US 20030068375A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0068375 A1**

Wright et al. (43) **Pub. Date: Apr. 10, 2003**

(54) **PHARMACEUTICAL FORMULATION CONTAINING GELLING AGENT**

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(21) Appl. No.: **10/214,412**

(22) Filed: **Aug. 6, 2002**

Related U.S. Application Data

(60) Provisional application No. 60/310,534, filed on Aug. 6, 2001.

Publication Classification

(51) **Int. Cl.**[7] **A61K 31/485**; A61K 9/20

(52) **U.S. Cl.** **424/468**; 514/282

(57) **ABSTRACT**

Disclosed in certain embodiments is a controlled release oral dosage form comprising a therapeutically effective amount of a drug susceptible to abuse together with one or more pharmaceutically acceptable excipients; the dosage form further including a gelling agent in an effective amount to impart a viscosity unsuitable for administration selected from the group consisting of parenteral and nasal administration to a solubilized mixture formed when the dosage form is crushed and mixed with from about 0.5 to about 10 ml of an aqueous liquid; the dosage form providing a therapeutic effect for at least about 12 hours when orally administered to a human patient.

PHARMACEUTICAL FORMULATION CONTAINING GELLING AGENT

[0001] This application claims the benefit of U.S. Provisional Serial No. 60/310,534, filed Aug. 6, 2001, hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Opioid analgesics are sometimes the subject of abuse. Typically, a particular dose of an opioid analgesic is more potent when administered parenterally as compared to the same dose administered orally. Therefore, one popular mode of abuse of oral opioid formulations involves the extraction of the opioid from the dosage form, and the subsequent injection of the opioid (using any "suitable" vehicle for injection) in order to achieve a "high." Also, some formulations can be tampered with in order to provide the opioid agonist contained therein better available for illicit use. For example, a controlled release opioid agonist formulation can be crushed in order to provide the opioid contained therein available for immediate release upon oral or nasal administration. An opioid formulation can also be abusable by administration of more than the prescribed dose of the drug.

[0003] Opioid antagonists have been combined with certain opioid agonists in order to deter the parenteral abuse of opioid agonists. In the prior art, the combination of immediate release pentazocine and naloxone has been utilized in tablets available in the United States, commercially available as Talwin®Nx from Sanofi-Winthrop. Talwin®Nx contains immediate release pentazocine hydrochloride equivalent to 50 mg base and naloxone hydrochloride equivalent to 0.5 mg base. A fixed combination therapy comprising tilidine (50 mg) and naloxone (4 mg) has been available in Germany for the management of pain since 1978 (Valoron™N, Goedecke). A fixed combination of buprenorphine and naloxone was introduced in 1991 in New Zealand (Temgesic®Nx, Reckitt & Colman) for the treatment of pain.

[0004] Purdue Pharma L.P currently markets sustained-release oxycodone in dosage forms containing 10, 20, 40, and 80 mg oxycodone hydrochloride under the tradename OxyContin.

[0005] U.S. Pat. Nos. 5,266,331; 5,508,042; 5,549,912 and 5,656,295 disclose sustained release oxycodone formulations.

[0006] U.S. Pat. Nos. 4,769,372 and 4,785,000 to Kreek describe methods of treating patients suffering from chronic pain or chronic cough without provoking intestinal dysmotility by administering 1 to 2 dosage units comprising from about 1.5 to about 100 mg of opioid analgesic or antitussive and from about 1 to about 18 mg of an opioid antagonist having little to no systemic antagonist activity when administered orally, from 1 to 5 times daily.

[0007] U.S. Pat. No. 6,228,863 to Palermo et al. describes compositions and methods of preventing abuse of opioid dosage forms.

[0008] WO 99/32119 to Kaiko et al. describes compositions and methods of preventing abuse of opioid dosage forms.

[0009] U.S. Pat. No. 5,472,943 to Crain et al. describes methods of enhancing the analgesic potency of bimodally acting opioid agonists by administering the agonist with an opioid antagonist.

[0010] U.S. Pat. No. 3,980,766 to Shaw et al., is related to drugs which are suitable for therapy in the treatment of narcotic drug addiction by oral use, e.g., methadone, formulated to prevent injection abuse through concentration of the active component in aqueous solution by incorporating in a solid dosage or tablet form of such drug an ingestible solid having thickening properties which cause rapid increase in viscosity upon concentration of an aqueous solution thereof.

[0011] However, there still exists a need for a safe and effective treatment of pain with opioid analgesic dosage forms which are less subject to abuse than current therapies.

