

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization

International Bureau



(10) International Publication Number

WO 2013/057570 A2

(43) International Publication Date

25 April 2013 (25.04.2013)

(51) International Patent Classification:

A61K 47/32 (2006.01)

(21) International Application Number:

PCT/IB2012/002093

(22) International Filing Date:

17 October 2012 (17.10.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/548,587 18 October 2011 (18.10.2011) US

(71) Applicant (for all designated States except US): PURDUE PHARMA L.P. [US/US]; One Stamford Forum, 201 Tresser Boulevard, Stamford, CT 06901-3431 (US).

(72) Inventor; and

(71) Applicant (for US only): MCKENNA, William [US/US]; 10 Longmeadow Road, Yonkers, NY 10704 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,

BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))



WO 2013/057570 A2

(54) Title: ACRYLIC POLYMER FORMULATIONS

(57) Abstract: Disclosed herein are oral solid dosage forms comprising purified neutral acrylic polymer, methods of treating a disease or condition using the same, and methods of preparing the same.

ACRYLIC POLYMER FORMULATIONS

FIELD OF THE INVENTION

5 [0001] The present invention relates to the field of pharmaceutical excipients and pharmaceutical dosage forms comprising pharmaceutical excipients.

BACKGROUND

10 [0002] 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. Opioid agonist formulations intended for oral use are sometimes crushed or subject to 15 extraction with solvents (e.g., ethanol) by drug abusers to provide the opioid contained therein for non-prescribed illicit use (e.g., nasal or parenteral administration).

20 [0003] Controlled release opioid agonist dosage forms that 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.

25 [0004] Polymers are often used in the preparation of pharmaceutical compositions. When preparing controlled release formulations, certain polymers can be intermixed with an active agent to retard the release of the active agent. Certain polymers can also be used in the preparation of pharmaceutical compositions to impart tamper resistance properties (e.g., resistance to crushing or to alcohol extraction). For example, by incorporating neutral acrylic copolymers in pharmaceutical 30 formulations, the resultant product can exhibit rubber-like characteristics, making them more resistant to crushing. The neutral acrylic copolymer may also make a pharmaceutical formulation resistant to extraction of the active agent by solvents

- 2 -

such as ethanol. Tamper resistance is of particular importance for products containing opioid analgesics or other active ingredients that are prone to abuse.

5 [0005] Neutral acrylic polymers, such as Eudragit® NE and Eudragit® NM, are manufactured such that the polymer formation occurs in a solvent and the final product is in the form of an aqueous dispersion. In the preparation of oral solid dosage forms, e.g. comprising a matrix including the neutral acrylic polymer, the aqueous dispersion of the neutral acrylic polymer as such is typically mixed with other excipients and/or with active agents in a wet granulation process.

10

15 [0006] Removing water from a pharmaceutical mixture can alter the chemical bonding among the materials in the mixture, and can slow down the formulation process by requiring an extra step of preparation to achieve a final product. The presence of excess liquid and moisture can also be problematic as many excipients and active agents are water labile which can result in a final formulation that does not have the stability required to obtain regulatory approval. Also, processing oral dosage forms comprising a matrix including the neutral acrylic polymer with an aqueous dispersion of neutral acrylic polymer places restrictions on the amount of polymer present in the dosage form/matrix. In many cases, it is difficult to achieve a 20 dosage form/matrix containing greater than 30% by weight of neutral acrylic polymer utilizing commercially available aqueous dispersions.

25 [0007] There exists a need in the art for novel neutral acrylic polymer compositions and for improved processes of preparing pharmaceutical formulations, e.g. matrix formulations, based on neutral acrylic polymers. Such compositions and processes could prove useful in providing beneficial characteristics of a final product, and may allow commercially beneficial continuous processing conditions, like extrusion.

30

SUMMARY OF THE INVENTION

[0008] It is an object of the present invention to provide an excipient for utilization in pharmaceutical formulations (e.g., immediate and controlled release oral solid dosage forms).
5

[0009] It is an object of the present invention to provide a method for preparing an excipient for utilization in pharmaceutical formulations.

10 [0010] It is an object of certain embodiments of the present invention to provide an oral solid dosage form comprising an active agent (e.g., an opioid analgesic), which is tamper resistant.

15 [0011] It is an object of certain embodiments of the present invention to provide an oral solid dosage form comprising an active agent (e.g., an opioid analgesic), which is resistant to crushing.

20 [0012] It is an object of certain embodiments of the present invention to provide an oral solid dosage form comprising an opioid analgesic, which is subject to less parenteral abuse than other dosage forms.

[0013] It is an object of certain embodiments of the present invention to provide an oral solid dosage form comprising an opioid analgesic, which is subject to less intranasal abuse than other dosage forms.
25

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

[0015] It is a further object of certain embodiments of the present invention to provide an oral solid dosage form comprising an opioid analgesic, which is subject to less diversion than other dosage forms.

5 [0016] It is a further object of certain embodiments of the present invention to provide a method of treating pain in human patients with an oral solid dosage form comprising an opioid analgesic while reducing the abuse potential of the dosage form.

10 [0017] It is a further object of certain embodiments of the present invention to treat a disease or condition (e.g., pain) by administering an oral solid dosage form as disclosed herein to a patient in need thereof.

15 [0018] It is a further object of certain embodiments of the present invention to provide a method of manufacturing an oral dosage form of an active agent (e.g., an opioid analgesic) as disclosed herein.

20 [0019] It is a further object of certain embodiments of the present invention to provide a use of an oral dosage form (e.g., comprising an opioid analgesic) in the manufacture of a medicament for the treatment of a disease state (e.g., pain).

[0020] The above objects of the present invention and others can be achieved by the present invention which in certain embodiments is directed to the use of purified neutral acrylic polymer as disclosed herein.

25 [0021] In certain embodiments, the present invention is directed to an oral solid dosage form comprising a purified neutral acrylic polymer and a prophylactically or therapeutically effective amount of an active agent.

[0022] In certain embodiments, the present invention is directed to a method of treating a condition or disease with an oral solid dosage form of the present invention, such method comprising administering an oral solid dosage form comprising purified neutral acrylic polymer and a prophylactically or therapeutically effective amount of an active agent to a patient in need thereof. For example the present invention is directed to a method of treating pain comprising administering an oral solid dosage form of the present invention to a patient in need thereof, wherein the oral solid dosage form comprises an opioid agonist.

5

10 [0023] In certain embodiments, the present invention is directed to the use of an oral solid dosage form of the present invention in the manufacture of a medicament for the treatment of pain, wherein the oral solid dosage form comprises an opioid agonist.

15 [0024] In certain embodiments, the present invention is directed to an oral solid dosage form of the present invention for use in the treatment of pain, wherein the oral solid dosage form comprises an opioid agonist.

20 [0025] In certain embodiments, the present invention is directed to a method of preparing an oral solid dosage form of the present invention comprising combining a purified neutral acrylic polymer with a prophylactically or therapeutically effective amount of an active agent (e.g., by extrusion).

25 [0026] In certain embodiments, the present invention is directed to a method of preparing an oral solid dosage form, comprising at least the following steps:

30 a) drying a dispersion (e.g., an aqueous dispersion) comprising a neutral acrylic polymer to obtain a purified neutral acrylic polymer;

 b) admixing the purified neutral acrylic polymer at least with an active agent to obtain a blend, and simultaneously and/or subsequently

 c) further processing the blend to obtain the oral solid dosage form.

[0027] In certain embodiments the present invention is directed to an oral solid dosage form obtainable by such a method.

5 [0028] In certain embodiments, the present invention is directed to a purified neutral acrylic polymer, or to a bulk powder comprising a purified neutral acrylic polymer and an active agent.

10 [0029] In certain embodiments, the present invention is directed to the use of a purified neutral acrylic polymer in the preparation of an oral solid dosage form, or to the use of a blend comprising a purified neutral acrylic polymer and an active agent in the preparation of an oral solid dosage form.

15 [0030] In describing the present invention, the following terms are to be used as indicated below. As used herein, the singular forms "a," "an," and "the" include plural references unless the context clearly indicates otherwise. Thus, for example, reference to "an active agent" includes a single active agent as well as a mixture of two or more different active agents, and reference to "a polymer" includes a single polymer as well as a mixture of two or more different polymers, and the like.

20

[0031] As used herein, the terms "active agent," "active ingredient," "pharmaceutical agent," and "drug" refer to any material that is intended to produce a therapeutic, prophylactic, or other intended effect, whether or not approved by a government agency for that purpose. These terms with respect to specific agents include all pharmaceutically active agents, all pharmaceutically acceptable salts thereof, and all complexes, stereoisomers, crystalline forms, cocrystals, ether, esters, hydrates and solvates thereof, and mixtures thereof.

30 [0032] As used herein, the term "therapeutically effective" refers to the amount of drug or the rate of drug administration needed to produce a desired therapeutic result.

[0033] As used herein, the terms "prophylactically effective" refers to the amount of drug or the rate of drug administration needed to produce a desired prophylactic result.

5

[0034] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with one or more chiral centers that are not mirror images of one another (diastereomers).

10

[0035] The term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

15

[0036] The term "chiral center" refers to a carbon atom to which four different groups are attached.

[0037] The term "racemic" refers to a mixture of enantiomers.

20

[0038] The term "resolution" refers to the separation or concentration or depletion of one of the two enantiomeric forms of a molecule.

25

[0039] The term "patient" means a subject who has presented a clinical manifestation of a particular symptom or symptoms suggesting the need for treatment, who is treated preventatively or prophylactically for a condition, or who has been diagnosed with a condition to be treated.

[0040] The term "subject" is inclusive of the definition of the term "patient" and does not exclude individuals who are entirely normal in all respects or with respect to a particular condition.

5 [0041] "Pharmaceutically acceptable salts" include, but are not limited to, inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, maleate, tartrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate and the like; amino acid salts such as arginate, asparaginate, glutamate and the like; alkali metal salts such as sodium salt, potassium salt, cesium salt and the like; alkaline earth metal salts such as calcium salt, magnesium salt and the like; and organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like.

10

15 [0042] The term "polyethylene oxide" is defined for purposes of the present invention as a composition of polyethylene oxide (PEO) without regard to molecular weight, and includes lower molecular weight PEOs usually referred to as polyethylene glycols. The term "high molecular weight polyethylene oxide (PEO)" is defined for purposes of the present invention as having an approximate molecular weight of at least 1,000,000, based on rheological measurements. Preferably the term "high molecular weight polyethylene oxide (PEO)" is defined for purposes of the present invention as having an approximate molecular weight of at least 1,000,000 and less than 10,000,000, based on rheological measurements. The term "low molecular weight polyethylene oxide (PEO)" is defined for purposes of the present invention as having an approximate molecular weight of less than 1,000,000, based on rheological measurements. Preferably the term "low molecular weight polyethylene oxide (PEO)" is defined for purposes of the present invention as having an approximate molecular weight of at least 1,000 and less than 1,000,000, based on rheological measurements. More preferably the term "low molecular weight

20

25

30

polyethylene oxide (PEO)" is defined for purposes of the present invention as having an approximate molecular weight of at least 10,000 (or at least 100,000) and less than 1,000,000, based on rheological measurements. Most preferably the term "low molecular weight polyethylene oxide (PEO)" is defined for purposes of the present

5 invention as having an approximate molecular weight of at least 10,000 (or at least 100,000) and less than 750,000, based on rheological measurements. Polyethylene oxide at the lower end of the spectrum, e.g. having an approximate molecular weight of less than 100,000, or less than 25,000, based on rheological measurements, may also be referred to as polyethylene glycol (PEG).

10

[0043] Polyethylene oxide is considered to have an approximate molecular weight of 1,000,000 when a 2% (by wt) aqueous solution of said polyethylene oxide using a Brookfield viscometer Model RVF, spindle No. 1, at 10 rpm, at 25°C shows a viscosity range of 400 to 800 mPa s (cP). Polyethylene oxide is considered to have an approximate molecular weight of 2,000,000 when a 2% (by wt) aqueous solution of said polyethylene oxide using a Brookfield viscometer Model RVF, spindle No. 3, at 10 rpm, at 25°C shows a viscosity range of 2000 to 4000 mPa s (cP). Polyethylene oxide is considered to have an approximate molecular weight of 4,000,000 when a 1% (by wt) aqueous solution of said polyethylene oxide using a Brookfield viscometer Model RVF, spindle No. 2, at 2 rpm, at 25°C shows a viscosity range of 1650 to 5500 mPa s (cP). Polyethylene oxide is considered to have an approximate molecular weight of 5,000,000 when a 1% (by wt) aqueous solution of said polyethylene oxide using a Brookfield viscometer Model RVF, spindle No. 2, at 2 rpm, at 25°C shows a viscosity range of 5500 to 7500 mPa s (cP). Polyethylene oxide is considered to have an approximate molecular weight of 7,000,000 when a 1% (by wt) aqueous solution of said polyethylene oxide using a Brookfield viscometer Model RVF, spindle No. 2, at 2 rpm, at 25°C shows a viscosity range of 7500 to 10,000 mPa s (cP). Polyethylene oxide is considered to have an approximate molecular weight of 8,000,000 when a 1% (by wt) aqueous solution of said 20 polyethylene oxide using a Brookfield viscometer Model RVF, spindle No. 2, at 25°C shows a viscosity range of 7500 to 10,000 mPa s (cP). Polyethylene oxide is considered to have an approximate molecular weight of 8,000,000 when a 1% (by wt) aqueous solution of said 25 polyethylene oxide using a Brookfield viscometer Model RVF, spindle No. 2, at 2 rpm, at 25°C shows a viscosity range of 7500 to 10,000 mPa s (cP). Polyethylene oxide is considered to have an approximate molecular weight of 8,000,000 when a 1% (by wt) aqueous solution of said 30 polyethylene oxide using a Brookfield viscometer Model RVF, spindle No. 2, at 2 rpm, at 25°C shows a viscosity range of 7500 to 10,000 mPa s (cP).

2 rpm, at 25°C shows a viscosity range of 10,000 to 15,000 mPa s (cP). Regarding the lower molecular weight polyethylene oxides; polyethylene oxide is considered to have an approximate molecular weight of 100,000 when a 5% (by wt) aqueous solution of said polyethylene oxide using a Brookfield viscometer Model RVT, 5 spindle No. 1, at 50 rpm, at 25°C shows a viscosity range of 30 to 50 mPa s (cP) and polyethylene oxide is considered to have an approximate molecular weight of 900,000 when a 5% (by wt) aqueous solution of said polyethylene oxide using a Brookfield viscometer Model RVF, spindle No. 2, at 2 rpm, at 25°C shows a viscosity range of 8800 to 17,600 mPa s (cP).

10

[0044] The term "neutral acrylic polymer" for the purposes of the present invention refers to poly(meth)acrylates which do not contain free acid groups, amino groups or quaternary ammonium groups. In particular the term "neutral acrylic polymer" for the purposes of the present invention refers to a copolymer or homopolymer of 15 acrylic acid (C₁-C₈) alkyl esters and/or methacrylic acid (C₁-C₈) alkyl esters. An example for a neutral acrylic polymer according to the present invention is a copolymer of ethyl acrylate and methyl methacrylate which is available as aqueous dispersions marketed under the tradenames Eudragit® NE 30 D and Eudragit® NE 40 D. In contrast, acrylic polymers marketed e.g. under the tradenames Eudragit® 20 RL or Eudragit® RS do not fall under the definition of the term "neutral acrylic polymer" according to the present invention since they contain amounts of ammonioalkyl esters.

[0045] The term "methyl", "ethyl", "propyl", "butyl", "pentyl", "hexyl", "heptyl" 25 or "octyl" for the purposes of the present invention refers to the respective alkyl radical(s) which may be unsubstituted or substituted. For example the alkyl radical(s) can be substituted with (C₁-C₈) alkyl groups, (C₁-C₈) alkenyl groups, (C₁-C₈) alkynyl groups, (C₁-C₈) hydroxyalkyl groups, (C₁-C₈) hydroxyalkenyl groups, (C₁-C₈) hydroxyalkynyl groups, (C₁-C₈) alkyloxy groups, (C₁-C₈) alkylcarbonyl groups, (C₁-30 C₈) alkyloxycarbonyl groups, (C₁-C₈) alkylcarboxy groups, hydroxy groups or keto

groups. In preferred embodiments the alkyl radicals are unsubstituted. The alkyl radical(s) can be linear or branched, e.g. "butyl" is meant to comprise n-butyl, i-butyl, sec-butyl, and tert-butyl.

5 [0046] The term "(C₁-C₈) alkyl esters" for the purposes of the present invention refers to substituted or unsubstituted methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and/or octyl esters. For example the substituents can be selected from (C₁-C₈) alkyl groups, (C₁-C₈) alkenyl groups, (C₁-C₈) alkinyl groups, (C₁-C₈) hydroxyalkyl groups, (C₁-C₈) hydroxyalkenyl groups, (C₁-C₈) hydroxyalkinyl groups, (C₁-C₈) alkyloxy groups, (C₁-C₈) alkylcarbonyl groups, (C₁-C₈) alkyloxycarbonyl groups, (C₁-C₈) alkylcarboxy groups, hydroxy groups or keto groups. In preferred embodiments the term "(C₁-C₈) alkyl esters" refers to unsubstituted methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and/or octyl esters.

10

15 [0047] The term "(C₁-C₄) alkyl esters" for the purposes of the present invention refers to substituted or unsubstituted methyl, ethyl, propyl, and/or butyl esters. For example the substituents can be selected from (C₁-C₈) alkyl groups, (C₁-C₈) alkenyl groups, (C₁-C₈) alkinyl groups, (C₁-C₈) hydroxyalkyl groups, (C₁-C₈) hydroxyalkenyl groups, (C₁-C₈) hydroxyalkinyl groups, (C₁-C₈) alkyloxy groups, (C₁-C₈) alkylcarbonyl groups, (C₁-C₈) alkyloxycarbonyl groups, (C₁-C₈) alkylcarboxy groups, hydroxy groups or keto groups. In preferred embodiments the term "(C₁-C₄) alkyl esters" refers to unsubstituted methyl, ethyl, propyl, and/or butyl esters.

