TAMPER RESISTANT DOSAGE FORMS

TECHNICAL FIELD OF THE INVENTION

[001] The present invention relates to a tamper resistant dosage form, in particular to a tamper resistant dosage form including an opioid analgesic, and the corresponding process of manufacture and use thereof in a method of treatment.

BACKGROUND OF THE INVENTION

[002] Pharmaceutical products are sometimes the subject of abuse. For example, a particular dose of opioid agonist may be more potent when administered parenterally as compared to the same dose administered orally. Some formulations can be tampered with to provide the opioid agonist contained therein for illicit use. Controlled release opioid agonist formulations are sometimes crushed, or subject to extraction with solvents (e.g., ethanol) by drug abusers to provide the opioid contained therein for immediate release upon oral or parenteral administration.

[003] Controlled release opioid agonist dosage forms which can liberate a portion of the opioid upon exposure to ethanol, can also result in a patient receiving the dose more rapidly than intended if a patient disregards instructions for use and concomitantly uses alcohol with the dosage form.

[004] There continues to exist a need in the art for an oral dosage form comprising an opioid agonist without significantly changed opioid release upon exposure to alcohol and/or with resistance to crushing.

OBJECTS AND SUMMARY OF THE INVENTION

[005] It is an object of certain embodiments of the present invention to provide an oral extended release dosage form comprising an active agent such as an opioid analgesic which is tamper resistant.

[006] It is an object of certain embodiments of the present invention to provide an oral extended release dosage form comprising an active agent such as an opioid analgesic which is resistant to crushing.

[007] It is an object of certain embodiments of the present invention to provide an oral extended release dosage form comprising an active agent such as an opioid analgesic which is resistant to alcohol extraction and dose dumping when concomitantly used with or exposed to alcohol.

[008] In certain embodiments, the present invention is directed to a solid oral extended release pharmaceutical dosage form comprising an extended release matrix formulation in the form of a tablet or multi particulates, wherein the tablet or the individual multi particulates can be at least flattened without breaking, characterized by a thickness of the tablet or of the individual multi particulate after the flattening which corresponds to no more than 60 % of the thickness of the tablet or the individual multi particulate before flattening, and wherein said flattened tablet or the flattened multi particulates provide an in-vitro dissolution rate, when measured in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C, characterized by the percent amount of active released at 0.5 hours of dissolution that deviates no more than 20 % points from the corresponding in-vitro dissolution rate of a non-flattened reference tablet or reference multi particulates.

[009] In certain embodiments, the present invention is directed to a solid oral extended release pharmaceutical dosage form comprising a extended release matrix formulation in the form of a tablet or multi particulates, wherein the tablet or the individual multi particulates can at least be flattened without breaking, characterized by a thickness of the tablet or the individual multi particulate after the flattening which corresponds to no more than 60% of the thickness of the tablet or the individual multi particulate before flattening, and wherein the flattened or non flattened tablet or the flattened or non flattened multi particulates provide an in-vitro dissolution rate, when measured in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) comprising 40% ethanol at 37° C, characterized by the percent amount of active released at 0.5 hours of dissolution that deviates no more than 20 % points from the corresponding in-vitro dissolution rate measured in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C without ethanol, using a flattened and non flattened reference tablet or flattened and non flattened reference multi particulates, respectively.

[0010] In certain embodiments, the present invention is directed to a solid oral extended release pharmaceutical dosage form comprising an extended release matrix formulation, the extended release matrix formulation comprising a composition comprising at least:

(1) at least one polyethylene oxide having, based on rheological measurements, an approximate molecular weight of at least 1,000,000; and

(2) at least one active agent; and

wherein the composition comprises at least 80 % (by wt) polyethylene oxide.

[0011] In certain embodiments, the present invention is directed to a solid oral extended release pharmaceutical dosage form comprising an extended release matrix formulation, the extended release matrix formulation comprising a composition comprising at least:

(1) at least one active agent;

(2) at least one polyethylene oxide having, based on rheological measurements, an approximate molecular weight of at least 1,000,000; and

(3) at least one polyethylene oxide having, based on rheological measurements, a molecular weight of less than 1,000,000.

[0012] In certain embodiments, the present invention is directed to a method of treatment wherein a dosage form according to the invention comprising an opioid analgesic is administered for treatment of pain to a patient in need thereof.

[0013] In certain embodiments, the present invention is directed to the use of a dosage form according to the invention comprising an opioid analgesic for the treatment of pain.

[0014] In certain embodiments, the present invention is directed to the use of high molecular weight polyethylene oxide that has, based on rheological measurements, a molecular weight of at least 1,000,000, as matrix forming material in the manufacture of a solid extended release oral dosage form comprising an active selected from opioids for imparting to the solid extended release oral dosage form resistance to alcohol extraction.

[0015] In certain embodiments, the present invention is directed to a process of preparing a solid oral extended release pharmaceutical dosage form, comprising at least the steps of:

(a) combining at least

(1) at least one polyethylene oxide having, based on rheological measurements, a molecular weight of at least 1,000,000, and

(2) at least one active agent,

to form a composition;

(b) shaping the composition to form the extended release matrix formulation; and

(c) curing said extended release matrix formulation comprising at least a curing step of subjecting the extended release matrix formulation to a temperature which is at least the softening temperature of said polyethylene oxide for a time period of at least 5 minutes.

[0016] The term "extended release" is defined for purposes of the present invention as to refer to products which are formulated to make the drug available over an extended period after ingestion thereby allowing a reduction in dosing frequency compared to a drug presented as a conventional dosage form (e.g. as a solution or an immediate release dosage form).

[0017] The term "immediate release" is defined for the purposes of the present invention as to refer to products which are formulated to allow the drug to dissolve in the gastrointestinal contents with no intention of delaying or prolonging the dissolution of absorption of the drug.

[0018] The term "solid oral extended release pharmaceutical dosage form" refers to the administration form comprising a unit dose of active agent in extended release form such as in form of a "extended release matrix formulation" and optionally other adjuvants and additives conventional in the art, such as a protective coating or a capsule and the like, and optionally any other additional features or components that are used in the dosage form. Unless specifically indicated the term "solid oral extended release pharmaceutical

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