[0012] All documents cited herein, including the foregoing, are incorporated by reference in their entireties for all purposes.

OBJECTS AND SUMMARY OF THE INVENTION

[0013] It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less parenteral abuse than other dosage forms.

[0014] It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less intranasal abuse than other dosage forms.

[0015] It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less oral abuse than other dosage forms.

[0016] It is a further object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less diversion than other dosage forms.

[0017] It is a further object of certain embodiments of the invention to provide a method of treating pain in human patients with an oral dosage form of an opioid analgesic while reducing the abuse potential of the dosage form.

[0018] It is a further object of certain embodiments of the invention to provide a method of manufacturing an oral dosage form of an opioid analgesic such that it has less abuse potential.

[0019] These objects and others are achieved by the present invention, which is directed in part to an oral dosage form comprising an opioid analgesic; and at least one aversive agent for reducing the abuse of the opioid analgesic.

[0020] In certain embodiments of the present invention, the oral dosage forms of the present invention comprising an opioid analgesic; and an aversive agent or agents as a component(s) of the dosage form helps to prevent injection, inhalation, and/or oral abuse by decreasing the "attractiveness" of the dosage form to a potential abuser.

[0021] In certain embodiments of the present invention, the dosage form comprises an aversive agent such as a bittering agent to discourage an abuser from tampering with the dosage form and thereafter inhaling or swallowing the tampered dosage form. Preferably, the bittering agent is released when the dosage form is tampered with and provides an unpleasant taste to the abuser upon inhalation and/or swallowing of the tampered dosage form.

[0022] In certain embodiments of the present invention, the dosage form comprises an aversive agent such as an irritant to discourage an abuser from tampering with the dosage form and thereafter inhaling, injecting, or swallowing the tampered dosage form. Preferably, the irritant is released when the dosage form is tampered with and provides a burning or irritating effect to the abuser upon inhalation, injection, and/or swallowing of the tampered dosage form.

[0023] In certain embodiments of the present invention, the dosage form comprises an aversive agent such as a gelling agent to discourage an abuser from tampering with the dosage form and thereafter inhaling, injecting, and/or swallowing the tampered dosage form. Preferably, the gelling agent is released when the dosage form is tampered with and provides a gel-like quality to the tampered dosage form which slows the absorption of the opioid analgesic such that an abuser is less likely to obtain a rapid "high". In certain preferred embodiments, when the dosage form is tampered with and exposed to a small amount (e.g., less than about 10 ml) of an aqueous liquid (e.g., water), the dosage form will be unsuitable for injection and/or inhalation. Upon the addition of the aqueous liquid, the tampered dosage form preferably becomes thick and viscous, rendering it unsuitable for injection. The term "unsuitable for injection" is defined for purposes of the present invention to mean that one would have substantial difficulty injecting the dosage form (e.g., due to pain upon administration or difficulty pushing the dosage form through a syringe) due to the viscosity imparted on the dosage form, thereby reducing the potential for abuse of the opioid analgesic in the dosage form. In certain embodiments, the gelling agent is present in such an amount in the dosage form that attempts at evaporation (by the application of heat) to an aqueous mixture of the dosage form in an effort to produce a higher concentration of the therapeutic agent, produces a highly viscous substance unsuitable for injection.

[0024] When nasally inhaling the tampered dosage form, the gelling agent can become gel like upon administration to the nasal passages due to the moisture of the mucous membranes. This also makes such formulations aversive to nasal administration, as the gel will stick to the nasal passage and minimize absorption of the abusable substance. In certain embodiments of the present invention, the dosage form comprises a combination of any or all of the aforementioned aversive agents (e.g., a bittering agent, an irritant, and/or a gelling agent) to discourage an abuser from tampering with the dosage form and thereafter inhaling, injecting, and/or swallowing the tampered dosage form.

[0025] Embodiments specifically contemplated include bittering agent; gelling agent; irritant; bittering agent and gelling agent; bittering agent and irritant; gelling agent and irritant; and bittering agent and gelling agent and irritant.

[0026] In certain preferred embodiments, the dosage forms are controlled release oral dosage forms comprising a therapeutically effective amount of an opioid analgesic with one or more of the aversive agents described above such that the dosage form provides effective pain relief for at least about 12 hours, or at least about 24 hours when orally administered to a human patient.

[0027] In certain embodiments of the present invention the aversive agent present in the dosage form is present in a substantially non-releasable form (i.e., "sequestered") when the dosage form is administered intact as directed. Preferably, because the aversive agent is present in the dosage form in a substantially non-releasable form, it is not substantially released in the gastrointestinal tract when the dosage form is orally administered intact.

