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

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See application file for complete search history.

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(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.

24 Claims, No Drawings

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PHARMACEUTICAL FORMULATION CONTAINING GELLING AGENT

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 12/653,115, filed Dec. 8, 2009, which is a continuation of U.S. patent application Ser. No. 10/214,412, filed Aug. 6, 2002, which claims the benefit of U.S. Provisional Application No. 60/310,534, filed Aug. 6, 2001. The contents of these applications are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

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.

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.

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

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

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.

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

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

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.

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 torr of such drug an ingestible solid having thickening properties which cause rapid increase in viscosity upon concentration of an aqueous solution thereof.

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.

All documents cited herein, including the foregoing, art incorporated by reference in their entireties for all purposes.

OBJECTS AND SUMMARY OF THE INVENTION

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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 tam-

pered 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.

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.

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.

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.

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.

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.

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.

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.

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.

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 Gastric 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.

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.

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.

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 aver-

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