxy nature of the formulation contents and the solubility of the excipients. The excipients can be both water and alcohol soluble to create a formulation that makes it time consuming and costly to extract oxycodone HCl from the formulation contents without also extracting the excipients. A high molecular weight PEG can be included because of its solubility properties (e.g., soluble in both alcohol and water) and its resistance to grinding to particle sizes of less than 500 μm. High-molecular weight PEGs are less viscous at melt temperatures than long chain PEO molecules and are soluble in both water and alcohol.

[0090] Dyes can also be used and chosen to be soluble in both water and alcohol to produce a dark colored solution upon extraction and filtering as a visual deterrent to abuse. The formulation can include the following components listed in the Table 8 below, including a number of different dyes. Table 8 below lists the components along with their solubility information taken from the various literature sources and tested experimentally (e.g., 200 proof ethanol and filtered through a 0.45 micrometer PTFE filter). The extraction of the active to a pure form can be very difficult using water or alcohol.

Table 8: Solubility of the Components of the Present Disclosure Formulation

Components	Water Solubility	Alcohol Solubility (Literature)	Alcohol Solubility (Tested)
Oxycodone HCl	Yes	Yes	Yes
Hydrocodone Bitartrate	Yes	Slightly	N/A
Polyethylene Glycol USP NF	Yes	Yes	N/A
Anhydrous Citric Acid	Yes	Yes	N/A
FD&C Blue #1	Yes	Yes	Yes
FD&C Yellow #6	Yes	Yes	Yes
FD&C Red #40	Yes	Yes	Yes

[0091] A conventional tablet or powder-filled capsule can be easily crushed to create a fine powder. The waxy material contained in the formulations of the present disclosure can make it difficult to manipulate into particles small enough to be easily absorbed by the nasal mucosa. The waxy material may also congeal once introduced to the semi-aqueous environment of the nasal passages, which can make it difficult to introduce the oxycodone HCl or hydrocodone bitartrate to the bloodstream via the nasal passages.

[0092] The formulations of the present disclosure can contain one or more of the following barriers to abuse. Insufflation - The formulation can be formulated to resist grinding to particle sizes of less than about 500 μm. Extraction and Purification - The formulation can be formulated with water- and alcohol-soluble dyes to create a dark colored solution upon extraction that can be visually unappealing to intravenous drug users. The water- and alcohol-soluble excipients can present obstacles to purification of the active. In some formulations, if the solvent is flashed off or otherwise evaporated, the excipients can return to the same waxy, dark-colored form as before being introduced to the solvent. Vaporization – The formulation can contain an active, such as oxycodone HCl, which can degrade at temperatures close to where vaporization occurs. Chewing – Because the formulation is an immediate release formulation, it is not expected that crushing or cutting the dosage form will result in an especially rapid release of the drug to produce a "euphoric high."

[0093] Table 9 below lists exemplary formulations for the oxycodone HCl abuse deterrent formulation capsules.

Table 9: Quantitative Composition of Oxycodone HCl ADF Capsules

Ingredients	Capsule Quantity (mg)
Oxycodone HCl USP API	5 - 30
Polyethylene Glycol 3350	100 – 150
Polyethylene Glycol 35,000	5 – 25
Anhydrous Citric Acid	1 – 2
Dye Blend	
FD&C Red #40 (DB-175000)	0.5 – 1.0
FD&C Yellow #6 (DB-175000)	0.3 – 0.6
FD&C Blue #1 (DB-175000)	0.1 – 0.3
Polyethylene Glycol 3350 (DB-175000)	10 - 15
Gelatin (Capsule)	
Total Fill Weight per capsule	100 - 200

[0094] Formulations of the present disclosure were manufactured by the following exemplary process. The components of the hot-melt suspension, consisting of Polyethylene Glycol 3350, Polyethylene Glycol 35000, Dye Blend, Grey Powder, Citric Acid and Oxycodone HCl were dispensed according to theoretical batch quantities based on formulation weight percents.

[0095] Polyethylene Glycol 3350, Polyethylene Glycol 35000, Dye Blend, Grey Powder, Oxycodone HCl and Citric Acid were added to an Olsa 150 Liter Kettle and heated to a temperature of 70 ± 20 °C. Utilizing the homogenizer mixer, external anchor blades and internal mixing blades, the melt was then mixed until uniform

[0096] Prior to transferring the hot-melt suspension from the kettle to the Shionogi F40 capsule filling machine hopper, a transfer pump and three heat traced hoses were set up and the melt/suspension was recirculated. Mixing and recirculating continued until capsule filling was completed.

[0097] The Shionogi F40 capsule filling machine target fill weight was set with an Action Limit of ± 3.5% and a Control Limit of ± 5.0% plus the average empty capsule weight.

[0098] In-process capsule samples were taken at the beginning, end, and every 30 minutes (for the average capsule weight of 15 filled capsules). Filled capsules were placed onto stainless steel cooling trays and allowed to cure. Following curing, 100% capsule weight inspection was performed using a Shionogi capsule weight inspection machine An exemplary manufacturing process is shown in Figure 3.