[0028] In other embodiments, the aversive agent may not be "sequestered" as disclosed above wherein the aversive agent is not released or minimally released from an intact dosage form, but may have a modified or sustained release so as not to dump the aversive agent in a particular section of the gastrointestinal tract, e.g. the stomach, where it may cause an unwanted effect such as excessive irritation. The aversive agent can be combined with an enteric carrier to delay its release or combined with a carrier to provide a sustained release of the aversive agent. However, it is contemplated in the present invention that the aversive agent will preferably not have any significant side effect (e.g., gastrointestinal side effect) even if all of the aversive agent is immediately released upon oral administration of an intact dosage form as directed.

[0029] The aversive agent(s) can also be in the dosage form in releasable form and non-releasable form in any combination. For example, a dosage form can have a bittering agent, irritant, gel or combination thereof in releasable form and non-releasable form as disclosed in U.S. Application entitled "Pharmaceutical Formulations Containing Opioid Agonist, Releasable Antagonist, and Sequestered Antagonist" filed Aug. 6, 2002, the disclosure of which is hereby incorporated by reference in its entirety.

[0030] The term "aversive agent" is defined for purposes of the present invention to mean a bittering agent, an irritant, a gelling agent, or combinations thereof.

[0031] The term "tampered dosage form" is defined for purposes of the present invention to mean that the dosage form has been manipulated by mechanical, thermal, and/or chemical means which changes the physical properties of the dosage form, e.g., to liberate the opioid agonist for immediate release if it is in sustained release form, or to make the opioid agonist available for inappropriate use such as administration by an alternate route, e.g., parenterally. The tampering can be, e.g., by means of crushing, shearing, grinding, chewing, dissolution in a solvent, heating, (e.g., greater than about 45° C.), or any combination thereof.

[0032] The term "substantially non-releasable form" for purposes of the present invention refers to an aversive agent that is not released or substantially not released at one hour after the intact dosage form containing an opioid agonist and at least one aversive agent is orally administered (i.e., without having been tampered with). The aversive agent in a substantially non-releasable form may be prepared in accordance with the teachings of U.S. application Ser. No. 09/781,081, entitled "Tamper Resistant Oral Opioid Agonist Formulations" filed Feb. 8, 2001, the disclosure of which is

hereby incorporated by reference in its entirety, which describes a dosage form comprising an opioid antagonist in a substantially non-releasable form. For purposes of the present invention, the amount released after oral administration of the intact dosage form may be measured in-vitro via the dissolution at 1 hour of the dosage form in 900 ml of Simulated Gastic Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37° C. Such a dosage form is also referred to as comprising a "sequestered aversive agent" depending on the agent or agents which are not released or substantially not released. In certain preferred embodiments of the invention, the substantially non-releasable form of the aversive agent is resistant to laxatives (e.g., mineral oil) used to manage delayed colonic transit and resistant to achlorhydric states. Preferably, the aversive agent is not released or not substantially released 4, 8, 12 and/or 24 hours after oral administration.

[0033] The phrase "analgesic effectiveness" is defined for purposes of the present invention as a satisfactory reduction in or elimination of pain, along with a tolerable level of side effects, as determined by the human patient.

[0034] The term "sustained release" is defined for purposes of the present invention as the release of the opioid analgesic from the oral dosage form at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range but below toxic levels over an extended period of time, e.g., from about 12 to about 24 hours as compared to an immediate release product. Preferably the sustained release is sufficient to provide a twice-a-day or a once-a-day formulation.

[0035] The term "particles" of aversive agent, as used herein, refers to granules, spheroids, beads or pellets comprising the aversive agent. In certain preferred embodiments, the aversive agent particles are about 0.2 to about 2 mm in diameter, more preferably about 0.5 to about 2 mm in diameter.

[0036] The term "parenterally" as used herein includes subcutaneous injections, intravenous injections, intramuscular injections, intrasternal injections, infusion techniques, or other methods of injection known in the art.

[0037] The term "inhaled" as used herein includes trans-mucosal, trans-bronchial, and trans-nasal abuse.

[0038] The term "bittering agent" as used herein includes a compound used to impart a bitter taste, bitter flavor, etc., to an abuser administering a tampered dosage form of the present invention.

[0039] The term "irritant" as used herein includes a compound used to impart an irritating or burning sensation to an abuser administering a tampered dosage form of the present invention.