20

25 [0048] The term "purified neutral acrylic polymer" refers to a composition comprising the neutral acrylic polymer that has been obtained by drying a dispersion (e.g., an aqueous dispersion) comprising the neutral acrylic polymer prior to admixing with the active agent or with other excipients which are optionally used in the preparation of the oral solid dosage form (such as polymers, poloxamers, bulking agents, release modifying agents, retardants, plasticizers, stabilizers, diluents, fillers,

30

lubricants, binders, granulating aids, colorants, flavorants, glidants, etc.), e.g. without the use of additional excipients to facilitate the drying process. Examples of drying utilized in the present invention include vacuum drying, lyophilization, pan drying, oven drying, freeze drying and evaporation. A purified neutral acrylic polymer of 5 the present invention (i.e. the above-described composition comprising the neutral acrylic polymer) may optionally include besides the neutral acrylic polymer additional ingredients that are typically included in the manufacture of commercially available aqueous dispersions of a neutral acrylic polymer, such as emulsifiers (e.g., nonoxynol 100), residual solvents (e.g., ethanol and methanol) and unavoidable 10 minor amounts of impurities (such as monomers of the neutral acrylic polymer). Furthermore, depending on the desired level of drying, a percentage of water may remain in the purified neutral acrylic polymer. The purified neutral acrylic polymer can be obtained and/or used in solid or semi-solid form, e.g., as a powder, film, granule, pastille or a condensed wet mass. In particular the purified neutral acrylic 15 polymer of the present invention (i.e. the composition comprising the neutral acrylic polymer) preferably comprises less than about 20% (w/w) water, or less than about 15% (w/w) water, or less than about 10% (w/w) water, or less than about 5% (w/w) water. For example, the purified neutral acrylic polymer of the present invention may further comprise 0-8 % (w/w) of residual water and/or 0-5 %(w/w) of residual 20 organic solvents (such as ethanol or methanol), and/or 0-3 % (w/w) of emulsifiers. The purified neutral acrylic polymer of the present invention (i.e. the composition comprising the neutral acrylic polymer) may additionally comprise 0-5 % (w/w) of further ingredients (such as further excipients or impurities originating from the manufacture of the aqueous dispersion comprising the neutral acrylic polymer). For 25 example the purified neutral acrylic polymer of the present invention (i.e. the composition comprising the neutral acrylic polymer) comprises (or substantially consists of) 70-100 % (w/w) of neutral acrylic polymer, 0-10 % (w/w) of water, 0-5 % (w/w) of organic solvents, such as ethanol or methanol, 0-2 % (w/w) of emulsifiers, and optionally 0-5 % (w/w) of further ingredients. The above indicated 30 amounts refer to the composition of the purified neutral acrylic polymer as obtained

after drying and/or as further used for preparing a solid oral dosage form. It is well understood that the composition of the purified neutral acrylic polymer in the final solid oral dosage form can differ from the composition as originally obtained and used, e.g. due to further evaporation of water or residual solvents during the

5 preparation of the oral solid dosage form. Hence, where the composition of the oral solid dosage form is defined by the percentage of purified neutral acrylic polymer, the respective values refer to the dry contents (solids content) of the purified neutral acrylic polymer, i.e. to the contents of the purified neutral acrylic polymer remaining in the final dosage form. In certain embodiments, the emulsifiers and/or residual

10 solvents present in the aqueous dispersion comprising the neutral acrylic polymer can be separated or partially separated from the neutral acrylic polymer by processes such as solvent extraction. The purified neutral acrylic polymer is obtained prior to subsequent processing with other ingredients in the manufacture of a pharmaceutical dosage form. In certain embodiments, the (aqueous) dispersion may have an amount

15 of alcohol (e.g., methanol or ethanol) added to the dispersion prior to the purification (drying) process. The amount of added alcohol may be, e.g., less than about 30% (w/w), less than about 20% (w/w), less than about 10% (w/w), or less than about 5% (w/w) of the composition before drying.

20 [0049] In certain embodiments, purified neutral acrylic polymer (e.g., in the form of a film or a lyophilization product) can be milled into granules or a powder. In order to improve flowability and processing, a flow agent such as colloidal silica dioxide or magnesium stearate can be added to the granules or powder. These products can then be further processed into a pharmaceutical formulation, e.g., by

25 extrusion or direct compression.

[0050] The term "strand" or "rod" are used interchangeably and refer to an elongated extrudate obtained by the processes of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0051] **FIGURE 1** depicts a graphical view of the dissolution data for sample tablets and pellets of Example 1.

5

[0052] **FIGURE 2** depicts the pellets of Example 4 before and after milling. Figure 2A depicts 1mm x 1mm pellets, and Figure 2B depicts 2 mm x 2 mm pellets.

10 [0053] **FIGURE 3** depicts the dissolution of the pellets of Example 5 in (i) simulated gastric fluid and (ii) simulated gastric fluid and ethanol.

[0054] **FIGURE 4** depicts the tamper resistance of the pellets of Example 5 when submitted to frozen hammering at -4°C in simulated gastric fluid.

15

DETAILED DESCRIPTION

20 [0055] The present invention addresses the above-described need in the art by providing a purified neutral acrylic polymer and an oral solid dosage form comprising the same. The present invention further provides methods of treating conditions or diseases using oral solid dosage forms of the present invention; methods of preparing oral solid dosage forms of the present invention, e.g., by extrusion; and bulk powders comprising a purified neutral acrylic polymer.

Oral Solid Dosage Forms

25

[0056] The present invention provides an oral solid dosage form comprising a purified neutral acrylic polymer and a prophylactically or therapeutically effective amount of an active agent. The purified neutral acrylic polymer is prepared by drying a dispersion (e.g., an aqueous dispersion) comprising the neutral acrylic polymer prior to admixing with the active agent or with other excipients which are

optionally used in the preparation of the oral solid dosage form (such as polymers, poloxamers, bulking agents, release modifying agents, retardants, plasticizers, stabilizers, diluents, fillers, lubricants, binders, granulating aids, colorants, flavorants, glidants, etc.), e.g. without the use of an additional ingredient that

5 facilitates the drying process. An example of the use of an additional ingredient in the drying process is granulation of a neutral acrylic polymer dispersion with an excipient such as lactose. The purified neutral acrylic polymer may, however, contain other ingredients typically used in preparing commercially available aqueous dispersions of neutral acrylic polymers (e.g., Eudragit® NE 30 D and Eudragit® NE

10 40 D), such as emulsifiers and other ingredients added by the commercial supplier of the aqueous dispersion, as well as minor amounts of impurities resulting from the preparation of the aqueous dispersion comprising the neutral acrylic polymer (e.g. minor amounts of monomers of the neutral acrylic polymer).

15 [0057] The purified neutral acrylic polymer is dried using any method that does not require the use of additional ingredients, such as drying agents. Such drying techniques utilized in the present invention include, without limitation, vacuum drying, lyophilization, pan drying, oven drying, freeze drying and evaporation. In certain embodiments, the purified neutral acrylic polymer obtained after drying may

20 retain a certain amount of water and be in the form of a condensed wet mass. The amount of retained water may depend on the contemplated processing steps of the purified neutral acrylic polymer. For example, the purified neutral acrylic polymer in the form of a condensed wet mass may be subsequently coextruded with an active agent.

25 [0058] In certain embodiments, the purified neutral acrylic polymer is obtained after drying and/or further used in solid or semi-solid form. In certain embodiments, the purified neutral acrylic polymer comprises less than about 20% (w/w) water or less than about 15% (w/w) water or less than about 10% (w/w) water or less than 5% (w/w) water. In certain embodiments, the purified neutral acrylic polymer comprises

less than about 3% (w/w) water. In certain embodiments, the purified neutral acrylic polymer comprises less than about 1% (w/w) water. In certain embodiments the purified neutral acrylic polymer comprises 0-8 % (w/w) of water and/or 0-5 % (w/w) of residual organic solvents (such as ethanol or methanol), and/or 0-3 % (w/w) of 5 emulsifiers. The purified neutral acrylic polymer may additionally comprise 0-5 % (w/w) of further ingredients (such as further excipients or impurities originating from the manufacture of the aqueous dispersion comprising the neutral acrylic polymer). In certain embodiments the purified neutral acrylic polymer comprises (or preferably 10 consists of) 70-100 % (w/w) of neutral acrylic polymer, 0-10 % (w/w) of water, 0-5 % (w/w) of organic solvents (such as ethanol or methanol), 0-2 % (w/w) of emulsifiers, and optionally 0-5 % (w/w) of further ingredients. In certain 15 embodiments the purified neutral acrylic polymer comprises (or preferably consists of) 90-100 % (w/w) of neutral acrylic polymer, 0-5 % (w/w) of water, 0-3 % (w/w) of organic solvents (such as ethanol or methanol), 0-2 % (w/w) of emulsifiers, and optionally 0-2 % (w/w) of further ingredients. The above indicated percentages refer 20 to the composition of the purified neutral acrylic polymer as obtained after drying and/or as used for further processing to a solid oral dosage form, and may not reflect the composition of the purified neutral acrylic polymer in the final oral solid dosage form, e.g. due to further evaporation of water or organic solvents during the preparation of the oral solid dosage form.

[0059] In certain embodiments, the purified neutral acrylic polymer is further processed prior to combining with the active agent or with other excipients. Examples of such further processing include milling, chopping, slicing or cutting the 25 purified neutral acrylic polymer into smaller particles that are of optimum size for the preparation of the oral solid dosage form. The milling can be performed in the presence of dry ice. The purified neutral acrylic polymer may also be screened to obtain particles of a desired size.

[0060] As disclosed above, the purified neutral acrylic polymer can be derived from an aqueous dispersion comprising the neutral acrylic polymer. Such aqueous dispersions can, for example, comprise from about 20% (w/w) to about 50% (w/w) neutral acrylic polymer, or from about 30% (w/w) to about 40% (w/w) neutral 5 acrylic polymer, or any other concentration level provided by a commercial supplier.

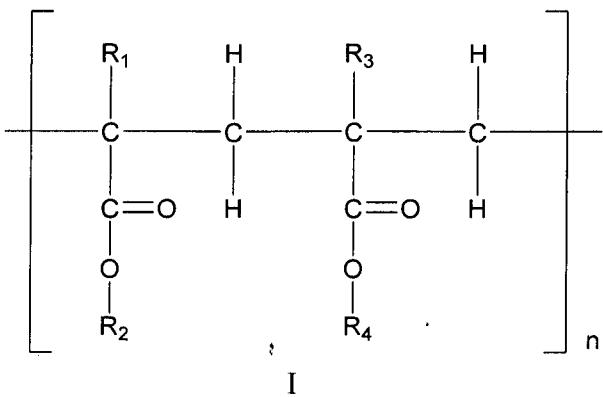
[0061] In certain embodiments, the oral solid dosage form of the present invention comprises an effective amount of purified neutral acrylic polymer to provide a controlled release of the active agent. The oral solid dosage form (e.g. a matrix 10 formulation comprising at least the purified neutral acrylic polymer and an active agent) can, for example, comprise from about 10% (w/w) to about 90% (w/w) purified neutral acrylic polymer, or from about 20% (w/w) to about 80% (w/w) purified neutral acrylic polymer, or from about 30% (w/w) to about 80% (w/w) purified neutral acrylic polymer, or from about 30% (w/w) to about 70% (w/w) purified neutral acrylic polymer, or from about 40% (w/w) to about 60% (w/w) purified neutral acrylic polymer. In preferred embodiments the oral solid dosage 15 form (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active agent) comprises greater than about 35% (w/w), or greater than about 40% (w/w), or greater than about 50% (w/w), or greater than about 60% (w/w) of the purified neutral acrylic polymer. In further preferred embodiments the oral solid dosage form (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active agent) comprises from about 35 % (w/w) to about 90% (w/w) of purified neutral acrylic polymer or from about 40 % (w/w) to about 90 % (w/w) of purified neutral acrylic polymer or from about 50 % (w/w) to about 90 % (w/w) of purified neutral acrylic polymer or from about 60 % (w/w) to about 90 % (w/w) of purified neutral acrylic polymer. The indicated percentages 20 refer to the dry contents of the purified neutral acrylic polymer.

[0062] In certain embodiments, the neutral acrylic polymer is a poly(meth)acrylate 30 which does not contain free acid groups, amino groups or quaternary ammonium

groups. In certain embodiments the neutral acrylic polymer is a copolymer or homopolymer of acrylic acid (C₁-C₈) alkyl esters and/or methacrylic acid (C₁-C₈) alkyl esters. In certain embodiments the neutral acrylic polymer is a copolymer or homopolymer of acrylic acid (C₁-C₄) alkyl esters and/or methacrylic acid (C₁-C₄) alkyl esters.

5

[0063] In certain embodiments, the neutral acrylic polymer is a copolymer having the structural formula I



10

wherein R₁ and R₃ are independently selected from H and methyl, R₂ and R₄ are independently selected from methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl or octyl,

15 and n is selected such that the copolymer has a mean relative molecular mass of at least about 100,000, preferably of at least about 300,000, most preferably of from about 600,000 to about 1,000,000.

In certain such embodiments, R₂ and R₄ are independently selected from methyl, ethyl, propyl, and butyl, preferably from methyl and ethyl.

20 [0064] In certain embodiments the neutral acrylic polymer is a copolymer of ethyl acrylate and methyl methacrylate. In certain embodiments the neutral acrylic polymer has a mean relative molecular mass of from about 600,000 to about 1,000,000, preferably of from about 600,000 to 900,000, most preferably of about 660,000, 770,000 or 800,000. In certain embodiments the neutral acrylic polymer is a

copolymer of ethyl acrylate and methyl methacrylate having a mean relative molecular mass of about 800,000. Such copolymers are commercially available as aqueous dispersions marketed under the tradenames Eudragit® NE 30 D and Eudragit® NE 40 D.

5

[0065] The oral solid dosage form of the present invention comprises a prophylactically or therapeutically effective amount of active agent. In certain embodiments, the oral solid dosage form (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active agent) comprises from about 10 1% (w/w) to about 50% (w/w) active agent, or from about 5% (w/w) to about 40% (w/w) active agent, or from about 10% (w/w) to about 30% (w/w) active agent, or from about 15% (w/w) to about 25% (w/w) active agent. The amount of active agent present in the oral solid dosage form will vary, for example, with the type of active agent, the desired rate of release, and the condition being treated.

15

[0066] In addition to the purified neutral acrylic polymer, the formulations of the present invention (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active agent) may include additional controlled release materials (retardants). Examples of additional controlled release materials include 20 cellulosic polymers, including but not limited to cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ethers, cellulose acylates, cellulose diacylates, cellulose triacylates, cellulose acetates, cellulose diacetates, cellulose triacetates, cellulose acetate propionates, cellulose acetate butyrates and mixtures thereof. Preferably, the cellulosic polymer is an alkyl cellulosic polymer such as 25 ethylcellulose.

[0067] In other embodiments of the present invention, the additional controlled release material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate 30 copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl

methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), poly(methacrylic acid) (anhydride), methyl methacrylate, polymethacrylate, poly(methyl methacrylate), poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate 5 copolymer, poly(methacrylic acid anhydride), glycidyl methacrylate copolymers and mixtures of any of the foregoing.

[0068] In other embodiments of the present invention, the dosage forms disclosed herein (e.g. a matrix formulation comprising at least the purified neutral acrylic 10 polymer and an active agent) further comprise a polyethylene oxide, e.g. a high molecular weight polyethylene oxide.

[0069] The oral solid dosage form of the present invention (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active 15 agent) may further comprise at least one excipient selected from the group consisting of polymers, poloxamers, bulking agents, release modifying agents, plasticizers, stabilizers, diluents, lubricants, binders, granulating aids, colorants, flavorants, and glidants. In certain embodiments, the excipient is a polymer. In certain embodiments, the excipient is a low molecular weight polyethylene oxide, a high molecular weight 20 polyethylene oxide, or a mixture thereof.

[0070] In embodiments comprising a low molecular weight polyethylene oxide, the low molecular weight polyethylene oxide can, for example, have an approximate 25 molecular weight from about 10,000 to about 750,000 Daltons, or from about 50,000 to about 500,000 Daltons, or from about 75,000 to about 300,000 Daltons, based on rheological measurements.

[0071] In embodiments comprising a high molecular weight polyethylene oxide, 30 the high molecular weight polyethylene oxide can, for example, have an approximate

molecular weight from about 1,000,000 to about 10,000,000 Daltons, or from about 2,000,000 to about 8,000,000 Daltons, or from about 4,000,000 to about 6,000,000 Daltons, based on rheological measurements.

5 [0072] In certain embodiments, the oral solid dosage form (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active agent) comprises from about 5% (w/w) to about 60% (w/w) polyethylene oxide, or from about 10% (w/w) to about 50% (w/w) polyethylene oxide, or from about 15% (w/w) to about 40% (w/w) polyethylene oxide, or from about 20% (w/w) to about 10 30% (w/w) polyethylene oxide. In addition to or in place of polyethylene oxide, the oral solid dosage form of the present invention (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active agent) can include a non-ionic triblock copolymer composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of 15 polyoxyethylene (poly(ethylene oxide)). These compounds are commercially available under the tradenames Lutrol® and Poloxamer®.

20 [0073] In certain embodiments, the oral solid dosage form of the present invention (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active agent) comprises from about 10% (w/w) to about 90% (w/w) purified neutral acrylic polymer, from about 1% (w/w) to about 50% (w/w) active agent (e.g. oxycodone hydrochloride), and from about 5% (w/w) to about 60% (w/w) polyethylene oxide.

25 [0074] In certain embodiments, the oral solid dosage form of the present invention (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active agent) comprises from about 35% (w/w) to about 80% (w/w) purified neutral acrylic polymer, from about 5% (w/w) to about 40% (w/w) active agent (e.g. oxycodone hydrochloride), and from about 10% (w/w) to about 50% (w/w) 30 polyethylene oxide.

[0075] In certain embodiments, the oral solid dosage form of the present invention (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active agent) comprises from about 50% (w/w) to about 70% (w/w) purified neutral acrylic polymer, from about 10% (w/w) to about 30% (w/w) active agent (e.g. oxycodone hydrochloride), and from about 15% (w/w) to about 40% (w/w) polyethylene oxide.

[0076] In certain embodiments, the oral solid dosage form of the present invention (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active agent) comprises from about 40% (w/w) to about 60% (w/w) purified neutral acrylic polymer, from about 15% (w/w) to about 25% (w/w) active agent (e.g. oxycodone hydrochloride), and from about 20% (w/w) to about 30% (w/w) polyethylene oxide.

15

[0077] In certain embodiments, the oral solid dosage form of the present invention (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active agent) comprises from about 35% (w/w) to about 90% (w/w) purified neutral acrylic polymer, from about 1% (w/w) to about 50% (w/w) active agent (e.g. oxycodone hydrochloride), and from about 5% (w/w) to about 60% (w/w) polyethylene oxide.

25

[0078] In certain embodiments, the oral solid dosage form of the present invention (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active agent) comprises from about 40% (w/w) to about 90% (w/w) purified neutral acrylic polymer, from about 5% (w/w) to about 50% (w/w) active agent (e.g. oxycodone hydrochloride), and from about 5% (w/w) to about 50% (w/w) polyethylene oxide.

[0079] In certain embodiments, the oral solid dosage form of the present invention (e.g. a matrix formulation comprising at least the purified neutral acrylic polymer and an active agent) comprises from about 50% (w/w) to about 90% (w/w) purified neutral acrylic polymer, from about 5% (w/w) to about 50% (w/w) active agent (e.g. 5 oxycodone hydrochloride), and from about 5% (w/w) to about 40% (w/w) polyethylene oxide.

[0080] In certain embodiments, the oral solid dosage form comprises a matrix formulation comprising the purified neutral acrylic polymer and the active agent. In 10 certain such embodiments the matrix formulation is a controlled release (extended release) matrix formulation. The matrix formulation can for example be obtained by subjecting a blend comprising the purified neutral acrylic polymer and the active agent to a direct compression step, an extrusion step, a wet granulation step, a dry granulation step, a hot molding step, or a heat compression step.