[0099] The formulations of the present disclosure are stable upon storage at 25, 30, 35, 40 or 45 °C, and at 60%, 65%, 70% or 75% relative humidity, e.g., 30 °C / 65% RH or 40 °C / 75% RH. The formulation of the present disclosure can be stable under any of these conditions for up to 1, 2, 3, 4, 5, 6, 9, 12, 16, 18, 24, or 36 months.

Example 5 – Abuse Deterrent Properties of Immediate Release Liquid Fill Capsule PEG Formulations

[00100] In one embodiment, there are at least three determining factors which deem an immediate release drug product "abuse deterrent," namely resistance to grinding, purity upon extraction, and visual evaluation following extraction. Cutting the dosage form can be performed in order to increase the surface area of the product prior to ingesting it in an effort to increase the rate of dissolution into the digestive tract. Cutting can also be used to increase the efficiency of grinding or extraction. Cutting alone, however, is not sufficient to render a formulation abusable. Grinding the dosage form can be performed in order to decrease the particle size of the product more efficiently than cutting in an effort to insufflate (snort) for immediate release into the blood vessels of the nasal passages. A readily available tool used for grinding is a commercially available coffee grinder. In one embodiment, a drug product is considered abuse deterrent if the % material in the pan (≤500μm) is ≤ 50%. A dosage form which, when ground, produces ≤ 50% of the material on a per-dosage form basis available for nasal insufflation (≤ 500μm) is considered abuse deterrent. The purpose of this study was to determine the grinding potential of different dosage forms of oxycodone HCl. Texture analysis is the mechanical testing of pharmaceutical products in order to measure their physical properties. The Retsch Knife Mill GRINDOMIX GM200 (TE96) was utilized to mimic a commercially available coffee grinder (Mr. Coffee) in order to grind the drug products into a

particle size that is suitable for intranasal abuse (insufflation). Particle size analysis was conducted utilizing an ATM L3P Sonic Sifter (TE47), utilizing a 500 micrometer (μm) particle size sieve (35 mesh). For the purposes of this study, any particle less than 500 μm in diameter is considered suitable for intranasal abuse. It is generally accepted that any particle greater than 500 μm in diameter cannot be sufficiently absorbed by the blood vessels in the nasal passages.

[00101] The Retsch Knife Mill GRINDOMIX GM200 utilizes a circular blade attachment to mimic commercially available coffee grinders. The GM200 has a top speed of 10,000 revolutions per minute (rpm), while commercially available coffee grinders have a top speed of approximately 20,000 rpm (an approximate two-fold increase in speed when comparing the GM200 to a Mr. Coffee grinder). However, the approximate two-fold increase in blade diameter (118 mm vs. 60 mm, when comparing the GM200 to a Mr. Coffee grinder, respectively) compensates for the approximate twofold decrease in top speed via the inversely proportional relationship of the two variables. Further, the torque provided by the GM200 is significantly higher than the torque provided by a Mr. Coffee grinder (0.860 Nm (Newton meters) of the GM200 vs. 0.062 Nm of the Mr. Coffee grinder, respectively), which additionally illustrates the ability (or lack thereof) of the Mr. Coffee grinder to modify the drug products into a particle size suitable for intranasal abuse. The study evaluated the difference in particle sizes of several different formulations of oxycodone HCl following modification (grinding) by the GM200.

[00102] Experimental: The samples tested are formulated according to Table 9. The following test equipment was used: Retsch Knife Mill GRINDOMIX GM200 (TE96), ATM L3P Sonic Sifter (TE47), and a 500 μm sieve (35 mesh). The following testing conditions were used: Analysis speed: 10,000 rpm; Analysis time: 30 seconds; Sieve Size: 500 μm (35 mesh); Analysis time: 1 minutes (no pulse). Each sample was prepared in triplicate (N=3).

[00103] The composite sample was transferred to a tared weigh boat and the weight of the sample was recorded. The following equation was used to calculate the % sample loss:

$$\text{Sample Loss (\%)} = 100 - \left(\frac{\text{Analyzed Sample (mg)}}{\text{Sample Weight (mg)}} \times 100\right)$$

[00104] The weight of the 35 mesh sieve and sample pan was recorded. The testing apparatus was assembled with the 35 mesh sieve above the sample pan. The composite sample was

transferred to the testing apparatus and analyzed utilizing the following parameters: 1 minute analysis time and no pulse. The analyzed 35 mesh sieve and sample pan were weighed. The % material remaining on the 35 mesh sieve (≥ 500 µm) and in the sample pan (≤ 500 µm) was calculated using the following equation:

$$\text{Percent on Sieve (\%)} = \frac{\text{Weight of Sample on Sieve (mg)}}{\text{Total Weight of Sample on Sieve(mg)}} \times 100$$

[00105] Table 10 below shows the particle size after grinding for the oxycodone HCl formulations tested. During testing it was observed by visual observation that the capsule portion of the dosage form of all evaluated batches was not being significantly modified by TE96, and that the majority of the capsule portion remained in the 35 mesh sieve (≥ 500µm). The grinding / particle size analysis for this protocol is based on weight differences, which, when the capsule portion is taken into account, can skew the results towards a higher proportion of particles ≥ 500 µm.