[0040] The term "gelling agent" as used herein includes a compound or composition used to impart-gel-like or thickening quality to a tampered dosage form upon the addition of moisture or liquid.

DETAILED DESCRIPTION OF THE INVENTION

[0041] The aversive agents of the present invention are preferably for use in connection with oral dosage forms including opioid analgesics, which provide valuable analgesia but which may be abused. This is particularly true for controlled release opioid analgesic products which have a large dose of opioid analgesic intended to be released over a period of time in each dosage unit. Drug abusers typically may take a controlled-release product and crush, shear, grind, chew, dissolve and/or heat, extract or otherwise damage the product so that the full contents of the dosage form become available for immediate absorption by injection, inhalation, and/or oral consumption.

[0042] In certain embodiments, the present invention comprises a method for preventing or deterring the abuse of opioid analgesics by the inclusion of at least one aversive agent in the dosage form with the opioid analgesic.

[0043] In certain alternative embodiments, the present invention comprises a method for preventing or deterring the abuse of drugs other than opioid analgesics which may also be the subject of abuse, by including at least one of the aversive agents described herein in a dosage form comprising the drug other than an opioid analgesic which is the subject of abuse.

[0044] In certain embodiments of the present invention wherein the dosage form includes an aversive agent comprising a bittering agent, various bittering agents can be employed including, for example and without limitation, natural, artificial and synthetic flavor oils and flavoring aromatics and/or oils, oleoresins and extracts derived from plants, leaves, flowers, fruits, and so forth, and combinations thereof. Nonlimiting representative flavor oils include spearmint oil, peppermint oil, eucalyptus oil, oil of nutmeg, allspice, mace, oil of bitter almonds, menthol and the like. Useful bittering agents can be artificial, natural and synthetic fruit flavors such as citrus oils including lemon, orange, lime, grapefruit, and fruit essences and so forth. Additional bittering agents include sucrose derivatives (e.g., sucrose octaacetate), chlorosucrose derivatives, quinine sulphate, and the like. The preferred bittering agent for use in the present invention is Denatonium Benzoate NF-Anhydrous, sold under the name Bitrex® (Macfarlan Smith Limited, Edinburgh, UK).

[0045] With the inclusion of a bittering agent in the formulation, the intake of the tampered dosage form produces a bitter taste upon inhalation or oral administration which in certain embodiments spoils or hinders the pleasure of obtaining a high from the tampered dosage form, and preferably prevents the abuse of the dosage form.

[0046] A bittering agent may be added to the formulation in an amount of less than about 50% by weight preferably less than about 10% by weight, most preferably less than about 5% by weight of the dosage form, and most preferably in an amount ranging from about 0.1 to 1.0 percent by weight of the dosage form, depending on the particular bittering agent(s) used. A dosage form including a bittering agent preferably discourages improper usage of the tampered dosage form by imparting a disagreeable taste or flavor to the tampered dosage form.

[0047] In certain embodiments of the present invention wherein the dosage form includes an aversive agent comprising an irritant, various irritants can be employed including, for example and without limitation capsaicin, a capsaicin analog with similar type properties as capsaicin, and the like. Some capsaicin analogues or derivatives include for

example and without limitation, resiniferatoxin, tinyatoxin, heptanoylisobutylamide, heptanoyl guaiacylamide, other isobutylamides or guaiacylamides, dihydrocapsaicin, homovanillyl octylester, nonanoyl vanillylamide, or other compounds of the class known as vanilloids. Resiniferatoxin is described, for example, in U.S. Pat. No. 5,290,816 (Blumberg), issued Mar. 1, 1994. U.S. Pat. No. 4,812,446 (Brand), issued Mar. 14, 1989, describes capsaicin analogs and methods for their preparation. Further, U.S. Pat. No. 4,424,205 (LaHann et al.), issued Jan. 3, 1984, cite Newman, "Natural and Synthetic Pepper-Flavored Substances" published in 1954 as listing pungency of capsaicin-like analogs. Ton et al., British Journal of Pharmacology, 10, pp. 175-182 (1955) discuss pharmacological actions of capsaicin and its analogs.

[**0048**] With the inclusion of an irritant (e.g., capsaicin) in the dosage form, when the dosage form is tampered with, the capsaicin imparts a burning or discomforting quality to the abuser to preferably discourage the inhalation, injection, or oral administration of the tampered dosage form, and preferably to prevent the abuse of the dosage form. Suitable capsaicin compositions include capsaicin (trans 8-methyl-N-vanillyl-6-noneamide) or analogues thereof in a concentration between about 0.00125% and 50% by weight, preferably between about 1 and about 7.5% by weight, and most preferably, between about 1 and about 5% by weight of the dosage form.