15

[0081] In certain such embodiments, the matrix formulation is obtained by subjecting the blend to a direct compression step, preferably by subjecting the blend to a direct compression step and a subsequent curing step. In further preferred embodiments, the matrix formulation is obtained by subjecting the blend to an 20 extrusion step, preferably a melt extrusion step.

[0082] In certain embodiments, the oral solid dosage form comprises a matrix formulation comprising the purified neutral acrylic polymer, the active agent and a polyethylene oxide. In certain such embodiments the matrix formulation is a 25 controlled release (extended release) matrix formulation. The matrix formulation can for example be obtained by subjecting a blend comprising the purified neutral acrylic polymer, the active agent and the polyethylene oxide to a direct compression step, an extrusion step, a wet granulation step, a dry granulation step, a hot molding step, or a heat compression step.

[0083] In certain such embodiments, the matrix formulation is obtained by subjecting the blend to a direct compression step, preferably by subjecting the blend to a direct compression step and a subsequent curing step. In further preferred embodiments, the matrix formulation is obtained by subjecting the blend to an extrusion step, preferably a melt extrusion step.

[0084] In certain embodiments, the purified neutral acrylic polymer and the active agent are in the form of an extruded blend (e.g., formed by standard extrusion or hot-melt extrusion). In further embodiments, the extruded blend further comprises polyethylene oxide. In certain embodiments, the extruded blend is in the form of a unitary dosage form that contains enough active agent for a single dose. In certain embodiments, the extruded blend is in the form of multiparticulates, such as pellets. Such pellets have, for example, a mean diameter from about 0.1 mm to about 5 mm and a mean height from about 0.1 mm to about 5 mm; or a mean diameter from about 0.5 mm to about 4 mm and a mean height from about 0.5 mm to about 4 mm, or a mean diameter from about 1 mm to about 3 mm and a mean height from about 0.5 mm to about 4 mm, or a mean diameter from about 1.5 mm to about 2.5 mm and a mean height from about 1.5 mm to about 2.5 mm. It will be appreciated by those in the art that the particular dimensions of the pellets can be varied depending on, for example, the active agent, the desired rate of release, and the specific dosage form. In certain embodiments, the pellets are in the form of spheres. The spheres have, for example, a mean diameter from about 0.1 mm to about 5 mm, or a mean diameter from about 0.5 mm to about 4 mm, or a mean diameter from about 1 mm to about 3 mm, or a mean diameter from about 1.5 mm to about 2.5 mm. In certain embodiments, the pellets are cylindrical or square. In certain embodiments, the oral solid dosage form comprises multiparticulates which are contained in a pharmaceutically acceptable capsule. In certain embodiments, the oral solid dosage form comprises multiparticulates which are compressed, e.g., into a tablet. In other embodiments, the extrudate can be injection molded into a final shape, cut from a rod or an extruded shape, or extruded into a film or slab and then punched or cut into a

final shape. In other embodiments, the formulation can include a co-extrusion, wherein a coating is extruded around a core or two or more layers are extruded together.

5 **[0085]** In certain embodiments, the active agent used in the oral solid dosage form of the present invention is selected from the group consisting of ACE inhibitors, adenohypophoseal hormones, adrenergic neuron blocking agents, adrenocortical steroids, inhibitors of the biosynthesis of adrenocortical steroids, alpha-adrenergic agonists, alpha-adrenergic antagonists, selective alpha-two-adrenergic agonists, 10 analgesics, anti-pyretics, anti-inflammatory agents, androgens, local and general anesthetics, anti-addictive agents, anti-androgens, anti-arrhythmic agents, anti-asthmatic agents, anti-cholinergic agents, anti-cholinesterase agents, anti-coagulants, anti-diabetic agents, anti-diarrheal agents, anti-diuretic, anti-emetic and pro-kinetic agents, anti-epileptic agents, anti-estrogens, anti-fungal agents, anti-hypertensive agents, anti-microbial agents, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents, anti-parasitic agents, anti-parkinson's agents, anti-platelet agents, 15 anti-progestins, anti-schizophrenia agents, anti-thyroid agents, anti-tussives, anti-viral agents, atypical anti-depressants, azaspirodecanediones, barbiturates, benzodiazepines, benzothiadiazides, beta-adrenergic agonists, beta-adrenergic antagonists, selective beta-one-adrenergic antagonists, selective beta-two-adrenergic agonists, bile salts, agents affecting volume and composition of body fluids, 20 butyrophenones, agents affecting calcification, calcium channel blockers, cardiovascular drugs, catecholamines and sympathomimetic drugs, cholinergic agonists, cholinesterase reactivators, contraceptive agents, dermatological agents, 25 diphenylbutylpiperidines, diuretics, ergot alkaloids, estrogens, ganglionic blocking agents, ganglionic stimulating agents, hydantoins, agents for control of gastric acidity and treatment of peptic ulcers, hematopoietic agents, histamines, histamine antagonists, hormones, 5-hydroxytryptamine antagonists, drugs for the treatment of hyperlipoproteinemia, hypnotics, sedatives, immunosuppressive agents, laxatives, 30 methylxanthines, monamine oxidase inhibitors, neuromuscular blocking agents,

organic nitrates, opioid agonists, opioid antagonists, pancreatic enzymes, phenothiazines, progestins, prostaglandins, agents for the treatment of psychiatric disorders, retinoids, sodium channel blockers, agents for spasticity and acute muscle spasms, succinimides, testosterone, thioxanthines, thrombolytic agents, thyroid agents, tricyclic antidepressants, inhibitors of tubular transport of organic compounds, drugs affecting uterine motility, vasodilators, vitamins, and mixtures thereof, among others.

[0086] In certain embodiments, the active agent is an opioid agonist. In such embodiments, the opioid agonist is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diamprodime, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof. In certain embodiments, the opioid agonist is selected from the group consisting of codeine, fentanyl, hydromorphone, hydrocodone, oxycodone, dihydrocodeine, dihydromorphine, morphine, tramadol, oxymorphone, pharmaceutically acceptable salts thereof, and mixtures thereof.

[0087] In certain embodiments, the opioid agonist is selected from the group consisting of codeine, morphine, oxycodone, hydrocodone, hydromorphone, oxymorphone, tapentadol or pharmaceutically acceptable salts, hydrates and solvates

thereof, and mixtures of any of the foregoing. In certain embodiments, the opioid agonist is oxycodone or a pharmaceutically acceptable salt thereof. In certain preferred embodiments, the opioid agonist is oxycodone hydrochloride.

5 [0088] In certain embodiments, the oral solid dosage form of the present invention comprises an active agent that is an opioid antagonist, e.g. the oral solid dosage form comprises an opioid agonist and an opioid antagonist. In such embodiments, the opioid antagonist is selected from the group consisting of amiphenazole, naltrexone, methylnaltrexone, naloxone, nalbuphine, nalorphine, nalorphine dinicotinate, 10 nalmefene, nadide, levallorphan, cyclozocine, pharmaceutically acceptable salts thereof and mixtures thereof.

[0089] In certain embodiments, the oral solid dosage form of the present invention comprises an active agent that is a non-opioid analgesic. In such embodiments, the 15 non-opioid analgesic is a non-steroidal anti-inflammatory agent selected from the group consisting of aspirin, celecoxib, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, 20 tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpina, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, pharmaceutically acceptable salts thereof and mixtures thereof.

25 [0090] The oral solid dosage form of the present invention may be formulated to have a certain desired release rate of active agent under certain specified conditions to provide, e.g., a 12 hour (i.e., twice-a-day) or 24 hour (i.e., once a day) formulation.

[0091] For 12 hour formulations, the dosage form can, e.g., provide a dissolution 30 release rate in-vitro of the active agent (e.g. an opioid analgesic, such as oxycodone

hydrochloride), when measured by the USP Basket Method at 100 rpm in 700 ml Simulated Gastric Fluid (SGF) at 37° C for 1 hour and thereafter switching to 900 ml Simulated Gastric Fluid (SGF) with Phosphate Buffer at a pH of 7.5 at 37° C, of at least about 15% by weight of the active agent released at 1 hour, from about 25% to 5 about 65% by weight of the active agent released at 2 hours, from about 45% to about 85% by weight of the active agent released at 4 hours, and at least about 60% by weight of the active agent released at 8 hours.

[0092] For 24 hour formulations, the dosage form can, e.g., provide a dissolution 10 release rate in-vitro of the active agent (e.g. an opioid analgesic, such as oxycodone hydrochloride), when measured by the USP Basket Method at 100 rpm in 700 ml Simulated Gastric Fluid (SGF) at 37° C for 1 hour and thereafter switching to 900 ml Simulated Gastric Fluid (SGF) with Phosphate Buffer at a pH of 7.5 at 37° C, of at least about 20% by weight of the active agent released at 4 hours, from about 20% to 15 about 65% by weight of the active agent released at 8 hours, from about 45% to about 85% by weight of the active agent released at 12 hours, and at least about 80% by weight of the active agent released at 24 hours.

[0093] In certain embodiments, the dosage form is resistant to dose dumping of the 20 active agent contained therein in the presence of alcohol. For example, in certain embodiments comprising an opioid agonist (such as oxycodone hydrochloride), the amount of opioid agonist released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is not more than the amount of opioid agonist released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) without EtOH using USP 25 Apparatus II at 50 rpm.

[0094] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is less than the amount of opioid agonist released

at 1 hour in 900 mL 0.1 N HCl (pH 1.5) without EtOH using USP Apparatus II at 50 rpm.

5 [0095] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is within 25% (w/w) of the amount of opioid agonist released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) without EtOH using USP Apparatus II at 50 rpm.

10 [0096] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is within 10% (w/w) of the amount of opioid agonist released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) without EtOH using USP Apparatus II at 50 rpm.

15 [0097] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is not more than the amount of opioid agonist released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) without EtOH using USP Apparatus II at 50 rpm.

20 [0098] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is less than the amount of opioid agonist released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) without EtOH using USP Apparatus II at 50 rpm.

30 [0099] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is within 25% (w/w) of the amount of opioid

agonist released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) without EtOH using USP Apparatus II at 50 rpm.

5 [00100] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is within 10% (w/w) of the amount of opioid agonist released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) without EtOH using USP Apparatus II at 50 rpm.

10 [00101] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is not more than the amount of opioid agonist released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) without EtOH using USP Apparatus II at 50 rpm.

15 [00102] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is less than the amount of opioid agonist released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) without EtOH using USP Apparatus II at 20 50 rpm.

25 [00103] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is within 25% (w/w) of the amount of opioid agonist released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) without EtOH using USP Apparatus II at 50 rpm.

30 [00104] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is within 10% (w/w) of the amount of opioid

agonist released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) without EtOH using USP Apparatus II at 50 rpm.

5 [00105] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 1 hour is from about 10% (w/w) to about 30% (w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

10 [00106] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 2 hours is from about 25% (w/w) to about 50% (w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

15 [00107] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 4 hours is from about 40% (w/w) to about 80% (w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

20 [00108] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 8 hours is from about 65% (w/w) to about 95% (w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

25 [00109] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 12 hours is greater than about 80% (w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

30 [00110] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 1 hour is from about 15% (w/w) to about 25% (w/w) as

measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

5 [00111] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 2 hours is from about 30% (w/w) to about 40% (w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

10 [00112] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 4 hours is from about 55% (w/w) to about 75% (w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

15 [00113] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 8 hours is from about 75% (w/w) to about 85% (w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

20 [00114] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 12 hours is greater than about 90% (w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

25 [00115] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 1 hour is from about 10% (w/w) to about 30% (w/w); the amount of opioid agonist released at 2 hours is from about 25% (w/w) to about 50% (w/w); the amount of opioid agonist released at 4 hours is from about 40% (w/w) to about 80% (w/w); the amount of opioid agonist released at 8 hours is from about 65% (w/w) to about 95% (w/w), and the amount of opioid agonist released at 12 hours is greater than about 80% (w/w); as measured by an in-vitro dissolution in a

USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

[00116] In certain embodiments, the amount of opioid agonist (e.g. oxycodone hydrochloride) released at 1 hour is from about 15% (w/w) to about 25% (w/w); the amount of opioid agonist released at 2 hours is from about 30% (w/w) to about 40% (w/w); the amount of opioid agonist released at 4 hours is from about 55% (w/w) to about 75% (w/w); the amount of opioid agonist released at 8 hours is from about 75% (w/w) to about 85% (w/w), and the amount of opioid agonist released at 12 hours is greater than about 90% (w/w); as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

[00117] In certain embodiments, the oral solid dosage form of the present invention demonstrates the tamper-resistant characteristic of not breaking or shattering when force is applied to it (by, for example, striking it with a hammer). Instead, the oral solid dosage form flattens without breaking or shattering. This characteristic makes it more difficult for the oral solid dosage form to be abused, by snorting the powder of a shattered tablet, chewing a tablet, or injecting a solution prepared from a shattered tablet.

[00118] In certain embodiments, the oral solid dosage form can be flattened without breaking, wherein the thickness of the dosage form after flattening corresponds to no more than about 60% of the thickness of the dosage form before flattening.

25

[00119] In certain embodiments, the dosage form can be flattened without breaking, wherein the thickness of the dosage form after flattening corresponds to no more than about 50% of the thickness of the dosage form before flattening.

[00120] In certain embodiments, the dosage form can be flattened without breaking, wherein the thickness of the dosage form after flattening corresponds to no more than about 40% of the thickness of the dosage form before flattening.

5 **[00121]** In certain embodiments, the dosage form can be flattened without breaking, wherein the thickness of the dosage form after flattening corresponds to no more than about 30% of the thickness of the dosage form before flattening.

10 **[00122]** In certain embodiments, the dosage form can be flattened without breaking, wherein the thickness of the dosage form after flattening corresponds to no more than about 20% of the thickness of the dosage form before flattening.

15 **[00123]** In certain embodiments, the amount of opioid agonist released at 0.5 hour from a flattened dosage form deviates no more than about 20% points from a non-flattened dosage form as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

20 **[00124]** In certain embodiments, the amount of opioid agonist released at 0.5 hour from a flattened dosage form deviates no more than about 15% points from a non-flattened dosage form as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

25 **[00125]** In certain embodiments, the amount of opioid agonist released at 0.5 hour from a flattened dosage form deviates no more than about 10% points from a non-flattened dosage form as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

[00126] In certain embodiments the oral solid dosage form according to the present invention is prepared by the method of preparing as described further below.

[00127] The invention also relates to an oral solid dosage form obtainable by the 5 method of preparing as described further below.

Methods of Treatment

[00128] The present invention is further directed to a method of treating a disease or 10 condition comprising administering any of the oral solid dosage forms described herein to a patient in need thereof. In certain embodiments, the patient is treated for pain, diarrhea, or constipation. In certain embodiments, wherein the oral solid dosage form comprises an opioid analgesic (e.g. oxycodone hydrochloride), the patient is treated for pain.

15

[00129] The method of treatment of the present invention may comprise administering the oral solid dosage form described herein with another pharmaceutical composition. In certain embodiments, the other pharmaceutical composition is administered to treat the same condition or disease. In other 20 embodiments, the other pharmaceutical composition is administered to treat a different condition or disease.

[00130] In certain embodiments, the method of treatment of the present invention further comprises monitoring the patient for how the patient metabolizes the active 25 agent, or how the patient responds to the active agent. In certain embodiments, the method of treatment further comprises altering the dose of the oral solid dosage form in response to said monitoring. In certain embodiments, certain baseline measurements are taken prior to administering the oral solid dosage form to the patient.

30

Methods of Preparation

The present invention is further directed to a method of preparing an oral solid dosage form as disclosed herein. In certain embodiments the method comprises at 5 least the following steps:

- a) drying a dispersion (e.g., an aqueous dispersion) comprising a neutral acrylic polymer to obtain a purified neutral acrylic polymer;
- b) admixing the purified neutral acrylic polymer at least with an active agent to obtain a blend, and simultaneously and/or subsequently
- 10 c) further processing the blend to obtain the oral solid dosage form.

[00131] In certain such embodiments, the drying is performed by vacuum drying, lyophilization, pan drying, oven drying, freeze drying and/or evaporation. Preferably the drying is performed by vacuum drying or oven drying. In one preferred embodiment the drying is performed by vacuum drying. In another preferred embodiment the drying is performed by oven drying.

[00132] Depending on the desired level of drying, a percentage of water may remain in the purified neutral acrylic polymer. In certain embodiments the purified neutral acrylic polymer (as obtained in step a) by drying and/or as further used in step b)) can be in solid or semi-solid form, e.g., in form of a powder, film, granule, pastille or a condensed wet mass.

[00133] In preferred embodiments the purified neutral acrylic polymer obtained in 25 step a) by drying the aqueous dispersion comprising the neutral acrylic polymer comprises less than about 20% (w/w) water or less than about 15% (w/w) water, preferably less than about 10% (w/w) water or less than about 5% (w/w) water, more preferably less than about 3% (w/w) water, and most preferably less than about 1% (w/w) water. For example the purified neutral acrylic polymer of the present invention may comprise 0-8 % (w/w) of residual water and/or 0-5 %(w/w) of

residual organic solvents (such as ethanol or methanol), and/or 0-3 % (w/w) of emulsifiers.

5 [00134] Depending on the conditions of drying, the purified neutral acrylic polymer obtained after drying can be e.g. in the form of sheets, and it may be appropriate to reduce the size of the purified neutral acrylic polymer before admixing it in step b) with the active agent and optionally with other excipients of the oral solid dosage form. Hence in step a), the purified neutral acrylic polymer obtained by drying the aqueous dispersion may subsequently be milled. In certain embodiments the milling 10 procedure is preceded by cutting, slicing or breaking the purified neutral acrylic polymer.

[00135] In certain embodiments the milling is conducted in the presence of dry ice.

15 [00136] In certain embodiments wherein step a) comprises a drying and a subsequent milling step, the purified neutral acrylic polymer is screened after being milled. For example the purified neutral acrylic polymer may be passed through a U.S. mesh screen of appropriate size, e.g. through a #14 U.S. mesh screen or through a #18 U.S. mesh screen.

20

[00137] In step b), the purified neutral acrylic polymer which is optionally milled or milled and screened, can, in addition to the active agent, be further admixed with at least one excipient selected from the group consisting of polymers, poloxamers, bulking agents, release modifying agents, plasticizers, stabilizers, diluents, 25 lubricants, binders, granulating aids, colorants, flavorants, and glidants.

30 [00138] In certain embodiments the purified neutral acrylic polymer is in step b) further admixed with a polymer. In certain such embodiments the polymer is a polyethylene oxide. The polyethylene oxide can be a high molecular weight polyethylene oxide, a low molecular weight polyethylene oxide, or a mixture thereof.

Preferably the polyethylene oxide is a low molecular weight polyethylene oxide. For example the polyethylene oxide has an approximate molecular weight of from about 10,000 Daltons to about 750,000 Daltons, based on rheological measurements, preferably an approximate molecular weight of from about 50,000 Daltons to about 5 500,000 Daltons, based on rheological measurements, and most preferably an approximate molecular weight of from about 75,000 Daltons to about 300,000 Daltons, based on rheological measurements.