[00106] In order to confirm the particle size of capsules modified by TE96, three empty size 3 capsules (N=1) were ground and analyzed. Table 11 shows that for size 3 capsules, 99% of the particles by weight were ≥ 500 µm. Additional calculations were made which compensated for the percentage of capsules ≥ or < 500 µm. These calculations removed the average capsule weight from the analyzed sample by subtracting it from the weight ≥ 500 µm and the weight <500 µm. The results adjusted for capsule weight are shown in Table 12.

Table 10: Particle size after grinding of oxycodone HCl capsules before adjusting for capsule weight. % RSD is percent relative standard deviation

Location	Replicate	Present Disclosure 5 mg	Present Disclosure 15 mg	Present Disclosure 30 mg
35 Mesh (≥500 µm) %	1	73.2	73.8	79.0
	2	75.9	82.2	79.2
	3	72.7	78.5	77.7
	Minimum	**72.7**	**73.8**	77.7
	Maximum	**75.9**	**82.2**	**79.2**
	Average	**74.0**	**78.1**	**78.7**
	%RSD	**2.3**	**5.4**	**1.0**
Pan (<500 µm) %	1	26.8	26.2	21.0
	2	24.1	17.8	20.8
	3	27.3	21.5	22.3
	Minimum	**24.1**	**17.8**	**20.8**
	Maximum	**27.3**	**26.2**	**22.3**
	Average	**26.0**	**21.9**	**21.3**
	%RSD	**6.6**	**19.3**	**3.8**

Table 11: Particle size of empty size 3 capsules after grinding.

Product	Initial Wt (mg)	After Grinding (mg)	% Loss In Grinding	Tare 35 Mesh (g)	Tare Pan (g)	After 35 Mesh (g)	After Pan (g)	35 Mesh (≥500 µm) %	Pan (<500 µm) %
Size 3 Capsules	143.8	144.5	-0.5	40.8367	4.4111	40.9724	4.4124	**99.1**	**0.9**

[00107] As shown in Table 12, after adjusting for the capsule portion, the average percentage of particles ≥ 500 µm after grinding for the oxycodone HCl capsules ranged from 62.3% to 68.2%. For comparison, approximately 20% of particles by weight of an Immediate Release (IR) Roxicodone® formulation were ≥ 500 µm after the same grinding procedure.

Table 12: Particle size after grinding of oxycodone HCl dosage forms, adjusted for capsule weight. % RSD is percent relative standard deviation.

Location	Replicate	Present Disclosure 5 mg	Present Disclosure 15 mg	Present Disclosure 30 mg
35 Mesh (≥500 µm) %	1	60.9	60.8	67.4
	2	63.6	72.8	69.0
	3	56.3	68.0	66.9
	Minimum	**56.3**	**60.8**	**66.9**
	Maximum	**63.6**	**72.8**	**69.0**
	Average	**62.3**	**66.8**	**68.2**
	% RSD	**6.1**	**9.0**	**1.7**
Pan (<500 µm) %	1	39.1	39.2	32.6
	2	36.4	27.2	31.0
	3	43.7	32.0	33.1
	Minimum	**36.4**	**27.2**	**31.0**
	Maximum	**43.7**	**39.2**	**33.1**
	Average	**39.7**	**32.8**	**32.2**
	% RSD	**9.3**	**18.4**	**3.5**

[00108] Table 13 summarizes the grinding results and statistical analysis of the % material ≤ 500 μm for the Present Disclosure 15mg and Roxicodone® 15mg tablets (Mallinckrodt Pharmaceuticals, Inc.).

Table 13: Particle Size Analysis of 15mg Dosages of Roxicodone® and the Present Disclosure

Grinding Results						
Product	**% Particles ≤ 500μm**	**Average**	**% RSD**	**F-test**	**t-test**	**Statistically Different?**
Roxicodone® 15mg - 1	76	76	1.9	0.672	4.85E-06	Yes
Roxicodone® 15mg - 2	75					
Roxicodone® 15mg - 3	78					
Present Disclosure 15mg -1	43	43	2.4			
Present Disclosure 15mg -2	42					
Present Disclosure 15mg -3	44					

[00109] Another method of rending a drug product abusable is via extraction of the active substance from the dosage form to produce a pure residue. This method can be performed, and is often performed, using a high proof alcohol or an aqueous media. The formulation of the present disclosure can be readily soluble in both aqueous and alcohol environments when the contents are removed from the capsule. Therefore, aqueous and alcohol extraction techniques were evaluated. Solutions were analyzed qualitatively for solution color following filtration, as well as quantitatively for % label claim (LC) (with regards to oxycodone HCl) of solution following filtration. Additionally, evaporated residual samples were analyzed qualitatively for residue color following evaporation, as well as quantitatively for purity determination following the %LC calculations. The quantitative results of the analysis determine the % purity (with regards to oxycodone HCl) of the extracted sample solution described above. A drug product can be considered abuse deterrent if the % residue purity is ≤ 50%. In other embodiments, less than or equal to 40%, 45%, 55%, 60%, 65%, 70% or 75%. Residue purity levels (with regards to the API) ≤ 50% can infer that the excipient load is greater than the API level contained in the residue. In one embodiment, this can be considered abuse deterrent with regards to potential intravenous abuse of a purified residue. Using the data analysis software functionality of

Microsoft Excel and a 95% significance interval (p-value = 0.05), the F-test and t-tests was analyzed in order to determine if the drug products provide statistically different % purity values.