[**0049**] In certain embodiments of the present invention wherein the dosage form includes an aversive agent comprising a gelling agent, various gelling agents can be employed including, for example and without limitation, sugars or sugar derived alcohols, such as mannitol, sorbitol, and the like, starch and starch derivatives, cellulose derivatives, such as microcrystalline cellulose, sodium caboxymethyl cellulose, methylcellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose, attapulgites, bentonites, dextrins, alginates, carrageenan, gum tragacanth, gum acacia, guar gum, xanthan gum, pectin, gelatin, kaolin, lecithin, magnesium aluminum silicate, the carbomers and carbopols, polyvinylpyrrolidone, polyethylene glycol, polyethylene oxide, polyvinyl alcohol, silicon dioxide, surfactants, mixed surfactant/wetting agent systems, emulsifiers, other polymeric materials, and mixtures thereof, etc. In certain preferred embodiments, the gelling agent is xanthan gum. In other preferred embodiments, the gelling agent of the present invention is pectin. The pectin or pectic substances useful for this invention include not only purified or isolated pectates but also crude natural pectin sources, such as apple, citrus or sugar beet residues which have been subjected, when necessary, to esterification or de-esterification, e.g., by alkali or enzymes. Preferably, the pectins used in this invention are derived from citrus fruits such as lime, lemon, grapefruit, and orange.

[**0050**] With the inclusion of a gelling agent in the dosage form, when the dosage form is tampered with, the gelling agent preferably imparts a gel-like quality to the tampered dosage form which preferably spoils or hinders the pleasure of obtaining a rapid high from the tampered dosage form due to the gel like consistency in contact with the mucous membrane, and in certain embodiments, prevents the abuse of the dosage form by minimizing absorption, e.g. in the nasal passages. A gelling agent may be added to the formulation in a ratio of gelling agent to opioid agonist of from about 1:40 to about 40:1 by weight, preferably from about 1:1 to about 30:1 by weight, and more preferably from about 2:1 to about 10:1 by weight of the opioid agonist. In certain alternative embodiments, the gelling agent may be present in a ratio to the opioid agonist of from about 1:15 to about 15:1, preferably in a ratio of from about 1:8 to about 8:1, and more preferably from about 1:3 to about 3:1 by weight of the opioid agonist.

[**0051**] In certain other embodiments, the dosage form forms a viscous gel after the dosage form is tampered with, dissolved in an aqueous liquid (from about 0.5 to about 10 ml and preferably from 1 to about 5 ml), causing the resulting mixture to have a viscosity of at least about 10 cP. Most preferably, the resulting mixture will have a viscosity of at least about 60 cP.

[**0052**] In certain other embodiments, the dosage form forms a viscous gel after the dosage form is tampered with, dissolved in an aqueous liquid (from about 0.5 to about 10 ml and preferably from 1 to about 5 ml) and then heated (e.g., greater than about 45° C.), causing the resulting mixture to have a viscosity of at least about 10 cP. Most preferably, the resulting mixture will have a viscosity of at least about 60 cP.

[**0053**] In certain embodiments, the dosage form may include one or more of the aforementioned aversive agents. For safety reasons, the amount of the bittering agent, irritant, or gelling agent in a formulation of the present invention should not be toxic to humans.

[**0054**] In certain embodiments, the aversive agent included in the dosage form may be in a substantially non-releasable form. Where the aversive agent is in a substanitially non-releasable form, the substantially non-releasable form of the aversive agent comprises an aversive agent that is formulated with one or more pharmaceutically acceptable hydrophobic materials, such that the aversive agent is not released or substantially not released during its transit through the gastrointestinal tract when administered orally as intended, without having been tampered with.

[**0055**] In certain embodiments of the present invention, the substantially non-releasable form of the aversive agent is vulnerable to mechanical, thermal and/or chemical tampering, e.g., tampering by means of crushing, shearing, grinding, chewing and/or dissolution in a solvent in combination with heating (e.g., greater than about 45° C.) of the oral dosage form. When the dosage form is tampered with, the integrity of the substantially non-releasable form of the aversive agent will be compromised, and the aversive agent will be made available to be released. In certain embodiments, when the dosage form is chewed, crushed or dissolved and heated in a solvent, the release of the aversive agent hinders, deters or prevents the administration of the tampered dosage form orally, intranasally, parenterally and/or sublingually.

[**0056**] The opioid agonists useful in the present invention include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate,

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