[00139] The amounts of purified neutral acrylic polymer, active agent and optional 10 further ingredients (e.g. polyethylene oxide) to be admixed in step b) are preferably selected such that the above-described compositional features (percentages) of the oral solid dosage form are achieved.

[00140] The oral solid dosage form obtained in step c) can be a unitary dosage form, 15 such as a tablet. Alternatively the oral solid dosage form is in the form of multiparticulates (e.g. pellets or spheres) which are e.g. filled into a capsule or compressed into a tablet.

[00141] In preferred embodiments the oral solid dosage form comprises a matrix 20 formulation comprising the purified neutral acrylic polymer and the active agent. Most preferably the matrix formulation is a controlled release matrix formulation.

[00142] In certain embodiments, the blend is further processed in step c) by subjecting it to a direct compression step, an extrusion step, a wet granulation step, a 25 dry granulation step, a hot molding step, or a heat compression step.

[00143] In one embodiment the blend is further processed in step c) by subjecting it to a direct compression step, yielding either a unitary oral solid dosage form in the form of a tablet, or multiparticulates.

[00144] In certain embodiments the blend is further processed in step c) by subjecting it to a direct compression step and a subsequent curing step. The conditions of the curing step depend inter alia on the amounts of purified neutral acrylic polymer and optional polyethylene oxide present in the oral solid dosage 5 form. Suitable conditions are described further below.

[00145] In certain preferred embodiments the blend is further processed in step c) by subjecting it to an extrusion step. The extrusion step can be a melt-extrusion step (e.g., at a temperature from about 100°C to about 120°C). The resulting extrudate can 10 subsequently be divided into unitary dosage forms, preferably in the form of a tablet. Alternatively the extrudate obtained in step c) is subsequently divided into multiparticulates, preferably in the form of pellets or spheres. The multiparticulates can be filled into a capsule, or can be compressed (e.g. with other excipients such as fillers or binders) into a tablet. In certain such embodiments the extrudate is not 15 allowed to cool before it is divided.

[00146] In certain embodiments, the method comprises at least the following steps: (i) mixing (e.g. in an extruder) the purified neutral acrylic polymer and the active agent; (ii) extruding the mixture as a strand; (iii) optionally cooling the strand; and 20 (iv) dividing the strand into unit doses. The divided unit dose can be in the form of a unitary tablet (molded or non-molded) or can be in the form of multiparticulates that are subsequently compressed to a tablet or contained in a capsule. In certain embodiments, the method comprises at least the following steps: (i) mixing (e.g. in an extruder) the purified neutral acrylic polymer, the active agent; and polyethylene 25 oxide (ii) extruding the mixture as a strand; (iii) optionally cooling the strand; and (iv) dividing the strand into unit doses. As explained above, oral solid dosage forms according to the present invention using the purified neutral acrylic polymer described herein may further be prepared by processes other than extrusion. For example, the ingredients can be blended and directly compressed or the ingredients 30 can be wet or dry granulated and subsequently compressed or contained in capsules.

[00147] In embodiments involving extrusion, the shape of the extruded strand can be varied, e.g., by changing the shape of the opening out of which the strand is extruded or changing the length of each individually divided strand. Varied strand shapes will

5 yield varied pellet shapes after the extruded strand is divided which may confer benefits depending on the type of active agent and the specific dosage form. The extruded strand may be cooled at room temperature, or at a temperature cooler than room temperature. The extruded strand may also be cooled in a step-wise fashion at different temperatures for specified amounts of time after the strand is extruded.

10 Controlling the rate and temperature at which a strand cools may confer a particular shape (which may affect the dissolution profile) upon the cooled strand. In certain embodiments, it may be advantageous to divide the strand after very little or no cooling; as the divided pellets cool, they may expand (or contract), thereby taking on a nearly spherical shape.

15

[00148] The preparation of oral solid dosage forms can also include the incorporation of additional pharmaceutically acceptable components, e.g., lubricants, binders, granulating aids, diluents, colorants, flavorants (e.g., bittering agents) and glidants.

20

BULK POWDERS

[00149] The present invention is further directed to a bulk powder comprising a purified neutral acrylic polymer and an active agent. In certain embodiments, the

25 purified neutral acrylic polymer has been dried by vacuum drying, lyophilization, pan drying, freeze drying or oven drying. The bulk powder of the present invention may, for example, be used to prepare the oral solid dosage forms described herein. The bulk powder of the present invention may, for example, be used in the method of preparation described herein, including, for example, extrusion.

CURED FORMULATIONS

[00150] In certain embodiments, in particular in certain embodiments wherein the oral solid dosage form is prepared by direct compression of a blend comprising a purified neutral acrylic polymer and an active agent and optionally polyethylene oxide, a the method of the present invention may further comprise in step c) the step of curing the final dosage form. Curing is a process wherein the dosage form is subjected to certain conditions such as heat or electromagnetic radiation for a specified time in order to obtain a functional or physical change in the dosage form.

5 The functional change can be the dosage form exhibiting a dissolution profile that does not change substantially over time. The physical change can be the hardening of certain polymers (e.g., polyethylene oxides) or a stable dissolution profile provided by certain polymers (e.g., neutral acrylic polymers) that may be included in the dosage form.

10

15 [00151] For embodiments comprising polyethylene oxide in a controlled release formulation, the curing step may comprise at least partially melting the polyethylene oxide in the formulation. In certain embodiments, at least about 20% or at least about 30% of the polyethylene oxide in the formulation melts. Preferably, at least about 40%, or at least about 50%, or at least about 60%, or at least about 75%, or at least about 90% of the polyethylene oxide in the formulation melts during the curing step. In a preferred embodiment, about 100% of the polyethylene oxide melts.

20

25 [00152] In other embodiments, the curing step comprises subjecting the formulation to an elevated temperature for a certain period of time. In such embodiments, the curing temperature is at least as high as the softening temperature of the polyethylene oxide. According to certain embodiments, the curing temperature is at least about 60°C, at least about 62°C, ranges from about 62°C to about 90°C, from about 62°C to about 85°C, from about 62°C to about 80°C, from about 65°C to about 90°C, from about 65°C to about 85°C, or from about 65°C to about 80°C. The curing

30

temperature preferably ranges from about 68°C to about 90°C, from about 68°C to about 85°C, from about 68°C to about 80°C, from about 70°C to about 90°C, from about 70°C to about 85°C, from about 70°C to about 80°C, from about 72°C to about 90°C, from about 72°C to about 85°C or from about 72°C to about 80°C.

5 The curing temperature may be at least about 60°C, at least about 62°C, less than about 90°C or less than about 80°C. Preferably, it is in the range of from about 62°C to about 72°C or from about 68°C to about 72°C. Preferably, the curing temperature is at least as high as the lower limit of the softening temperature range of the polyethylene oxide, or at least about 62°C, or at least about 68°C. In further 10 embodiments, the curing temperature is at least as high as the upper limit of the softening temperature range of the polyethylene oxide, or at least about 72°C. In further embodiments, the curing temperature is higher than the upper limit of the softening temperature range of the polyethylene oxide, or at least about 75°C, or at least about 80°C.

15

[00153] In those embodiments where the curing step involves subjecting the formulation to an elevated temperature for a certain period of time, this period of time is hereinafter referred to as the curing time. For the measurement of the curing time, a starting point and an end point of the curing step are defined. For the 20 purposes of the present invention, the starting point of the curing step is defined to be the point in time when the curing temperature is reached.

[00154] In certain embodiments, the temperature profile during the curing step shows a plateau-like form between the starting point and the end point of the curing.

25 In such embodiments, the end point of the curing step is defined to be the point in time when the heating is stopped or at least reduced, e.g. by terminating or reducing the heating and/or by starting a subsequent cooling step, and the temperature subsequently drops below the curing temperature by more than about 10°C and/or below the lower limit of the softening temperature range of polyethylene oxide, for 30 example, below about 62°C. When the curing temperature is reached and the curing

step is thus started, deviations from the curing temperature in the course of the curing step can occur. Such deviations are tolerated as long as they do not exceed a value of about $\pm 10^{\circ}\text{C}$, preferably about $\pm 6^{\circ}\text{C}$, and more preferably about $\pm 3^{\circ}\text{C}$. For example, if a curing temperature of at least about 75°C is to be maintained, the 5 measured temperature may temporarily increase to a value of about 85°C , about 81°C , or about 78°C , and the measured temperature may also temporarily drop down to a value of about 65°C , about 69°C or about 72°C . In the cases of a larger decrease of the temperature and/or in the case that the temperature drops below the lower limit of the softening temperature range of polyethylene oxide, for example below about 10 62°C , the curing step is discontinued, i.e. an end point is reached. Curing can be restarted by again reaching the curing temperature.

15 [00155] In other embodiments, the temperature profile during the curing step shows a parabolic or triangular form between the starting point and the end point of the curing. This means that after the starting point, i.e., the point in time when the curing temperature is reached, the temperature further increases to reach a maximum, and then decreases. In such embodiments, the end point of the curing step is defined to be the point in time when the temperature drops below the curing temperature.

20 [00156] Depending on the apparatus used for the curing (i.e., curing device), different temperatures within the curing device can be measured to characterize the curing temperature.

25 [00157] In certain embodiments, the curing step may take place in an oven. In such embodiments, the temperature inside the oven is measured. Based thereon, when the curing step takes place in an oven, the curing temperature is defined to be the target inside temperature of the oven and the starting point of the curing step is defined to be the point in time when the inside temperature of the oven reaches the curing temperature. The end point of the curing step is defined to be (1) the point in time 30 when the heating is stopped or at least reduced and the temperature inside the oven

subsequently drops below the curing temperature by more than about 10°C and/or below the lower limit of the softening temperature range of the polyethylene oxide, for example below about 62°C, in a plateau-like temperature profile or (2) the point in time when the temperature inside the oven drops below the curing temperature in a 5 parabolic or triangular temperature profile. Preferably, the curing step starts when the temperature inside the oven reaches a curing temperature of at least about 62°C, at least about 68°C, at least about 70°C, at least about 72°C or at least about 75°C. In preferred embodiments, the temperature profile during the curing step shows a 10 plateau-like form, wherein the curing temperature, i.e. the inside temperature of the oven, is at least about 68°C, about 70°C, about 72°C, about 73°C, or lies within a range of from about 70°C to about 75°C, and the curing time is preferably in the range of from about 30 minutes to about 20 hours, from about 30 minutes to about 15 hours, from about 30 minutes to about 4 hours, or from about 30 minutes to about 2 hours. In certain embodiments, the curing time is in the range of from about 30 15 minutes to about 90 minutes.

[00158] In certain other embodiments, the curing takes place in curing devices that are heated by an air flow and comprise a heated air supply (inlet) and an exhaust, e.g., a coating pan or fluidized bed. Such curing devices will hereinafter be called 20 convection curing devices. In such curing devices, it is possible to measure the temperature of the inlet air, i.e., the temperature of the heated air entering the convection curing device and/or the temperature of the exhaust air, i.e., the temperature of the air leaving the convection curing device. It is also possible to determine or at least estimate the temperature of the formulations inside the 25 convection curing device during the curing step, e.g., by using infrared temperature measurement instruments (such as an IR gun) or by measuring the temperature using a temperature probe that was placed inside the curing device near the formulations. Based thereon, when the curing step takes place in a convection curing device, the curing temperature can be defined and the curing time can be measured as follows.

[00159] In one embodiment (method 1), the curing temperature is defined to be the target inlet air temperature and the starting point of the curing step is defined to be the point in time when the inlet air temperature reaches the curing temperature. The end point of the curing step is defined to be (1) the point in time when the heating is stopped or at least reduced and the inlet air temperature subsequently drops below the curing temperature by more than about 10°C and/or below the lower limit of the softening temperature range of the polyethylene oxide, for example below about 62°C, in a plateau-like temperature profile, or (2) the point in time when the inlet air temperature drops below the curing temperature in a parabolic or triangular temperature profile. Preferably, the curing step starts according to method 1, when the inlet air temperature reaches a curing temperature of at least about 62°C, at least about 68°C, at least about 70°C, at least about 72°C or at least about 75°C. In a preferred embodiment, the temperature profile during the curing step shows a plateau-like form, wherein the curing temperature, i.e. the target inlet air temperature, is preferably at least about 72°C, for example, about 75°C, and the curing time which is measured according to method 1 is preferably in the range of from about 15 minutes to about 2 hours, for example, about 30 minutes or about 1 hour.

[00160] In another embodiment (method 2), the curing temperature is defined to be the target exhaust air temperature, and the starting point of the curing step is defined to be the point in time when the exhaust air temperature reaches the curing temperature. The end point of the curing step is defined to be (1) the point in time when the heating is stopped or at least reduced and the exhaust air temperature subsequently drops below the curing temperature by more than about 10°C and/or below the lower limit of the softening temperature range of the polyethylene oxide, for example below about 62°C, in a plateau-like temperature profile, or (2) the point in time when the exhaust air temperature drops below the curing temperature in a parabolic or triangular temperature profile. Preferably, the curing step starts according to method 2, when the exhaust air temperature reaches a curing

temperature of at least about 62°C, at least about 68°C, at least about 70°C, at least about 72°C or at least about 75°C. In preferred embodiments, the temperature profile during the curing step shows a plateau-like form, wherein the curing temperature, i.e. the target exhaust air temperature, is preferably at least about 68°C,

5 at least about 70°C or at least about 72°C, for example the target exhaust air temperature is about 68°C, about 70°C, about 72°C, about 75°C or about 78°C, and the curing time which is measured according to method 2 is preferably in the range of from about 1 minute to about 2 hours or from about 5 minutes to about 90 minutes, for example, the curing time is about 5 minutes, about 10 minutes, about 15

10 minutes, about 30 minutes, about 60 minutes, about 70 minutes, about 75 minutes or about 90 minutes. In a more preferred embodiment, the curing time which is measured according to method 2 is in the range of from about 15 minutes to about 1 hour.

15 [00161] In a further embodiment (method 3), the curing temperature is defined to be the target temperature of the formulations and the starting point of the curing step is defined to be the point in time when the temperature of the formulations, which can be measured for example by an IR gun, reaches the curing temperature. The end point of the curing step is defined to be (1) the point in time when the heating is stopped or at least reduced and the temperature of the formulations subsequently drops below the curing temperature by more than about 10°C and/or below the lower limit of the softening temperature range of the polyethylene oxide, for example below about 62°C, in a plateau-like temperature profile or (2) the point in time when the temperature of the formulations drops below the curing temperature in a

20 parabolic or triangular temperature profile. Preferably, the curing step starts according to method 3, when the temperature of the formulations reaches a curing temperature of at least about 62°C, at least about 68°C, at least about 70°C, at least about 72°C or at least about 75°C.

25

[00162] In still another embodiment (method 4), the curing temperature is defined to be the target temperature measured using a temperature probe, such as a wire thermocouple, that is placed inside the curing device near the formulations, and the starting point of the curing step is defined to be the point in time when the 5 temperature measured using the temperature probe reaches the curing temperature. The end point of the curing step is defined to be (1) the point in time when the heating is stopped or at least reduced and the temperature measured using the temperature probe subsequently drops below the curing temperature by more than about 10°C and/or below the lower limit of the softening temperature range of 10 polyethylene oxide, for example below about 62°C, in a plateau-like temperature profile, or (2) the point in time when the temperature measured using the temperature probe drops below the curing temperature in a parabolic or triangular temperature profile. Preferably, the curing step starts when the temperature measured using a temperature probe registers a temperature in the curing device of at least about 62°C, 15 at least about 68°C, at least about 70°C, at least about 72°C or at least about 75°C. In a preferred embodiment, the temperature profile during the curing step shows a plateau-like form, wherein the curing temperature is at least about 68°C, for example, about 70°C, and the curing time which is measured according to method 4 is preferably in the range of from about 15 minutes to about 2 hours or about 60 20 minutes or about 90 minutes.

[00163] If curing takes place in a convection curing device, the curing time can be measured by any of the methods described above.

25 [00164] In certain embodiments, the curing temperature is defined as a target temperature range, for example, the curing temperature is defined as a target inlet air temperature range or a target exhaust air temperature range. In such embodiments, the starting point of the curing step is defined to be the point in time when the lower limit of the target temperature range is reached, and the end point of the curing step 30 is defined to be the point in time when the heating is stopped or at least reduced, and

the temperature subsequently drops below the lower limit of the target temperature range by more than about 10°C and/or below the lower limit of the softening temperature range of polyethylene oxide, for example, below about 62°C.

5 [00165] The curing time, i.e., the time period the formulation is subjected to the curing temperature, which can, for example, be measured according to the methods described above, is at least about 1 minute or at least about 5 minutes. The curing time may vary from about 1 minute to about 24 hours, from about 5 minutes to about 20 hours, from about 10 minutes to about 15 hours, from about 15 minutes to about 10 hours, or from about 30 minutes to about 5 hours depending on the specific formulation and the curing temperature. According to certain embodiments, the curing time varies from about 15 minutes to about 30 minutes. According to further embodiments, wherein the curing temperature is at least about 60°C, at least about 62°C, at least about 68°C, at least about 70°C, at least about 72°C or at least about 15 75°C, or varies from about 62°C to about 85°C or from about 65°C to about 85°C, then the curing time is preferably at least about 15 minutes, at least about 30 minutes, at least about 60 minutes, at least about 75 minutes, at least about 90 minutes or at least about 120 minutes. In preferred embodiments, wherein the curing temperature is, for example, at least about 62°C, at least about 68°C, at least about 70°C, at least 20 about 72°C or at least about 75°C, or ranges from about 62°C to about 80°C, from about 65°C to about 80°C, from about 68°C to about 80°C, from about 70°C to about 80°C or from about 72°C to about 80°C, then the curing time is preferably at least about 1 minute, at least about 5 minutes, at least about 10 minutes, at least about 15 minutes or at least about 30 minutes. In certain such embodiments, the curing 25 time can be chosen to be as short as possible while still achieving the desired result (e.g., increased tamper resistance). For example, the curing time preferably does not exceed about 5 hours, does not exceed about 3 hours or does not exceed about 2 hours. Preferably, the curing time is in the range of from about 1 minute to about 5 hours, from about 5 minutes to about 3 hours, from about 15 minutes to about 2 hours, or from about 15 minutes to about 1 hour. Any combination of the curing 30

temperatures and the curing times as disclosed herein lies within the scope of the present invention.

[00166] In certain embodiments, the composition is only subjected to the curing 5 temperature until the polyethylene oxide present in the formulation has reached its softening temperature and/or at least partially melts. In certain such embodiments, the curing time may be less than about 5 minutes, for example the curing time may vary from greater than 0 minutes to about 3 hours, from about 1 minute to about 2 hours or from about 2 minutes to about 1 hour. Instant curing is possible by 10 choosing a curing device which allows for an instant heating of the polyethylene oxide in the formulation to at least its softening temperature, so that the polyethylene oxide at least partially melts. Such curing devices are, for example, microwave ovens, ultrasound devices, light irradiation apparatus such as UV-irradiation apparatus, ultra-high frequency (UHF) fields or any other apparatus known to the 15 person skilled in the art.