[00110] Tables 14 and 15 show the formulation of the present disclosure results in 9% and 9% purity with regards to oxycodone HCl, in alcohol and aqueous environments, respectively. This is in comparison to Roxicodone® 15mg, which has a purity of 68% and 19% purity in alcohol and aqueous environments, respectively. This data proves the formulation of the present disclosure is statistically different than Roxicodone® in both alcohol and aqueous extracts.

Table 14

% Purity Results - Alcohol						
Product	**% Purity**	**Average**	**% RSD**	**F-test**	**t-test**	**Statistically Different?**
Roxicodone® 15mg - 1	66	68	2.5	0.208	5.77E-07	Yes
Roxicodone® 15mg - 2	69					
Roxicodone® 15mg - 3	68					
Present Disclosure 15mg -1	10	9	6.4			
Present Disclosure 15mg -2	8					
Present Disclosure 15mg -3	9					

Table 15

% Purity Results - Aqueous						
Product	**% Purity**	**Average**	**% RSD**	**F-test**	**t-test**	**Statistically Different?**
Roxicodone® 15mg - 1	20	19	2.6	0.823	1.02E-05	Yes
Roxicodone® 15mg - 2	19					
Roxicodone® 15mg - 3	19					
Present Disclosure 15mg -1	10	9	4.6			
Present Disclosure 15mg -2	9					
Present Disclosure 15mg -3	9					

[00111] Color is one identifying characteristic of commercial drug products. Color can be applied to the dosage form in two ways: dye or coating. High potency alcohol (i.e., ≥190 proof (95%)) is one extraction solvent that can be used by abusers for APIs which are insoluble in water or in order to separate the API from other water soluble excipients. Dyes or coatings can

potentially be used to alter the physical appearance of the extracted solution of drug product (i.e., turn the resulting solution a noticeable color).

[00112] Accordingly, the inclusion of one or more dyes in a drug formulation is one method to render a formulation abuse deterrent. Significant discoloration of an extraction product from a formulation subject to abuse can discourage a potential abuser from using (e.g., injecting or ingesting) the extraction product.

[00113] A study was conducted to investigate the effect of dyes in the formulations of the present disclosure. Extraction products from whole formulations were visually inspected to determine abuse deterrence following alcohol extraction. Capsules were added to a flask containing 190 proof ethanol and shaken at 250 rpm for 3 hours. After 3 hours all capsule contents were fully dissolved. Solutions were filtered with a syringe filter and then visually analyzed for color intensity. The samples tested were the immediate release oxycodone HCl capsules according to Table 9 above.

[00114] The unfiltered and filtered solutions are shown in Figures 4 and 5, respectively. As shown in Table 16 below, all of the filtered solutions had a color value of 5, indicating that all seven evaluated batches produced a filtered solution which was significantly dark in color. This significant dark color provides potential abuse deterrence to CII narcotic drug products.

Table 16: Color Scale Designation – Post-Syringe Filter Analysis for Oxycodone HCl Formulations of the Present Disclosure

Active Ingredient(s)	Color Value
5 mg oxycodone HCl	5
15 mg oxycodone HCl	5
30 mg oxycodone HCl	5

[00115] Additionally, the color of filtered solutions and resulting evaporated residues of alcoholic and aqueous extracts of the formulations of the present disclosure and Roxicodone® were compared. Table 17 below shows both of these dosage forms, with the formulation of the present disclosure providing the most visual deterrence for both the filtered solution and evaporated residue in both media.

Table 17

Product	Solution	Color Determination	
		Filtered Solution	Evaporated Residue
Roxicodone® 15mg	Alcohol	1	3
	Aq.	0	3
Present Disclosure 15mg	Alcohol	5	5
	Aq.	5	5

[00116] While this disclosure has been particularly shown and described with reference to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

We Claim:

1. An immediate release, abuse deterrent capsule comprising:
   (a) an active substance susceptible to abuse;
   (b) a first polyethylene glycol (PEG) having an average molecular weight between about 30,000 Daltons and about 40,000 Daltons; and
   (c) a second PEG having an average molecular weight between about 3000 Daltons and about 4000 Daltons,
   wherein the ratio of the first PEG to the second PEG is less than about 1:4 w/w.

2. The capsule of claim 1, wherein the first PEG has an average molecular weight of about 35,000 Daltons and the second PEG has an average molecular weight of about 3350 Daltons.

3. The capsule of claim 1 or 2, wherein the first PEG and the second PEG together are at least about 60 wt% of the dosage form.

4. The capsule of claim 1 or 2, wherein at least 80% of the contents are soluble both water and alcohol.

5. The capsule of claim 1 or 2, wherein the active substance is hydrocodone bitartrate.

6. The capsule of claim 1 or 2, wherein the active substance is oxycodone HCl.

7. The capsule of claim 1 or 2, further comprising a grey dye comprising FD&C Blue #1, FD&C Yellow #6, and FD&C Red #40.

8. The capsule of claim 7, wherein the dye provides a visual deterrent to abuse.

9. The capsule of claim 1 or 2, wherein the ratio of the first PEG to the second PEG is between about 1:7 w/w and about 1:11 w/w.