[00167] The size of the formulation may determine the required curing time and curing temperature to achieve the desired tamper resistance.

20 [00168] In certain embodiments, the curing step leads to a decrease in the density of the formulation, such that the density of the cured formulation is lower than the density of the formulation prior to the curing step. Preferably, the density of the cured formulation in comparison to the density of the uncured formulation decreases by at least about 0.5%. More preferably, the density of the cured formulation in 25 comparison to the density of the uncured formulation decreases by at least about 0.7%, at least about 0.8%, at least about 1.0%, at least about 2.0% or at least about 2.5%.

[00169] In certain embodiments, the solid controlled release dosage form is cured at a temperature of at least the softening point of the polyethylene oxide for at least 1 minute, at least 5 minutes or at least 15 minutes.

5 **[00170]** In other embodiments, the solid controlled release dosage form is cured at a temperature of at least the softening point of the polyethylene oxide from about 1 minute to about 48 hours, from about 5 minutes to about 24 hours, from about 15 minutes to about 1 hour or about 30 minutes.

10 **[00171]** The solid controlled release dosage form can be cured, e.g., at a temperature of at least about 60° C, at least about 65° C, at least about 70° C, at least about 75° C or at a temperature of about 72° C.

15 **[00172]** In alternative embodiments, the solid controlled release dosage form can be cured at a temperature from about 60° C to about 90° C, from about 62° C to about 72° C, from about 65° C to about 85° C, from about 70° C to about 80° C, from about 75° C to about 80° C or from about 70° C to about 75° C.

FLATTENING PROCEDURES

20

[00173] In certain embodiments, dosage forms of the present invention may be flattened without substantially compromising the release of the active or the integrity of the dosage form. Flatness is described in terms of the thickness of the smallest diameter of the flattened shape compared to the thickness of the smallest diameter of the non-flattened shape. This comparison is expressed in % thickness, based on either (i) the thickness of the smallest diameter of the non-flattened shape when the initial shape is non-spherical or (ii) the thickness of the diameter when the initial shape is spherical. The thickness may be measured using a thickness gauge (e.g., a digital thickness gauge or digital caliper). The flattening force may be applied by any possible method. For purposes of testing the dosage forms of the present

invention, a carver style bench press may be used (unless otherwise specified) so as to achieve the target flatness or reduced thickness. According to certain embodiments of the invention, the flattening does not result in breaking of the dosage form into separate pieces; however, edge splits and cracks may occur.

5

[00174] In certain embodiments of the invention, a hammer can be used for flattening a dosage form. In such a process, hammer strikes can be manually applied from a direction substantially normal to the thickest dimension of the dosage form. The flatness is then described in the same manner as disclosed above.

10

[00175] In other embodiments, flattening can be measured relative to breaking strength or hardness tests, as described in Remington's Pharmaceutical Sciences, 18th edition, 1990, Chapter 89 "Oral Solid Dosage Forms", pages 1633-1665, using the Schleuniger Apparatus. In such an embodiment, the dosage form is pressed between a pair of flat plates arranged in parallel such that the force is applied substantially normal to the thickest dimension of the dosage form, thereby flattening the dosage form. The flattening of the dosage form may be described in terms of % flattening, based on the thickness of the dimension being flattened before conducting the breaking strength test. The breaking strength (or hardness) is defined as the force at which the tested dosage form breaks. Dosage forms that do not break, but which are deformed due to a force applied, are considered to be break-resistant at that particular force.

[00176] The term "resistant to crushing" is defined for the purposes of certain embodiments of the present invention as referring to dosage forms that can be flattened with a bench press as described above, without breaking, to no more than about 60% thickness, preferably to no more than about 50% thickness, more preferably to no more than about 40% thickness, even more preferably to no more than about 30% thickness, and most preferably to no more than about 20% thickness, 30 10% thickness or 5% thickness.

[00177] In certain embodiments, the amount of active agent (e.g., opioid analgesic) released at 0.5 hour from a flattened dosage form deviates no more than about 10 % points, 15 % points or 20% points from the amount released at 0.5 hour from a non-flattened dosage form as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 5 37° C.

[00178] In alternative embodiments, the solid controlled release dosage form can be flattened without breaking, wherein the thickness of the dosage form after flattening corresponds to no more than about 60% of the thickness of the dosage form before flattening, or to no more than about 50% of the thickness of the dosage form before flattening, or to no more than about 40% of the thickness of the dosage form before flattening, or to no more than about 30% of the thickness of the dosage form before 10 flattening, or to no more than about 20% of the thickness of the dosage form before flattening, or to no more than about 10% of the thickness of the dosage form before 15 flattening.

USES

[00179] The present invention is further directed to the use of a purified neutral 20 acrylic polymer in the preparation of an oral solid dosage form, preferably as described herein.

[00180] The present invention is also directed to the use of a blend comprising a purified neutral acrylic polymer and an active agent and optionally polyethylene 25 oxide, in the preparation of an oral solid dosage form, preferably as described herein.

[00181] In certain embodiments the blend is in the form of a bulk powder. In certain 30 embodiments the blend comprises less than 20% (w/w) water or less than 10% (w/w) water, and preferably comprises less than 5 % (w/w) water or less than 3% (w/w) water. The blend may further comprise less than 10% (w/w) organic solvents,

preferably less than 5 % (w/w) organic solvents, most preferably less than 3% (w/w) or less than 1% (w/w) organic solvents.

[00182] The present invention is also directed to the use of a composition

5 comprising at least one neutral acrylic polymer, at least one active agent, from 0-8% (w/w) of water, and from 0-5 % (w/w) of organic solvents (e.g. methanol or ethanol), in the preparation of an oral solid dosage form. Preferably the composition further comprises a polyethylene oxide.

10 [00183] The present invention is also directed to the use of a solid composition comprising at least one neutral acrylic polymer, and at least one active agent, for the preparation of a solid oral pharmaceutical dosage form. Preferably the composition further comprises a polyethylene oxide.

15 [00184] The present invention is also directed to the use of an oral solid dosage form as described herein in the manufacture of a medicament for the treatment or prevention of a disease. The present invention is also directed to the use of an oral solid dosage form as described herein in the manufacture of a medicament for the treatment of pain, wherein the oral solid dosage form comprises an opioid agonist.

20 [00185] The present invention is also directed to an oral solid dosage form as described herein for use in the treatment of pain, wherein the oral solid dosage form comprises an opioid agonist.

25

FURTHER EMBODIMENTS

[00186] The present invention is also directed to the following further embodiments of items 1 to 102:

1. An oral solid dosage form comprising purified neutral acrylic polymer and a prophylactically or therapeutically effective amount of an active agent.
2. The oral solid dosage form of item 1, wherein the purified neutral acrylic polymer is derived from a dried neutral acrylic polymer aqueous dispersion.
3. The oral solid dosage form of item 1, wherein the purified neutral acrylic polymer is derived from a vacuum dried neutral acrylic polymer aqueous dispersion.
4. The oral solid dosage form of item 1, wherein the purified neutral acrylic polymer is derived from a lyophilized neutral acrylic polymer aqueous dispersion.
- 15 5. The oral solid dosage form of item 1, wherein the purified neutral acrylic polymer is derived from a pan dried neutral acrylic polymer aqueous dispersion.
6. The oral solid dosage form of item 1, wherein the purified neutral acrylic polymer is derived from an oven dried neutral acrylic polymer aqueous dispersion.
- 20 7. The oral solid dosage form of any of items 2-6, wherein the purified neutral acrylic polymer is milled.
- 25 8. The oral solid dosage form of item 1, wherein the purified neutral acrylic polymer is derived from an aqueous dispersion comprising from about 20% (w/w) to about 50% (w/w) neutral acrylic polymer.

9. The oral solid dosage form of item 1, wherein the purified neutral acrylic polymer is derived from an aqueous suspension comprising from about 30%(w/w) to about 40%(w/w) neutral acrylic polymer.
- 5 10. The oral solid dosage form of item 1, comprising an effective amount of the purified neutral acrylic polymer to provide a controlled release of the active agent.
11. The oral solid dosage form of item 1, comprising from about 10% (w/w) to 10 about 90% (w/w) purified neutral acrylic polymer.
12. The oral solid dosage form of item 1, comprising from about 20% (w/w) to about 80% (w/w) purified neutral acrylic polymer.
- 15 13. The oral solid dosage form of item 1, comprising from about 30% (w/w) to about 70% (w/w) purified neutral acrylic polymer.
14. The oral solid dosage form of item 1, comprising from about 40% (w/w) to about 60% (w/w) purified neutral acrylic polymer.
- 20 15. The oral solid dosage form of item 1, wherein the purified neutral acrylic polymer comprises less than about 5% (w/w) water.
16. The oral solid dosage form of item 1, wherein the purified neutral acrylic 25 polymer comprises less than about 3% (w/w) water.
17. The oral solid dosage form of item 1, wherein the purified neutral acrylic polymer comprises less than about 1% (w/w) water.

18. The oral solid dosage form of item 1, comprising from about 1% (w/w) to about 50% (w/w) active agent.
19. The oral solid dosage form of item 1, comprising from about 5% (w/w) to about 5 40% (w/w) active agent.
20. The oral solid dosage form of item 1, comprising from about 10% (w/w) to about 30% (w/w) active agent.
- 10 21. The oral solid dosage form of item 1, comprising from about 15% (w/w) to about 25% (w/w) active agent.
22. The oral solid dosage form of item 1, further comprising at least one excipient selected from the group consisting of polymers, poloxamers, bulking agents, 15 release modifying agents, plasticizers, stabilizers, diluents, lubricants, binders, granulating aids, colorants, flavorants, and glidants.
23. The oral solid dosage form of item 22, wherein the excipient is a polymer.
- 20 24. The oral solid dosage form of item 23, wherein the polymer is polyethylene oxide.
- 25 25. The oral solid dosage form of item 24, wherein the polyethylene oxide is a low molecular weight polyethylene oxide.
26. The oral solid dosage form of item 25, wherein the polyethylene oxide has an average molecular weight from about 10,000 Daltons to about 750,000 Daltons.
- 30 27. The oral solid dosage form of item 25, wherein the polyethylene oxide has an average molecular weight from about 50,000 Daltons to about 500,000 Daltons.

28. The oral solid dosage form of item 25, wherein the polyethylene oxide has an average molecular weight from about 75,000 Daltons to about 300,000 Daltons.
- 5 29. The oral solid dosage form of item 24, comprising from about 5% (w/w) to about 60% (w/w) polyethylene oxide.
30. The oral solid dosage form of item 24, comprising from about 10% (w/w) to about 50% (w/w) polyethylene oxide.
- 10 31. The oral solid dosage form of item 24, comprising from about 15% (w/w) to about 40% (w/w) polyethylene oxide.
- 15 32. The oral solid dosage form of item 24, comprising from about 20% (w/w) to about 30% (w/w) polyethylene oxide.
- 20 33. The oral solid dosage form item 24, comprising from about 10%(w/w) to about 90%(w/w) purified neutral acrylic polymer, from about 1%(w/w) to about 50%(w/w) active agent and from about 5%(w/w) to about 60%(w/w) polyethylene oxide.
- 25 34. The oral solid dosage form item 24, comprising from about 20%(w/w) to about 80%(w/w) purified neutral acrylic polymer, from about 5%(w/w) to about 40%(w/w) active agent and from about 10%(w/w) to about 50%(w/w) polyethylene oxide.
- 30 35. The oral solid dosage form item 24, comprising from about 30%(w/w) to about 70%(w/w) purified neutral acrylic polymer, from about 10%(w/w) to about 30%(w/w) active agent and from about 15%(w/w) to about 40%(w/w) polyethylene oxide.

36. The oral solid dosage form of item 24, comprising from about 40%(w/w) to about 60%(w/w) purified neutral acrylic polymer, from about 15%(w/w) to about 25%(w/w) active agent and from about 20%(w/w) to about 30%(w/w) 5 polyethylene oxide.
37. The oral solid dosage form of item 1, wherein the purified neutral acrylic polymer and the active agent are in the form of an extruded blend.
- 10 38. The oral solid dosage form of item 24, wherein the purified neutral acrylic polymer, the active agent and the polyethylene oxide are in the form of an extruded blend.
- 15 39. The oral solid dosage form of item 37 or 38, wherein the extruded blend is in the form of a unitary dosage form.
40. The oral solid dosage form of item 37 or 38, wherein the extruded blend is in the form of multiparticulates.
- 20 41. The oral solid dosage form of item 40, wherein the multiparticulates are in the form of pellets.
- 25 42. The oral solid dosage form of item 41, wherein the pellets have a mean diameter from about 0.1 mm to about 5 mm and a mean height from about 0.1 mm to about 5 mm.
43. The oral solid dosage form of item 41, wherein the pellets have a mean diameter from about 0.5 mm to about 4 mm and a mean height from about 0.5 mm to about 4 mm.

44. The oral solid dosage form of item 41, wherein the pellets have a mean diameter from about 1 mm to about 3 mm and a mean height from about 0.5 mm to about 4 mm.
- 5 45. The oral solid dosage form of item 41, wherein the pellets have a mean diameter from about 1.5 mm to about 2.5 mm and a mean height from about 1.5 mm to about 2.5 mm.
- 10 46. The oral solid dosage form of item 40, wherein the particles are in the form of spheres.
47. The oral solid dosage form of item 36, wherein the spheres have a mean diameter from about 0.1 mm to about 5 mm.
- 15 48. The oral solid dosage form of item 36, wherein the spheres have a mean diameter from about 0.5 mm to about 4 mm.
49. The oral solid dosage form of item 36, wherein the spheres have a mean diameter from about 1 mm to about 3 mm.
- 20 50. The oral solid dosage form of item 36, wherein the spheres have a mean diameter from about 1.5 mm to about 2.5 mm.
51. The oral solid dosage form of item 40, wherein the multiparticulates are contained in a pharmaceutically acceptable capsule.
- 25 52. The oral solid dosage form of item 40, wherein the multiparticulates are compressed.

53. The oral solid dosage form of item 1 or 24, wherein the active agent is selected from the group consisting of ACE inhibitors, adenohypophoseal hormones, adrenergic neuron blocking agents, adrenocortical steroids, inhibitors of the biosynthesis of adrenocortical steroids, alpha-adrenergic agonists, alpha-
5 adrenergic antagonists, selective alpha-two-adrenergic agonists, analgesics, antipyretics, anti-inflammatory agents, androgens, local and general anesthetics, antiaddictive agents, antiandrogens, antiarrhythmic agents, antiasthmatic agents, anticholinergic agents, anticholinesterase agents, anticoagulants, antidiabetic agents, antidiarrheal agents, antidiuretic, antiemetic and prokinetic agents, 10 antiepileptic agents, antiestrogens, antifungal agents, antihypertensive agents, antimicrobial agents, antimigraine agents, antimuscarinic agents, antineoplastic agents, antiparasitic agents, antiparkinson's agents, antiplatelet agents, antiprogestins, antischizophrenia agents, antithyroid agents, antitussives, 15 antiviral agents, atypical antidepressants, azaspirodecanediones, barbituates, benzodiazepines, benzothiadiazides, beta-adrenergic agonists, beta-adrenergic antagonists, selective beta-one-adrenergic antagonists, selective beta-two-adrenergic agonists, bile salts, agents affecting volume and composition of body fluids, butyrophenones, agents affecting calcification, calcium channel blockers, cardiovascular drugs, catecholamines and sympathomimetic drugs, cholinergic 20 agonists, cholinesterase reactivators, contraceptive agents, dermatological agents, diphenylbutylpiperidines, diuretics, ergot alkaloids, estrogens, ganglionic blocking agents, ganglionic stimulating agents, hydantoins, agents for control of gastric acidity and treatment of peptic ulcers, hematopoietic agents, histamines, histamine antagonists, hormones, 5-hydroxytryptamine antagonists, drugs for the 25 treatment of hyperlipoproteinemia, hypnotics, sedatives, immunosuppressive agents, laxatives, methylxanthines, monamine oxidase inhibitors, neuromuscular blocking agents, organic nitrates, opioid agonists, opioid antagonists, pancreatic enzymes, phenothiazines, progestins, prostaglandins, agents for the treatment of psychiatric disorders, retinoids, sodium channel 30 blockers, agents for spasticity and acute muscle spasms, succinimides,

testosterones, thioxanthines, thrombolytic agents, thyroid agents, tricyclic antidepressants, inhibitors of tubular transport of organic compounds, drugs affecting uterine motility, vasodilators, vitamins, and mixtures thereof.

5 54. The oral solid dosage form of item 1 or 24, wherein the active agent is an opioid agonist.

55. The oral solid dosage form of item 54, wherein the opioid agonist is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, 10 benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diamprodime, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, 15 heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, 20 pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof.

25 56. The oral solid dosage form of item 54, wherein the opioid agonist is selected from the group consisting of codeine, fentanyl, hydromorphone, hydrocodone, oxycodone, dihydrocodeine, dihydromorphine, morphine, tramadol, oxymorphone, pharmaceutically acceptable salts thereof, and mixture thereof.

57. The oral solid dosage form of item 54, wherein the opioid agonist is oxycodone or a pharmaceutically acceptable salt thereof.
58. The oral solid dosage form of item 1 or 24, wherein the active agent is an opioid antagonist.
59. The oral solid dosage form of item 58, wherein the opioid antagonist is selected from the group consisting of amiphenazole, naltrexone, methylnaltrexone, naloxone, nalbuphine, nalorphine, nalorphine dinicotinate, nalmefene, nadide, levallorphan, cyclozocine, pharmaceutically acceptable salts thereof and mixtures thereof.
60. The oral solid dosage form of item 1 or 24, wherein the active agent is a non-opioid analgesic.
- 15 61. The oral solid dosage form of item 60, wherein the non-opioid analgesic is a non-steroidal anti-inflammatory agent selected from the group consisting of aspirin, celecoxib, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, pharmaceutically acceptable salts thereof and mixtures thereof.
- 20 25 62. The oral solid dosage form of item 54, wherein the amount of opioid agonist thereof released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is not more than the amount of opioid agonist

released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) using USP Apparatus II at 50 rpm.

- 5 63. The oral solid dosage form of item 54, wherein the amount of opioid agonist thereof released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is less than the amount of opioid agonist released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) using USP Apparatus II at 50 rpm.
- 10 64. The oral solid dosage form of item 54, wherein the amount of opioid agonist thereof released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is within 25%(w/w) of the amount of opioid agonist released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) using USP Apparatus II at 50 rpm.
- 15 65. The oral solid dosage form of item 54, wherein the amount of opioid agonist thereof released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is within 10%(w/w) of the amount of opioid agonist released at 1 hour in 900 mL 0.1 N HCl (pH 1.5) using USP Apparatus II at 50 rpm.
- 20 66. The oral solid dosage form of item 54, wherein the amount of opioid agonist thereof released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is not more than the amount of opioid agonist released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) using USP Apparatus II at 50 rpm.
- 25 67. The oral solid dosage form of item 54, wherein the amount of opioid agonist thereof released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is less than the amount of opioid agonist released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) using USP Apparatus II at 50 rpm.

68. The oral solid dosage form of item 54, wherein the amount of opioid agonist thereof released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is within 25%(w/w) of the amount of opioid agonist released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) using USP Apparatus II at 50 rpm.
5
69. The oral solid dosage form of item 54, wherein the amount of opioid agonist thereof released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is within 10%(w/w) of the amount of opioid agonist released at 2 hour in 900 mL 0.1 N HCl (pH 1.5) using USP Apparatus II at 50 rpm.
10
70. The oral solid dosage form of item 54, wherein the amount of opioid agonist thereof released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is not more than the amount of opioid agonist released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) using USP Apparatus II at 50 rpm.
15
71. The oral solid dosage form of item 54, wherein the amount of opioid agonist thereof released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is less than the amount of opioid agonist released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) using USP Apparatus II at 50 rpm.
20
72. The oral solid dosage form of item 54, wherein the amount of opioid agonist thereof released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is within 25%(w/w) of the amount of opioid agonist released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) using USP Apparatus II at 50 rpm.
25

73. The oral solid dosage form of item 54, wherein the amount of opioid agonist thereof released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) with 40% EtOH using USP Apparatus II at 50 rpm is within 10%(w/w) of the amount of opioid agonist released at 4 hour in 900 mL 0.1 N HCl (pH 1.5) using USP Apparatus II at 50 rpm.

5

74. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 1 hour is from about 10%(w/w) to about 30%(w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

10

75. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 2 hours is from about 25%(w/w) to about 50%(w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

15

76. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 4 hours is from about 40%(w/w) to about 80%(w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

20

77. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 8 hours is from about 65%(w/w) to about 95%(w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

25

78. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 12 hours is greater than about 80%(w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

30

79. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 1 hour from about 15%(w/w) to about 25%(w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

5

80. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 2 hours is from about 30%(w/w) to about 40%(w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

10

81. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 4 hours is from about 55%(w/w) to about 75%(w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

15

82. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 8 hours is from about 75%(w/w) to about 85%(w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

20

83. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 12 hours is greater than about 90%(w/w) as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

25

84. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 1 hour is from about 10%(w/w) to about 30%(w/w); the amount of opioid agonist released at 2 hours is from about 25%(w/w) to about 50%(w/w); the amount of opioid agonist released at 4 hours is from about 40%(w/w) to

30

about 80%(w/w); the amount of opioid agonist released at 8 hours is from about 65%(w/w) to about 95%(w/w) and the amount of opioid agonist released at 12 hours is greater than about 80%(w/w); as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

5

85. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 1 hour is from about 15%(w/w) to about 25%(w/w); the amount of opioid agonist released at 2 hours is from about 30%(w/w) to about 40%(w/w); the amount of opioid agonist released at 4 hours is from about 55%(w/w) to about 75%(w/w); the amount of opioid agonist released at 8 hours is from about 75%(w/w) to about 85%(w/w) and the amount of opioid agonist released at 12 hours is greater than about 90%(w/w); as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

10

15

86. The oral solid dosage form of item 54, wherein the dosage form can be flattened without breaking, wherein the thickness of the dosage form after flattening corresponds to no more than about 60% of the thickness of the dosage form before flattening.

20

87. The oral solid dosage form of item 54, wherein the dosage form can be flattened without breaking, wherein the thickness of the dosage form after flattening corresponds to no more than about 50% of the thickness of the dosage form before flattening.

25

88. The oral solid dosage form of item 54, wherein the dosage form can be flattened without breaking, wherein the thickness of the dosage form after flattening corresponds to no more than about 40% of the thickness of the dosage form before flattening.

30

89. The oral solid dosage form of item 54, wherein the dosage form can be flattened without breaking, wherein the thickness of the dosage form after flattening corresponds to no more than about 30% of the thickness of the dosage form before flattening.

5

90. The oral solid dosage form of item 54, wherein the dosage form can be flattened without breaking, wherein the thickness of the dosage form after flattening corresponds to no more than about 20% of the thickness of the dosage form before flattening.

10

91. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 0.5 hour from a flattened dosage form deviates no more than about 20% points from a non-flattened dosage form as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

15

92. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 0.5 hour from a flattened dosage form deviates no more than about 15% points from a non-flattened dosage form as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

20

93. The oral solid dosage form of item 54, wherein the amount of opioid agonist released at 0.5 hour from a flattened dosage form deviates no more than about 10% points from a non-flattened dosage form as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

25

94. A method of treating a disease or condition comprising administering an oral solid dosage form of any of items 1-93 to a patient in need thereof.
- 5 90. A method of treating pain comprising administering an oral solid dosage form of any of items 54-57 and 60-93 to a patient in need thereof.
- 10 95. A method of preparing an oral solid dosage form of any of items 1-23, 37 and 39-93 comprising (i) mixing in an extruder the purified neutral acrylic polymer and the active agent; (ii) extruding the mixture as a strand; (iii) cooling the strand; and (iv) dividing the strand into unit doses.
- 15 96. A method of preparing an oral solid dosage form of any of items 24-36 and 38-93 comprising (i) mixing in an extruder the purified neutral acrylic polymer, the active agent; and the polyethylene oxide (ii) extruding the mixture as a strand; (iii) cooling the strand; and (iv) dividing the strand into unit doses.
97. Purified neutral acrylic polymer.
- 20 98. Vacuum dried neutral acrylic polymer.
99. Freeze dried neutral acrylic polymer.
- 25 100. A bulk powder comprising (i) purified neutral acrylic polymer and (ii) an active agent.
101. A bulk powder comprising (i) vacuum dried neutral acrylic polymer and (ii) an active agent.
- 30 102. A bulk powder comprising (i) freeze dried neutral acrylic polymer and (ii) an active agent.

[00187] The following examples are set forth to assist in understanding the invention and should not be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all 5 equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in formulation or minor changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

10

EXAMPLES

Example 1

[00188] The formulations of Example 1 were prepared in accordance with the 15 following ingredients of Table 1:

TABLE 1

Ingredient	Amt/unit (%)		Amt/unit (mg)		Amt/Batch (gm)	
	Sub-Lot A	Sub-Lot B	Sub-Lot A	Sub-Lot B	Sub-Lot A	Sub-Lot B
Oxycodone HCl	20%	20%	30	30	100	100
Eudragit NE 40 D Solids Vacuum Dried	60%	60%	90	90	300	300
PEO N10	20%	--	30	--	100	--
Lutrol Micro 127 MP	--	20%	--	30	--	100
Total	100%	100%	150	150	500	500

The formulations were prepared according to the following procedures:

1. **Drying and Milling.**

[00189] Approximately 700 grams of Eudragit NE 40D Solids was prepared by 5 drying approximately 1,750 grams of aqueous Eudragit NE 40D dispersion in a vacuum oven to yield sheets of polymer. The sheets of polymer were sliced with a paper cutter into 2.5 inch squares. The squares were then milled in a Waring blender with dry ice. Then, 600 grams of the milled polymer was passed through a #14 mesh screen.

10

2. **Blending.**

[00190] Sub-Lot A. The above-indicated amounts of Eudragit NE 40D and PEO N10 were weighed into a tared 16-ounce jar. The jar was rotated until the materials 15 were sufficiently blended. Then, 100 grams of oxycodone HCl was added to the jar, and the jar was further rotated until a uniform blend was achieved.

[00191] Sub-Lot B. The above-indicated amounts of Eudragit NE 40D and Lutrol were weighed into a tared plastic bag and blended for about 20 seconds. Then, 20 100 grams of oxycodone HCl was added and the mixture was blended for an additional 30 seconds.

3. **Extrusion.** The blends from above were extruded using a ZSE Extruder according to the following parameters in Table 1A:

25

TABLE 1A

Time	Sub-Lot B, Run 1	Sub-Lot B, Run 2	Sub-Lot B, Run 3	Sub-Lot A, Run 1	Sub-Lot A, Run 2	Sub-Lot A, Run 3
Screw Speed (rpm)	50	50	50	50	50	50
Motor Torque (%)	24%	24%	27%	53%	60%	55%
Melt Pressure (psi)	370	640	1060	630	2520	1560
Melt Temp (°C)	108	111	111	103	103	101
Vacuum (m bar)	---	953	953	946	946	944
Feed Rate (g/min)	24	24	24	24	24	24
Temp (°C)						
Zone 1	12.4	12.4	12.4	12.3	13.1	13.8
Zone 2	40	40	40	40	40	40
Zone 3	75	75	75	75	75	75
Zone 4	100	100	100	100	100	100
Zone 5	100	100	100	100	100	100
Zone 6	100	100	100	100	100	100
Zone 7	100	100	100	100	100	100
Zone 8	100	100	100	100	100	100
Zone 9	100	100	100	100	100	100
Zone 10	100	100	100	100	100	100
Zone 11 Main Gate Adapter (MGA)	100	103	104.7	103.3	102.7	99.5
Zone 12 Die	100	91.9	111.5	100.8	93.9	100.6
Strand Thickness (mm) and Die type	No Die .5 inch rod collected	Vary 22 holes x 2 mm	Vary 20 holes x 1mm	No Die .5 inch strand collected	Vary 20 holes x 1mm	Vary 22 holes x 2mm

The bulk extrudates from the various runs comprised .5 inch strands, 3mm strands, 5 and 1mm strands.

4. **Tablet/pellet preparation.** Individual doses were created as follows:

[00192] **Sub-Lot A.** The following tablets/pellets were made using the Sub-Lot A 10 blend/extrudate:

- Four .25 inch tablets were made by compressing the pre-extrusion blend. Of these, two tablets were cured in the loss on drying (LOD) tester for 30 minutes at 105°C. The weight of the tablets ranged from 105.6 mg to 113.5 mg, and the thickness ranged from 3.83 mm to 4.30 mm.

- .25 inch tablets were punched out from a slice cut from a .5 inch strands from sub-lot A, run 1 using an F3 press under high pressure. The weight of the tablets ranged from 74.1 mg to 105.3 mg, and the thickness ranged from 5 2.30 mm to 3.24 mm.
- 2mm x 2mm pellets were cut from sections of the 1 mm bulk strands from sub-lot A, run 2 that had a diameter of about 2mm (due to die swell).

10 10 [00193] Sub-Lot B. The following tablets/pellets were made using the Sub-Lot B extrudate:

- .25 inch tablets were punched out from a slice cut from a .5 inch strands from sub-lot B, run 1 using an F3 press under high pressure. The weight of the tablets ranged from 86.8 mg to 112.8 mg, and the thickness ranged from 15 2.72 mm to 3.65 mm.
- 13/32 inch (0.4063 inch) tablets were punched out from a slice cut from a .5 inch strands from sub-lot B, run 1. The weight of the tablets ranged from 324.7 mg to 536.7 mg, and the thickness ranged from 3.75 mm to 6.67 mm.

20 20 • 2mm x 2mm pellets were cut from sections of the 1mm bulk extrudate from sub-lot B, run 3 where the diameter had expanded to about 2mm (due to die swell).

25 5. **Dissolution Testing**. Tablets and pellets from Sub-Lot A and Sub-Lot B were subjected to dissolution testing and the results are set forth in Table 1B. The dissolution parameters were as follows:

Media: SGF pH actual of 1.15 (target 1.2). Baskets @ 100 RPM in 900 ml of SGF. The system was a UV flow through. Data was normalized by setting the signal for 30 2mm x 2mm pellets from sample B, run 3, at 360 min to 100% released. The other curves were adjusted by sample weight relative to the sample weight of 2mm x 2mm

- 74 -

pellets from subplot B, run 3, corresponding to 40 mg active. These all had the same active agent concentration of about 20%.

TABLE 1B

Time (min)	Sub-Lot A .25 inch tab 20 mg (from rod)	Sub-Lot A .25 inch tab 20 mg (from rod)	Sub-Lot A 2mm x 2mm pellets 40 mg	Sub-Lot A 2mm x 2mm pellets 40 mg	Sub-Lot B .25 inch tab 20 mg	Sub-Lot B 13/32 inch tab 90 mg	Sub-Lot B 13/32 inch tab 90 mg	Sub-Lot B 2mm x 2mm pellets 40 mg
0	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
30	12.1%	11.9%	10.7%	11.2%	26.5%	14.9%	14.0%	61.3%
60	16.3%	15.7%	14.7%	15.2%	36.1%	20.9%	20.2%	81.0%
120	21.6%	20.6%	19.6%	20.1%	47.5%	29.0%	28.0%	96.3%
180	25.1%	23.9%	22.9%	23.3%	55.0%	34.5%	33.3%	99.5%
240	27.8%	26.3%	25.3%	25.7%	60.4%	38.4%	37.5%	100.0%
480	34.4%	32.3%	31.4%	31.5%	74.1%	48.8%	48.1%	100.0%
720	38.1%	35.8%	35.1%	35.0%	82.0%	55.1%	54.4%	100.4%
960	40.7%	38.1%	37.7%	37.5%	85.3%	59.9%	58.8%	100.1%
1200	42.4%	39.8%	39.6%	39.4%	86.6%	63.5%	62.4%	100.0%
1440	43.8%	41.0%	41.1%	40.8%	87.1%	66.7%	65.4%	99.7%
1680	43.4%	41.1%	41.8%	41.7%	86.9%	69.0%	67.4%	99.4%
1920	44.4%	42.1%	42.9%	42.7%	87.0%	71.7%	69.8%	99.7%
2372	45.7%	43.3%	44.2%	44.0%	86.8%	74.9%	72.7%	100.2%

5

[00194] Figure 1 depicts a graphical view of the dissolution data for the sample tablets and pellets of sub-lots A and B. The target identified on the graph is the current reformulated Oxycontin®. The dissolution of the Sub-Lot A preparations may be increased with the inclusion of a screening step after blending.

10

[00195] The dissolution of the 13/32 inch tablet from Sub-Lot B is slower than the dissolution of the .25 inch tablet from Sub-Lot B. This demonstrates that a dissolution can be targeted by selecting and/or adjusting the shape of the tablet or pellet.

15

5 - 75 -

Example 2

[00196] The formulations of Example 2 were prepared in accordance with the following ingredients of Table 2:

10 TABLE 2

Ingredient (by % and grams)	Sub-Lot A	Sub-Lot B	Sub-Lot C	Sub-Lot D	Sub-Lot E	Sub-Lot F
Oxycodone HCl	10.00% 40.00 g	10.00% 40.00 g	20.00% 80.00 g	20.00% 80.00 g	16.6667% 66.66668 g	16.6667% 66.66668 g
Eudragit NE Solids Oven Dried	40.00% 16.00 g	50.00% 200.00 g	40.00% 160.00 g	50.00% 200.00 g	46.6667% 186.66668 g	36.6667% 146.66668 g
PEO N10	50.00% 200.00 g	40.00% 160.00 g	40.00% 160.00 g	30.00% 120.00 g	36.6667% 146.66668 g	46.6667% 186.66668 g
Total	100.00% 400.00 g	100.00% 400.00 g	100.00% 400.00 g	100.00% 400.00 g	100.00% 400.00004 g	100.00% 400.00004 g

15 The formulations were prepared by the following procedures:

1. **Drying.**

10

[00197] Eudragit NE was dried in a hot pack oven at 55°C overnight in a layer about 2 mm thick.

15 2. **Milling.**

15

[00198] The dried Eudragit NE was sliced into small pieces measuring approximately 3 cm² and milled with dry ice in a Waring blender. Then, the milled Eudragit NE was screened through a #18 U.S. mesh screen.

3. Blending.

[00199] For each sub-lot, the above-indicated amounts of Eudragit NE and PEO N10 were added to a 32-ounce amber glass bottle and blended by rotating the bottle for 30 seconds. Then, the oxycodone HCl was added to the bottle and the bottle was further rotated for 30 seconds to achieve a uniform blend. Each blend was screened through a #12 mesh screen and then further blended for another 30 seconds prior to extrusion.

10

4. Extrusion.

[00200] The blends from above were extruded using a ZSE Extruder according to the following parameters in Table 2A:

15

TABLE 2A

- 77 -

Zone 11 MGA	98.1	102.3	101.2	101.3	99.5	98.8	103.4	98.6	104.0
Zone 12 Die	No die	92.6	95	No die	95.5	101.3	No die	108.5	107.2
Strand Thickness (mm) and Die type	.5 inch rod No die	Vary 2mm x 22 holes	Vary 1mm x 20 holes	.5 inch Rod No die	Vary 2mm x 22 holes	Vary 1mm x 20 holes	.5 inch rod No die	2 mm 2mm x 22 holes	1mm 1mm x 20 holes

	Sub-Lot C, Run 1	Sub-Lot C, Run 2	Sub-Lot C, Run 3	Sub-Lot F, Run 1	Sub-Lot F, Run 2	Sub-Lot F, Run 3	Sub-Lot B, Run 1	Sub-Lot B, Run 2	Sub-Lot B, Run 3	
Screw Speed (rpm)	50	50	50	50	50	50	50	50	50	
Motor Torque (%)	55	55	55	55	55	55	56	54	55	
Melt Pressure (psl)	300	500	1100	300	430	950	300	800	1680	
Melt Temp (°C)	108	106	108	105	105	105	108	108	108	
Vacuum (m bar)	944	944	944	935	934	936	943	944	944	
Feed Rate (g/min)	24	24	24	24	24	24	24	24	24	
Temp (°C)	Zone 1	16.7	16.5	16.4	16.3	16.3	16.6	19.4	18.6	17.3
	Zone 2	40	40	40	40	40	40	40.8	40.4	40.4
	Zone 3	100	100	100	100	100	100	75	75	75
	Zone 4	100	100	100	100	100	100	100	100	100
	Zone 5	100	100	100	100	100	100	100	100	100
	Zone 6	100	100	100	100	100	100	100	100	100
	Zone 7	100	100	100	100	100	100	100	100	100
	Zone 8	100	100	100	100	100	100	100	100	100
	Zone 9	100	100	100	100	100	100	100	100	100
	Zone 10	100	100	100	100	100	100	100	100	100
	Zone 11 MGA	102.8	98.9	101.8	102.3	100	100	103.8	98.5	102.3
	Zone 12 Die	No die	115.7	107.0	No die	107	100	99.8	90.2	102.2
	Strand Thickness (mm)	.5 inch Rod	2 mm	1 mm	.5 inch Rod	2 mm	1 mm	.5 inch rod	2 mm	1 mm

The bulk extrudates from the various runs comprised various thicknesses, including .5 inch rods, 3mm strands, 2mm strands, and 1mm strands.

5

5. Tablet/pellet preparation.

[00201] Individual doses were created as follows:

[00202] Sub-Lot B

- .25 inch tablets were cut from the bulk extrudate of sub-lot B, run 1. The tablets had a weight in the range of 161.3 mg to 172.7 mg, and a thickness in the range of 5.31 mm to 5.73 mm.
- 1mm x 1mm pellets, and 2mm x 2mm pellets were also obtained from the strands of bulk extrudate from sub-lot B, runs 2 and 3.