10. The capsule of claim 1 or 2, wherein the capsule comprises at least about 2.5 wt% of the active substance.

11. The capsule of claim 1 or 2, wherein the capsule is prepared by filling a capsule body with a heated homogenized suspension comprising the active substance, the first PEG and the second PEG.

12. A process for the production of an immediate release, abuse deterrent capsule comprising at least one active substance susceptible to abuse comprising:
   (a) preparing a homogenized suspension of:
      (i) the at least one active substance susceptible to abuse;

(ii) a first PEG having an average molecular weight between about 30,000 Daltons and about 40,000 Daltons; and

(iii) a second PEG having an average molecular weight between about 3000 Daltons and about 4000 Daltons; and

(b) filling the homogenized suspension into a capsule body to produce the capsule,

wherein the ratio of the first PEG to the second PEG is less than about 1:4 w/w.

13. The process of claim 12, wherein the first PEG and the second PEG together are at least about 60 wt% of the capsule.

14. The process of claim 12, wherein the active substance is hydrocodone bitartrate.

15. The process of claim 12, wherein the active substance is oxycodone HCl.

16. The process of claim 12, wherein the capsule is formed by joining a capsule body with a capsule cap.

17. The process of claim 12, wherein the first PEG has an average molecular weight of about 35,000 Daltons and the second PEG has an average molecular weight of about 3350 Daltons.

18. Use of a therapeutically effective amount of the capsule of any one of claims 1-11, for treating pain in a subject in need thereof.

19. Use of a therapeutically effective amount of the capsule of any one of claims 1-11, for the preparation of a medicament for treating pain in a subject in need thereof.

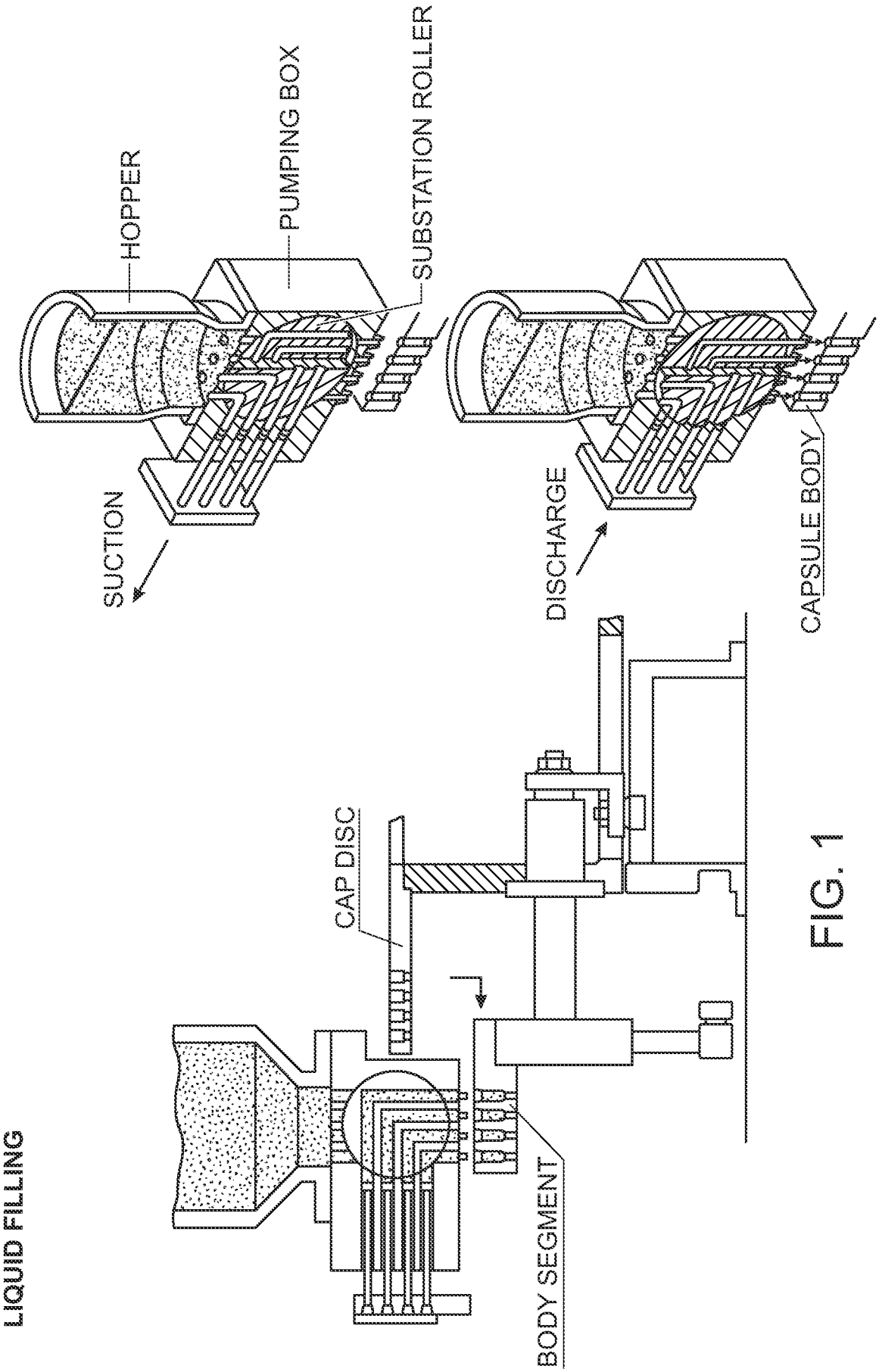
HOPPER
PUMPING BOX
SUBSTATION ROLLER
SUCTION
DISCHARGE
CAPSULE BODY
CAP DISC
BODY SEGMENT
LIQUID FILLING

FIG. 1

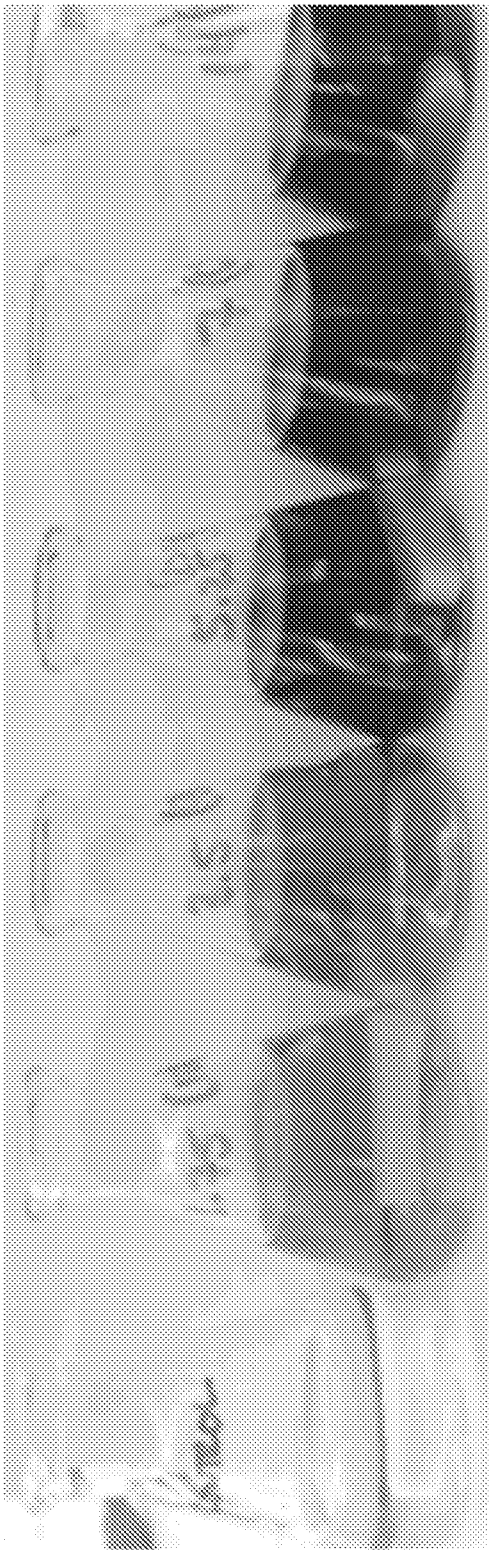

FIG. 2A

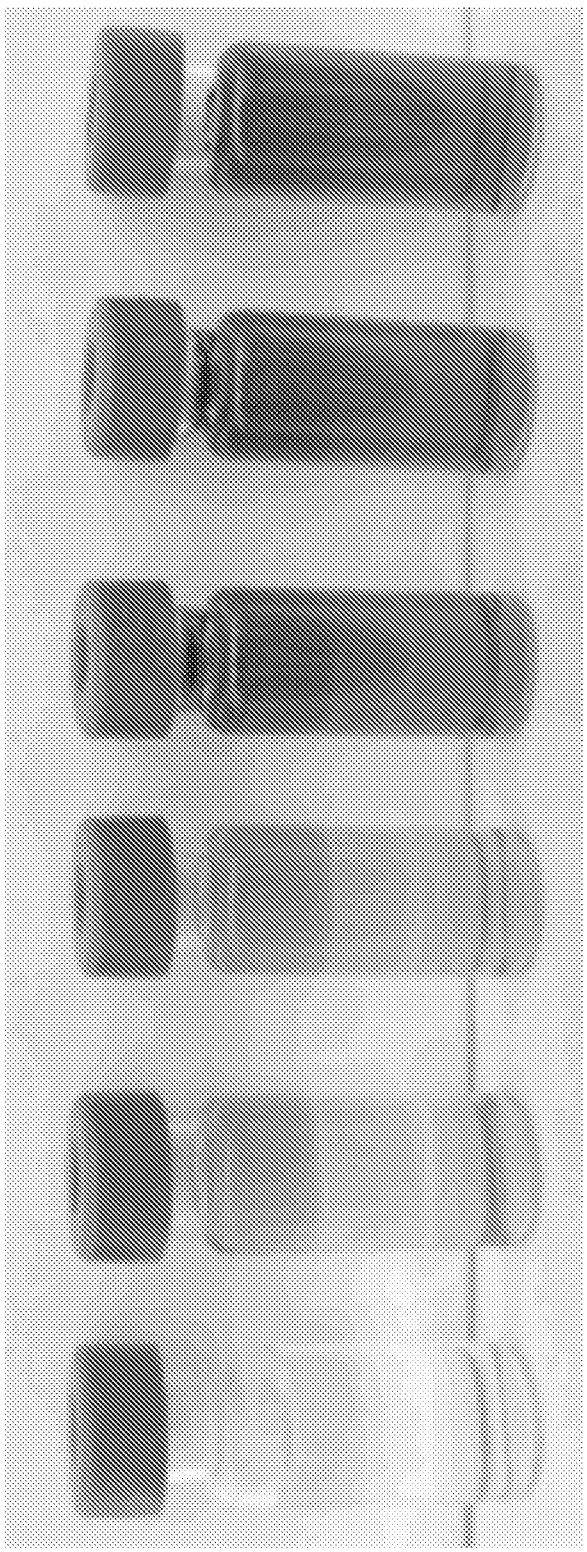

FIG. 2B

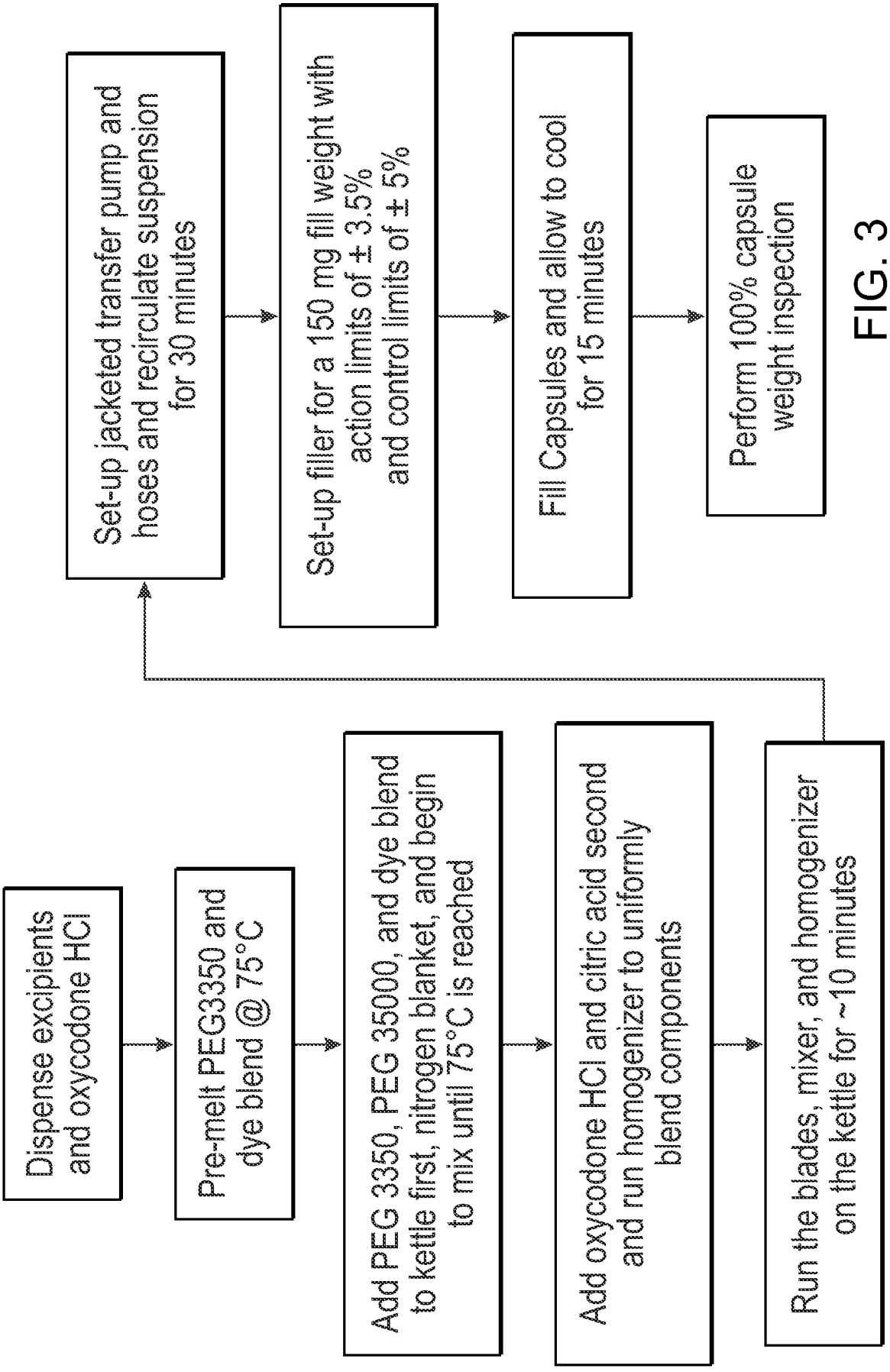
Dispense excipients and oxycodone HCl
Pre-melt PEG3350 and dye blend @ 75°C
Add PEG 3350, PEG 35000, and dye blend to kettle first, nitrogen blanket, and begin to mix until 75°C is reached
Add oxycodone HCl and citric acid second and run homogenizer to uniformly blend components
Run the blades, mixer, and homogenizer on the kettle for ~10 minutes
Set-up jacketed transfer pump and hoses and recirculate suspension for 30 minutes
Set-up filler for a 150 mg fill weight with action limits of ± 3.5% and control limits of ± 5%
Fill Capsules and allow to cool for 15 minutes
Perform 100% capsule weight inspection