10 [00203] Sub-Lot C

- The .5 inch rod from sub-lot C, run 1, above was divided into .25 inch tablets. The tablets had a weight in the range of 152.0 mg to 185.8 mg, and a thickness in the range of 4.95 mm to 6.43 mm.
- 1mm x 1mm pellets, and 2mm x 2mm pellets were also obtained from the strands of bulk extrudate from sub-lot C, runs 2 and 3.

[00204] Sub-Lot D

- The .5 inch rod from sub-lot D, run 1 above was divided into .25 inch tablets. The tablets had a weight in the range of 148.9 mg to 178.6 mg, and had a thickness in the range of 4.91 mm to 5.66 mm.
- Pellets measuring approximately 1mm x 1mm and approximately 2mm x 2mm were cut by hand with a razor blade from strands of bulk extrudate from sub-lot D, runs 2 and 3.

[00205] Sub-Lot E

- Pellets measuring approximately 1mm x 1mm and approximately 2mm x 2mm were cut by hand with a razor blade from strands of bulk extrudate from sub-lot E, runs 2 and 3.

- .25 inch tablets were also obtained from the .5 inch rod of bulk extrudate from sub-lot E, run 1.

5 [00206] Sub-Lot F

- The .5 inch rod from sub-lot F, run 1, was divided into .25 inch tablets. The tablets had a weight in the range of 156.7 mg and 180.2 mg, and a thickness in the range of 5.37 mm and 6.31 mm.
- 10 • .25 inch hot molded tablets were also made using the extrudate from sub-lot F, run 1.

Example 3

15 [00207] The formulations of Example 3 were prepared in accordance with the following ingredients of Table 3:

- 80 -

TABLE 3

Ingredient Wt in (g) and by %	Sub-Lot A	Sub-Lot B	Sub-Lot C	Sub-Lot D
Oxycodone HCl	80.00 g 20.00%	60.00 g 15.00%	47.10 g 12.73%	63.12 g 15.78%
Eudragit NE Solids Oven Dried	220.00 g 55.00%	220.00 g 55.00%	222.00 g 60.00%	231.52 g 57.88%
PEO N10	100.00 g 25.00%	120.00 g 30.00%	100.90 g 27.27%	105.36 g 26.34%
Total	400.00 g 100.00%	400.00 g 100.00%	370.00 g 100.00%	400.00 g 100.00%

The formulations were prepared by the following procedures:

5 1. Drying.

[00208] Eudragit NE was dried into thin sheets in a hot pack oven overnight at 55°C.

10 2. Milling.

[00209] The dried Eudragit NE was milled with dry ice. The milled Eudragit NE was then passed through a #14 mesh screen.

15 3. Blending.

[00210] For each sub-lot, the above-indicated amounts were blended in a jar. The PEO and Eudragit NE were first blended for 20 seconds. Then the oxycodone HCl was added, and the mixture blended for another 20 seconds. The blend was passed through a #8 US mesh screen prior to extrusion.

4. **Extrusion.**

[00211] The blends from above were extruded using a ZSE Extruder according to
 5 the following parameters in Table 3A:

TABLE 3A

	Sub-Lot A, Run 1	Sub-Lot A, Run 2	Sub-Lot A, Run 3	Sub-Lot B, Run 1	Sub-Lot B, Run 2	Sub-Lot B, Run 3
Screw Speed (rpm)	50	50	50	50	50	50
Motor Torque (%)	60%	61%	65%	52%	52%	52%
Melt Pressure (psi)	550	1000	2020	500	1080	1550
Melt Temp (°C)	105	111	109	110	110	109
Vacuum (m bar)	933	933	933	935	935	935
Feed Rate (g/min)	24	24	24	24	24	24
Temp (°C)	Zone 1	16.3	17.6	17.0	18.2	19.9
	Zone 2	40	40	40	40	40
	Zone 3	100	100	100	100	100
	Zone 4	100	100	100	100	100
	Zone 5	100	100	100	100	100
	Zone 6	100	100	100	100	100
	Zone 7	100	100	100	100	100
	Zone 8	100	100	100	100	100
	Zone 9	100	100	100	100	100
	Zone 10	100	100	100	100	100
	Zone 11	97.0	106.0	99.0	103.5	9.5
	MGA					97.7
Zone 12 Die	No DIE	2 mm 92.1	100.8	No DIE 100.7	100.8	97
Strand Thickness (mm)	.5 inch Rod No die	2 mm	1 mm	.5 inch Rod No die	1 mm	2 mm

	Sub-Lot C, Run 1	Sub-Lot C, Run 2	Sub-Lot C, Run 3	Sub-Lot D, Run 1	Sub-Lot D, Run 2	Sub-Lot D, Run 3
Screw Speed (rpm)	50	50	50	50	50	50
Motor Torque (%)	50%	51%	51%	50%	50%	58%
Melt Pressure (psl)	600	1090	1860	520	1210	2400
Melt Temp (°C)	107	107	108	106	109	108
Vacuum (m bar)	936	936	936	942	941	942
Feed Rate (g/min)	24	24	24	24	24	24
Temp (°C)	Zone 1	15.8	16.0	18.1	15.9	16.3
	Zone 2	40	40	40	40	40
	Zone 3	100	100	100	100	100
	Zone 4	100	100	100	100	100
	Zone 5	100	100	100	100	100
	Zone 6	100	100	100	100	100
	Zone 7	100	100	100	100	100
	Zone 8	100	100	100	100	100
	Zone 9	100	100	100	100	100
	Zone 10	100	100	100	100	100
	Zone 11	104.7	107.2	98.3	101.2	98.1
	MGA					101.1
	Zone 12 Die	No DIE	104.5	101.8	No die	95
Strand Thickness (mm)	.5 inch rod	2 mm	1 mm	.5 inch rod	2mm x 22	1mm x 20
	No die					

The bulk extrudates from the various runs comprised .5 inch rods, 2mm strands, and 1mm strands.

5

5. Tablet/pellet preparation.

[00212] Individual doses were created as follows:

10 **[00213]** Sub-Lot A

- Pellets measuring approximately 2mm x 2mm were cut with a razor from the 2mm strand extrudate of sub-lot A, run 2.
- Pellets measuring approximately 1mm x 1mm were cut with a razor from the 1mm strand extrudate of sub-lot A, run 3.

15

[00214] Sub-Lot B

- Pellets measuring approximately 2mm x 2mm were cut with a razor from the 2mm strand extrudate of sub-lot B, run 3.

5

- Pellets measuring approximately 1mm x 1mm were cut with a razor from the 1mm strand extrudate of sub-lot B, run 2.

[00215] Sub-Lot C

10

- Pellets measuring approximately 2mm x 2mm were cut with a razor from the 2mm strand extrudate of sub-lot C, run 2.
- Pellets measuring approximately 1mm x 1mm were cut with a razor from the 1mm strand extrudate of sub-lot C, run 3.

15

[00216] Sub-Lot D

20

- Pellets measuring approximately 2mm x 2mm were cut with a razor from the 2mm strand extrudate of sub-lot D, run 2.
- Pellets measuring approximately 1mm x 1mm were cut with a razor from the 1mm strand extrudate of sub-lot D, run 3.
- .25 inch tablets were cut from the .5 inch rod extrudate of sub-lot D, run 1 and hot pressed.

25

Example 4

[00217] The formulations of Example 4 were prepared in accordance with the following ingredients of Table 4:

5

TABLE 4

Ingredient (%) and weight (g)	A	B	C
Oxycodone HCl	20.00% 80.00 g	15.00% 60.00 g	15.00% 59.90 g
Eudragit NE Solids Oven Dried	70.00% 280.00 g	75.00% 300.00 g	70.00% 280.00 g
PEO N10	10.00% 40.00 g	10.00% 40.00 g	15.00% 60.00 g
Total	100.00% 400.00 g	100.00% 400.00 g	100.00% 399.90 g

The formulations were prepared by the following procedures:

1. **Drying.**

10

[00218] Eudragit NE 40D was dried in an oven (e.g., a Hotpack®) at approx. 50°C until clear (approximately 6 hours). The sheet of dried polymer (approximately 1 mm thick) was cut into squares measuring about .5 inches with a paper cutter.

15 2. **Milling.**

[00219] The squares were milled in a Waring blender with dry ice and passed through a #14 U.S. mesh screen.

20 3. **Blending.**

[00220] For each sub-lot, the above-indicated amounts of milled Eudragit and PEO were added to a 32-ounce wide mouth jar and blended for approximately 1 minute. The oxycodone HCl was added, blended, and discharged through a US mesh screen

- 85 -

to remove any lumps that may have formed. The blend was then placed back into the jar and blended for an additional 1 minute.

4. Extrusion

5

[00221] The above blends were extruded using a ZSE Extruder according to the following parameters in Table 4A:

TABLE 4A

	Sub-Lot A, Run 1	Sub-Lot A, Run 2	Sub-Lot A, Run 3	Sub-Lot B, Run 1	Sub-Lot B, Run 2	Sub-Lot B, Run 3	Sub-Lot C, Run 1	Sub-Lot C, Run 2	Sub-Lot C, Run 3	
Screw Speed (rpm)	50	50	50	50	50	50	50	50	50	
Motor Torque (%)	55%	54%	57%	48%	52%	57%	52%	56%	67%	
Melt Pressure (psl)	700	1800	off scale	800	1750	off scale	800	1600	off scale	
Melt Temp (°C)	111	106	109	109	109	109	109	110	101	
Vacuum (m bar)	934	933	933	942	941	941	943	943	943	
Feed Rate (g/min)	24	24	24	24	24	24	24	24	24	
Temp (°C)	Zone 1	15.8	16.3	16.0	15.2	15.6	15.7	14.8	15.9	15.7
	Zone 2	100	40.6	39.3	40	40	40	40	40	40
	Zone 3	100	100	100	100	100	100	100	100	100
	Zone 4	100	100	100	100	100	100	100	100	100
	Zone 5	100	100	100	100	100	100	100	100	100
	Zone 6	100	100	100	100	100	100	100	100	100
	Zone 7	100	100	100	100	100	100	100	100	100
	Zone 8	100	100	100	100	100	100	100	100	100
	Zone 9	100	100	100	100	100	100	100	100	100
	Zone 10	100	100	100	100	100	99	100	100	100
	Zone 11	104	103	101.3	105.0	104.7	99	107.1	102	103.2
	MGA									
	Zone 12 Die	--	97.1	96.9	--	100.3	97.5	--	102.0	99.2
Strand Thickness (mm)	.5 inch Rod	2 mm	1 mm	.5 inch Rod	2 mm	1 mm	.5 inch Rod	2 mm	1 mm	

10 The extrudate included .5 inch rods, 1 mm strands, and 2mm strands.

5. **Pellet preparation**

[00222] Individual doses were created as follows:

5 [00223] Sub-Lot A

- Pellets measuring approximately 1mm x 1mm and 2mm x 2mm were cut by hand with a razor from the extruded strands of sub-lot A, runs 3 and 2.

[00224] Sub-Lot B

10

- Pellets measuring approximately 1mm x 1mm and 2mm x 2mm were cut by hand with a razor from the extruded strands of sub-lot B, runs 3 and 2.

[00225] Sub-Lot C

15

- Pellets measuring approximately 1mm x 1mm and 2mm x 2mm were cut by hand with a razor from the extruded strands of sub-lot B, runs 3 and 2.

6. **Pellet Milling**

[00226] Pellets from sub-lot C were milled in a Krupps mill in six 10-second bursts.

20

Figure 2 depicts the pellets before and after milling (Figure 2A depicts 1 mm x 1 mm pellets, figure 2B depicts 2 mm x 2 mm pellets).

Example 5

25 [00227] The formulations of Example 5 were prepared in accordance with the following ingredients of Table 5:

TABLE 5

Ingredient (%) and weight (g)	%	Amt/batch (g)
Oxycodone HCl	15.00%	120.000
Eudragit NE Solids, Oven Dried	70.00%	560.000
PEO N10	15.00%	120.000
Total	100.00%	800.000

The formulations were prepared by the following procedures:

5 1. Blending.

[00228] Dried and milled materials from Example 4 were placed into a glass jar in the amounts indicated above and blended for about 1 minute. The blend was then passed through a #8 U.S. mesh screen, returned to the jar, and blended for an 10 additional 1 minute.

2. Extrusion.

[00229] The blend was extruded on a ZSE Extruder using a 20 x 1 mm die plate 15 according to the following parameters in Table 5A:

TABLE 5A

	Run 1	Run 2	Run 3	Run 4	Run 5
Screw Speed (rpm)	50	50	50	50	50
Motor Torque (%)	3	43	43	43	43
Melt Pressure (psi)	--	--	2000	1750	1550
Melt Temp (°C)	112	112	112	125	131
Vacuum (m bar)	--	953	953	953	953
Feed Rate (g/min)	24	24	24	24	24
T E M P (°C)	Zone 1	12.8	14	14.2	18
	Zone 2	15	16.5	16.8	17.3
	Zone 3	15	15	15.5	15
	Zone 4	15	15	15	15
	Zone 5	50	50	50	50
	Zone 6	75	75	75	75
	Zone 7	100	100	100	100
	Zone 8	100	100	100	100
	Zone 9	100	100	100	100
	Zone 10	100	100	100	100

	Zone 11 MGA	106.1	105	105.4	115	125
	Zone 12 Die	105.7	105	109.4	118	128
	Strand Thickness (mm)	1mm	1mm	1mm	1mm	1mm

The parameters of this example were similar to those of Example 4 except a lower sheer screw design was used and the pelletization was by machine.

5 3. **Pellet Preparation; Dissolution and Tamper Resistance Testing.**

[00230] Two extruded strands with approximately a 1mm diameter were fed into a pelletizer machine to produce individual pellets. The pellets were then subject to dissolution and tamper resistance testing. Figure 3 depicts the dissolution of the 10 pellets of this example in (i) simulated gastric fluid (SGF) and (ii) (SGF) and ethanol (EtOH). The dissolution utilized 900 ml SGF with a Basket mesh size of 40 and a height of 25 mm at 100 RPM. Figure 4 depicts the tamper resistance of the pellets of this example, in which pellets in SGF were frozen and subjected to hammering at -4°C.

15

[00231] The present invention is not to be limited in scope by the specific embodiments disclosed in the examples, which are intended as illustrations of a few aspects of the invention, and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in 20 addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

CLAIMS

1. An oral solid dosage form comprising a purified neutral acrylic polymer and a prophylactically or therapeutically effective amount of an active agent.

5

2. The oral solid dosage form of claim 1, wherein the purified neutral acrylic polymer is obtained by drying a dispersion comprising a neutral acrylic polymer, and wherein the drying is preferably performed by vacuum drying, lyophilization, pan drying, oven drying, freeze drying and/or evaporation.

10

3. The oral solid dosage form of claim 2, wherein the purified neutral acrylic polymer is obtained by drying a dispersion comprising a neutral acrylic polymer and subsequent milling, preferably in the presence of dry ice.

15

4. The oral solid dosage form of claim 2 or 3, wherein the dispersion is an aqueous dispersion preferably comprising from about 20% (w/w) to about 50% (w/w) neutral acrylic polymer, more preferably comprising from about 30% (w/w) to about 40% (w/w) neutral acrylic polymer.

20

5. The oral solid dosage form of any one of claims 1 to 4, wherein the neutral acrylic polymer is a poly(meth)acrylate which does not contain free acid groups, amino groups or quaternary ammonium groups.

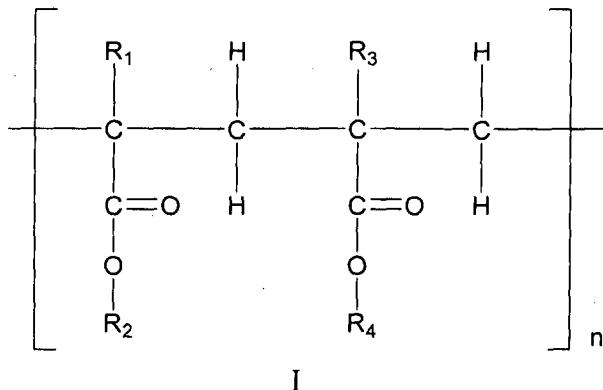
25

6. The oral solid dosage form of any one of claims 1 to 5, wherein the neutral acrylic polymer is a copolymer or homopolymer of acrylic acid (C₁-C₈) alkyl esters and/or methacrylic acid (C₁-C₈) alkyl esters, preferably a copolymer or homopolymer of acrylic acid (C₁-C₄) alkyl esters and/or methacrylic acid (C₁-C₄) alkyl esters.

30

7. The oral solid dosage form of any one of claims 1 to 5, wherein the neutral acrylic polymer is a copolymer having the structural formula I

- 90 -



wherein R₁ and R₃ are independently selected from H and methyl,
 R₂ and R₄ are independently selected from methyl, ethyl, propyl, butyl, pentyl, hexyl,
 5 heptyl or octyl,
 and n is selected such that the copolymer has a mean relative molecular mass of at
 least about 100,000, preferably of at least about 300,000, most preferably of from
 about 600,000 to about 1,000,000.

10 8. The oral solid dosage form of claim 7, wherein R₂ and R₄ are independently selected from methyl, ethyl, propyl, and butyl, preferably from methyl and ethyl.

9. The oral solid dosage form of any one of claims 1 to 8, wherein the neutral acrylic polymer is a copolymer of ethyl acrylate and methyl methacrylate.

15 10. The oral solid dosage form of any one of claims 1 to 9, wherein the neutral acrylic polymer has a mean relative molecular mass of from about 600,000 to about 1,000,000, preferably of from about 600,000 to 900,000, most preferably of about 660,000, 770,000 or 800,000.

20 11. The oral solid dosage form of any one of claims 1 to 10, comprising an effective amount of the purified neutral acrylic polymer to provide a controlled release of the active agent, and/or comprising from about 10% (w/w) to about 90% (w/w) purified neutral acrylic polymer, and/or comprising from about 20% (w/w) to

about 80% (w/w) purified neutral acrylic polymer, and/or comprising from about 30% (w/w) to about 80% (w/w) purified neutral acrylic polymer.

12. The oral solid dosage form of any one of claims 1 to 11, wherein the oral
5 solid dosage form comprises greater than about 35% (w/w), greater than about 40% (w/w), greater than about 50% (w/w), or greater than about 60% (w/w) of the purified neutral acrylic polymer, and preferably comprises from about 35 % (w/w) to about 90% (w/w) of purified neutral acrylic polymer or from about 40 % (w/w) to about 90 % (w/w) of purified neutral acrylic polymer or from about 50 % (w/w) to 10 about 90 % (w/w) of purified neutral acrylic polymer or from about 60 % (w/w) to about 90 % (w/w) of purified neutral acrylic polymer.

13. The oral solid dosage form of any one of claims 2 to 12, wherein the purified neutral acrylic polymer obtained after drying the dispersion comprising the neutral
15 acrylic polymer comprises less than about 20% (w/w) water or less than about 15% (w/w) water, preferably less than about 10% (w/w) water or less than about 5% (w/w) water, more preferably less than about 3% (w/w) water, and most preferably less than about 1% (w/w) water.