FIG. 3

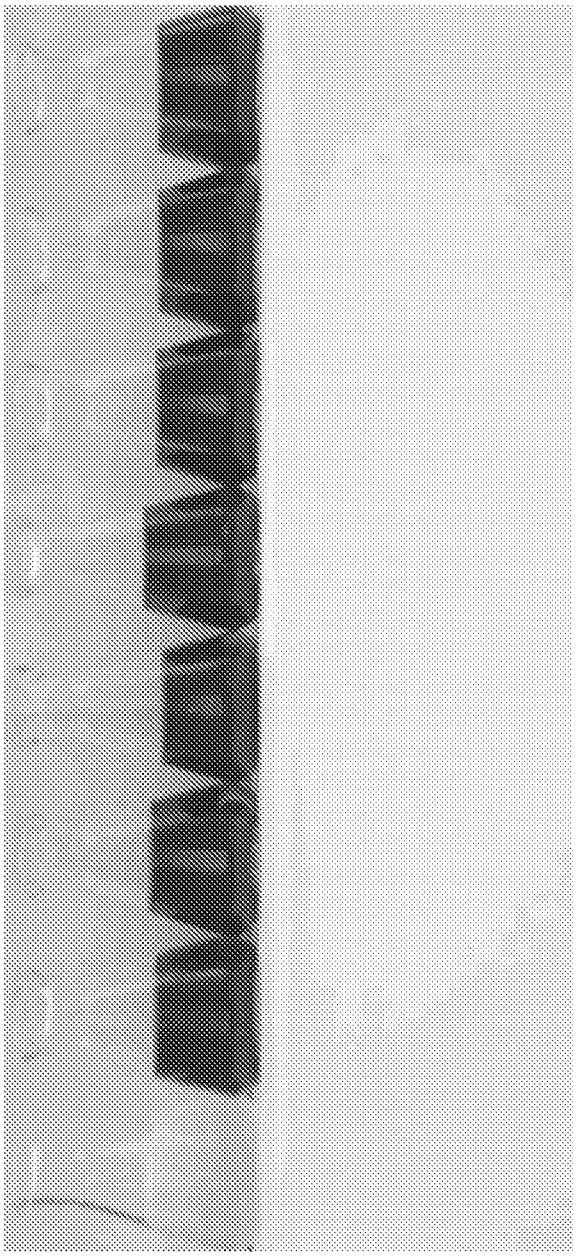

FIG. 4

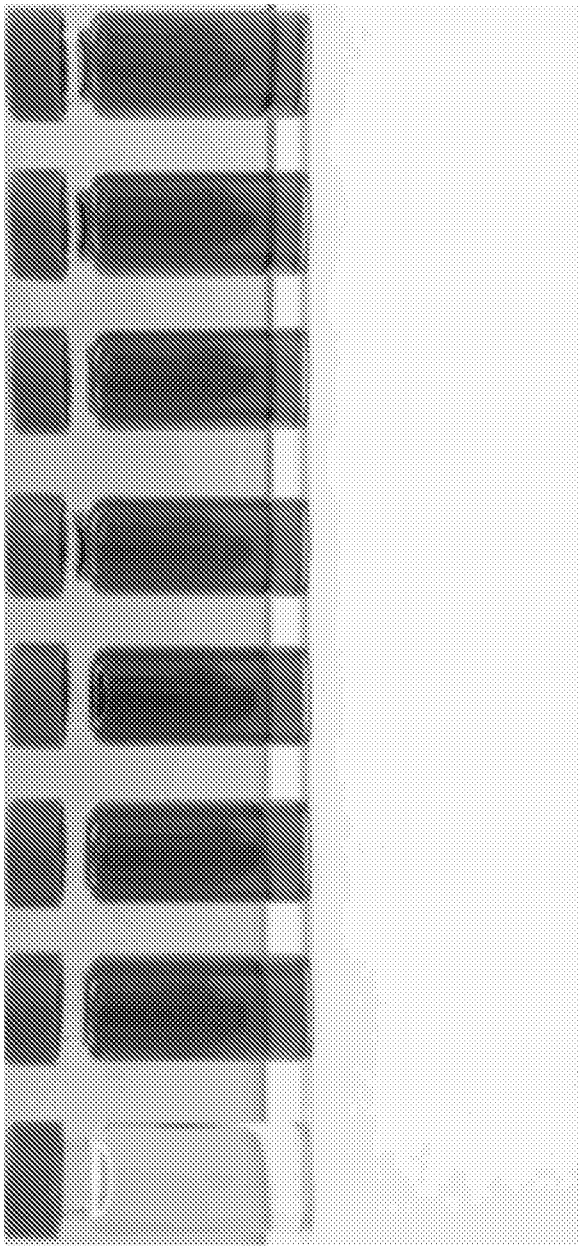

FIG. 5

LIQUID FILLING