20 14. The oral solid dosage form of any one of claims 1 to 13, wherein the oral solid dosage form comprises from about 1% (w/w) to about 50% (w/w) active agent or from about 5% (w/w) to about 40% (w/w) active agent, preferably from about 10% (w/w) to about 30% (w/w) active agent and most preferably from about 15% (w/w) to about 25% (w/w) active agent.

25

15. The oral solid dosage form of any one of claims 1 to 14, wherein the oral solid dosage form further comprises at least one excipient selected from the group consisting of polymers, poloxamers, bulking agents, release modifying agents, plasticizers, stabilizers, diluents, lubricants, binders, granulating aids, colorants,
30 flavorants, and glidants.

16. The oral solid dosage form of any one of claims 1 to 15, wherein the oral solid dosage form further comprises a polymer.

5 17. The oral solid dosage form of claim 16, wherein the polymer is a polyethylene oxide.

18. The oral solid dosage form of claim 17, wherein the polyethylene oxide is a low molecular weight polyethylene oxide.

10

19. The oral solid dosage form of claim 17 or 18, wherein the polyethylene oxide has an approximate molecular weight of from about 10,000 Daltons to about 750,000 Daltons, based on rheological measurements, preferably an approximate molecular weight of from about 50,000 Daltons to about 500,000 Daltons, based on rheological 15 measurements, and most preferably an approximate molecular weight of from about 75,000 Daltons to about 300,000 Daltons, based on rheological measurements.

20. The oral solid dosage form of any one of claims 17 to 19, wherein the oral solid dosage form comprises from about 5% (w/w) to about 60% (w/w) polyethylene 20 oxide, preferably from about 10% (w/w) to about 50% (w/w) polyethylene oxide, most preferably from about 15% (w/w) to about 40% (w/w) polyethylene oxide.

21. The oral solid dosage form of any one of claims 17 to 20, comprising

25 - from about 10% (w/w) to about 90% (w/w) purified neutral acrylic polymer,
- from about 1% (w/w) to about 50% (w/w) active agent and
- from about 5% (w/w) to about 60% (w/w) polyethylene oxide;

or comprising

30 - from about 35% (w/w) to about 80% (w/w) purified neutral acrylic polymer,

- from about 5% (w/w) to about 40% (w/w) active agent and
- from about 10% (w/w) to about 50% (w/w) polyethylene oxide;

or comprising

- from about 50% (w/w) to about 70% (w/w) purified neutral acrylic polymer,
- from about 10% (w/w) to about 30% (w/w) active agent and
- from about 15% (w/w) to about 40% (w/w) polyethylene oxide;

or comprising

- from about 35% (w/w) to about 90% (w/w) purified neutral acrylic polymer,
- from about 1% (w/w) to about 50% (w/w) active agent and
- from about 5% (w/w) to about 60% (w/w) polyethylene oxide;

or comprising

- from about 40% (w/w) to about 90% (w/w) purified neutral acrylic polymer,
- from about 5% (w/w) to about 50% (w/w) active agent and
- from about 5% (w/w) to about 50% (w/w) polyethylene oxide;

or comprising

- from about 50% (w/w) to about 90% (w/w) purified neutral acrylic polymer,
- from about 5% (w/w) to about 50% (w/w) active agent and
- from about 5% (w/w) to about 40% (w/w) polyethylene oxide.

22. The oral solid dosage form of any one of claims 1 to 21, wherein the oral solid dosage form comprises a matrix formulation comprising the purified neutral acrylic polymer and the active agent, and wherein the matrix formulation is preferably a controlled release matrix formulation.

23. The oral solid dosage form of claim 22, wherein the matrix formulation is obtained by subjecting a blend comprising the purified neutral acrylic polymer and

the active agent to a direct compression step, an extrusion step, a wet granulation step, a dry granulation step, a hot molding step, or a heat compression step.

24. The oral solid dosage form of any one of claims 1 to 21, wherein the oral
5 solid dosage form comprises a matrix formulation comprising the purified neutral acrylic polymer, the active agent and a polyethylene oxide, and wherein the matrix formulation is preferably a controlled release matrix formulation.

25. The oral solid dosage form of claim 24, wherein the matrix formulation is
10 obtained by subjecting a blend comprising the purified neutral acrylic polymer, the active agent and the polyethylene oxide to a direct compression step, an extrusion step, a wet granulation step, a dry granulation step, a hot molding step, or a heat compression step.

15 26. The oral solid dosage form of claim 23 or 25, wherein the matrix formulation is obtained by subjecting the blend to a direct compression step, preferably by subjecting the blend to a direct compression step and a subsequent curing step.

27. The oral solid dosage form of claim 23 or 25, wherein the matrix formulation
20 is obtained by subjecting the blend to an extrusion step, preferably a melt extrusion step.

28. The oral solid dosage form of any one of claims 22 to 27, wherein the matrix formulation is in the form of a unitary dosage form, preferably in the form of a tablet.

25

29. The oral solid dosage form of any one of claims 22 to 27, wherein the matrix formulation is in the form of multiparticulates.

30. The oral solid dosage form of claim 29, wherein the multiparticulates are in the form of pellets, wherein the pellets preferably have a mean diameter from about 0.1 mm to about 5 mm and a mean height from about 0.1 mm to about 5 mm.

5 31. The oral solid dosage form of claim 29, wherein the multiparticulates are in the form of spheres, wherein the spheres preferably have a mean diameter from about 0.1 mm to about 5 mm.

32. The oral solid dosage form of any one of claims 29 to 31, wherein the 10 multiparticulates are contained in a pharmaceutically acceptable capsule.

15 33. The oral solid dosage form of any one of claims 29 to 31, wherein the multiparticulates are compressed to a tablet.

20 34. The oral solid dosage form of any one of claims 1 to 33, wherein the active agent is selected from the group consisting of ACE inhibitors, adenohypophoseal hormones, adrenergic neuron blocking agents, adrenocortical steroids, inhibitors of the biosynthesis of adrenocortical steroids, alpha-adrenergic agonists, alpha-adrenergic antagonists, selective alpha-two-adrenergic agonists, analgesics, antipyretics, anti-inflammatory agents, androgens, local and general anesthetics, antiaddictive agents, antiandrogens, antiarrhythmic agents, antiasthmatic agents, anticholinergic agents, anticholinesterase agents, anticoagulants, antidiabetic agents, antidiarrheal agents, antidiuretic, antiemetic and prokinetic agents, antiepileptic agents, antiestrogens, antifungal agents, antihypertensive agents, antimicrobial agents, antimigraine agents, antimuscarinic agents, antineoplastic agents, 25 antiparasitic agents, antiparkinson's agents, antiplatelet agents, antiprogestins, antischizophrenia agents, antithyroid agents, antitussives, antiviral agents, atypical antidepressants, azaspirodecanediones, barbituates, benzodiazepines, benzothiadiazides, beta-adrenergic agonists, beta-adrenergic antagonists, selective 30 beta-one-adrenergic antagonists, selective beta-two-adrenergic agonists, bile salts,

agents affecting volume and composition of body fluids, butyrophenones, agents affecting calcification, calcium channel blockers, cardiovascular drugs, catecholamines and sympathomimetic drugs, cholinergic agonists, cholinesterase reactivators, contraceptive agents, dermatological agents, diphenylbutylpiperidines, 5 diuretics, ergot alkaloids, estrogens, ganglionic blocking agents, ganglionic stimulating agents, hydantoins, agents for control of gastric acidity and treatment of peptic ulcers, hematopoietic agents, histamines, histamine antagonists, hormones, 5-hydroxytryptamine antagonists, drugs for the treatment of hyperlipoproteinemia, hypnotics, sedatives, immunosuppressive agents, laxatives, methylxanthines, 10 monamine oxidase inhibitors, neuromuscular blocking agents, organic nitrates, opioid agonists, opioid antagonists, pancreatic enzymes, phenothiazines, progestins, prostaglandins, agents for the treatment of psychiatric disorders, retinoids, sodium channel blockers, agents for spasticity and acute muscle spasms, succinimides, 15 testosterones, thioxanthines, thrombolytic agents, thyroid agents, tricyclic antidepressants, inhibitors of tubular transport of organic compounds, drugs affecting uterine motility, vasodilators, vitamins, and mixtures thereof.

35. The oral solid dosage form of any one of claims 1 to 33, wherein the active agent is an opioid agonist, wherein the opioid agonist is preferably selected from the 20 group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diamprodime, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, 25 ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, 30 oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan,

phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof.

5 36. The oral solid dosage form of claim 35, wherein the opioid agonist is selected from the group consisting of codeine, fentanyl, hydromorphone, hydrocodone, oxycodone, dihydrocodeine, dihydromorphone, morphine, tramadol, oxymorphone, pharmaceutically acceptable salts thereof, and mixtures thereof.

10 37. The oral solid dosage form of claim 35, wherein the opioid agonist is oxycodone or a pharmaceutically acceptable salt thereof, preferably oxycodone hydrochloride.

15 38. The oral solid dosage form of any one of claims 1 to 37, wherein the active agent further comprises an opioid antagonist, wherein the opioid antagonist is preferably selected from the group consisting of amiphenazole, naltrexone, methylnaltrexone, naloxone, nalbuphine, nalorphine, nalorphine dinicotinate, nalmefene, nadide, levallorphan, cyclozocine, pharmaceutically acceptable salts thereof and mixtures thereof.

20

39. The oral solid dosage form of any one of claims 1 to 33, wherein the active agent is a non-opioid analgesic, wherein the non-opioid analgesic is preferably a non-steroidal anti-inflammatory agent selected from the group consisting of aspirin, celecoxib, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, 25 flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, 30 sudoxicam, isoxicam, pharmaceutically acceptable salts thereof and mixtures thereof.

40. The oral solid dosage form of any one of claims 35 to 37, wherein the amount of opioid agonist released at 1 hour is from about 10%(w/w) to about 30% (w/w); the amount of opioid agonist released at 2 hours is from about 25% (w/w) to about 50%
5 (w/w); the amount of opioid agonist released at 4 hours is from about 40% (w/w) to about 80% (w/w); the amount of opioid agonist released at 8 hours is from about 65%(w/w) to about 95%(w/w) and the amount of opioid agonist released at 12 hours is greater than about 80% (w/w); as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes
10 (SGF) at 37° C, and preferably wherein the amount of opioid agonist released at 1 hour is from about 15% (w/w) to about 25% (w/w); the amount of opioid agonist released at 2 hours is from about 30% (w/w) to about 40% (w/w); the amount of opioid agonist released at 4 hours is from about 55% (w/w) to about 75% (w/w); the amount of opioid agonist released at 8 hours is from about 75% (w/w) to about 85%
15 (w/w) and the amount of opioid agonist released at 12 hours is greater than about 90% (w/w); as measured by an in-vitro dissolution in a USP Apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid without enzymes (SGF) at 37° C.

41. The oral solid dosage form of any one of claims 1 to 40, wherein the dosage
20 form can be flattened without breaking, wherein the thickness of the dosage form after flattening corresponds to no more than about 60% of the thickness of the dosage form before flattening, and preferably corresponds to no more than about 50% or no more than about 40% or no more than about 30% or no more than about 20% of the thickness of the dosage form before flattening.

25

42. A method of preparing an oral solid dosage form, comprising at least the following steps:

- a) drying a dispersion comprising a neutral acrylic polymer to obtain a purified neutral acrylic polymer;

- b) admixing the purified neutral acrylic polymer at least with an active agent to obtain a blend, and simultaneously and/or subsequently
- c) further processing the blend to obtain the oral solid dosage form.

5 43. The method of claim 42, wherein the drying is performed by vacuum drying, lyophilization, pan drying, oven drying, freeze drying and/or evaporation.

44. The method of claim 42 or 43, wherein in step a) the obtained purified neutral acrylic polymer is subsequently milled, preferably in the presence of dry ice.

10

45. The method of claim 42 or 43, wherein in step a) the obtained purified neutral acrylic polymer is subsequently milled, preferably in the presence of dry ice, and thereafter screened.

15

46. The method of any one of claims 42 to 45, wherein the dispersion is an aqueous dispersion preferably comprising from about 20% (w/w) to about 50% (w/w) neutral acrylic polymer, more preferably comprising from about 30% (w/w) to about 40% (w/w) neutral acrylic polymer.

20

47. The method of any one of claims 42 to 46, wherein the neutral acrylic polymer is a poly(meth)acrylate which does not contain free acid groups, amino groups or quaternary ammonium groups.

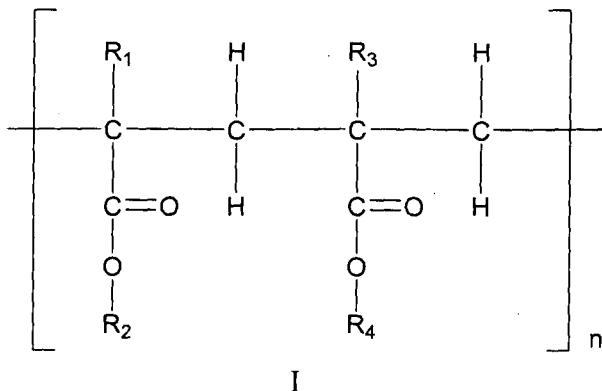
25

48. The method of any one of claims 42 to 47, wherein the neutral acrylic polymer is a copolymer or homopolymer of acrylic acid (C₁-C₈) alkyl esters and/or methacrylic acid (C₁-C₈) alkyl esters, preferably a copolymer or homopolymer of acrylic acid (C₁-C₄) alkyl esters and/or methacrylic acid (C₁-C₄) alkyl esters.

30

49. The method of any one of claims 42 to 48, wherein the neutral acrylic polymer is a copolymer having the structural formula I

- 100 -



wherein R₁ and R₃ are independently selected from H and methyl,
 R₂ and R₄ are independently selected from methyl, ethyl, propyl, butyl, pentyl, hexyl,
 5 heptyl or octyl,
 and n is selected such that the copolymer has a mean relative molecular mass of at
 least about 100,000, preferably of at least about 300,000, most preferably of from
 about 600,000 to about 1,000,000.

10 50. The method of claim 49, wherein R₂ and R₄ are independently selected from
 methyl, ethyl, propyl, and butyl, preferably from methyl and ethyl.

51. The method of any one of claims 42 to 50, wherein the neutral acrylic
 polymer is a copolymer of ethyl acrylate and methyl methacrylate.

15 52. The method of any one of claims 42 to 51, wherein the neutral acrylic
 polymer has a mean relative molecular mass of from about 600,000 to about
 1000,000, preferably of from about 600,000 to 900,000, most preferably of about
 660,000, 770,000 or 800,000.

20 53. The method of any one of claims 42 to 52, wherein in step b) the purified
 neutral acrylic polymer is admixed in an amount effective to provide a controlled
 release of the active agent, and/or in an amount such that the oral solid dosage form
 comprises from about 10% (w/w) to about 90% (w/w) purified neutral acrylic

polymer, preferably from about 20% (w/w) to about 80% (w/w) purified neutral acrylic polymer, most preferably from about 30% (w/w) to about 80% (w/w) purified neutral acrylic polymer.

5 54. The method of any one of claims 42 to 53, wherein in step b) the purified neutral acrylic polymer is admixed in an amount such that the oral solid dosage form comprises greater than about 35% (w/w), greater than about 40% (w/w), greater than about 50% (w/w), or greater than about 60% (w/w) of the purified neutral acrylic polymer, and preferably comprises from about 35 % (w/w) to about 90% (w/w) of purified neutral acrylic polymer or from about 40 % (w/w) to about 90 % (w/w) of purified neutral acrylic polymer or from about 50 % (w/w) to about 90 % (w/w) of purified neutral acrylic polymer or from about 60 % (w/w) to about 90 % (w/w) of purified neutral acrylic polymer.

10 15. 55. The method of any one of claims 42 to 54, wherein the purified neutral acrylic polymer obtained in step a) by drying the dispersion comprising the neutral acrylic polymer comprises less than about 20% (w/w) water or less than about 15% (w/w) water, preferably less than about 10% (w/w) water or less than about 5% (w/w) water, more preferably less than about 3% (w/w) water, and most preferably less than about 1% (w/w) water.

20 56. The method of any one of claims 42 to 55, wherein in step b) the active agent is admixed in an amount such that the oral solid dosage form comprises from about 1% (w/w) to about 50% (w/w) active agent or from about 5% (w/w) to about 40% (w/w) active agent, preferably from about 10% (w/w) to about 30% (w/w) active agent and most preferably from about 15% (w/w) to about 25% (w/w) active agent.

25 57. The method of any one of claims 42 to 56, wherein in step b) the purified neutral acrylic polymer is further admixed with at least one excipient selected from 30 the group consisting of polymers, poloxamers, bulking agents, release modifying

agents, plasticizers, stabilizers, diluents, lubricants, binders, granulating aids, colorants, flavorants, and glidants.

58. The method of any one of claims 42 to 57, wherein in step b) the purified
5 neutral acrylic polymer is further admixed with a polymer.

59. The method of claim 58, wherein the polymer is a polyethylene oxide.

60. The method of claim 59, wherein the polyethylene oxide is a low molecular
10 weight polyethylene oxide.

61. The method of claim 58 or 59, wherein the polyethylene oxide has an
approximate molecular weight of from about 10,000 Daltons to about 750,000
15 Daltons, based on rheological measurements, preferably an approximate molecular
weight of from about 50,000 Daltons to about 500,000 Daltons, based on rheological
measurements, and most preferably an approximate molecular weight of from about
75,000 Daltons to about 300,000 Daltons, based on rheological measurements .

62. The method of any one of claims 59 to 61, wherein in step b) the
20 polyethylene oxide is admixed in an amount such that the oral solid dosage form
comprises from about 5% (w/w) to about 60% (w/w) polyethylene oxide, preferably
from about 10% (w/w) to about 50% (w/w) polyethylene oxide, most preferably from
about 15% (w/w) to about 40% (w/w) polyethylene oxide.

25 63. The method of any one of claims 59 to 62, wherein in step b) the purified
neutral acrylic polymer, the active agent and the polyethylene oxide are admixed in
amounts such that the oral solid dosage form comprises

- from about 10% (w/w) to about 90% (w/w) purified neutral acrylic
polymer,
- from about 1% (w/w) to about 50% (w/w) active agent, and

- from about 5% (w/w) to about 60% (w/w) polyethylene oxide; or are admixed in amounts such that the oral solid dosage form comprises
 - from about 35% (w/w) to about 80% (w/w) purified neutral acrylic polymer,
 - from about 5% (w/w) to about 40% (w/w) active agent, and
 - from about 10% (w/w) to about 50% (w/w) polyethylene oxide;
- 5 or are admixed in amounts such that the oral solid dosage form comprises
 - from about 50% (w/w) to about 70% (w/w) purified neutral acrylic polymer,
 - from about 10% (w/w) to about 30% (w/w) active agent, and
 - from about 15% (w/w) to about 40% (w/w) polyethylene oxide;
- 10 or are admixed in amounts such that the oral solid dosage form comprises
 - from about 35% (w/w) to about 90% (w/w) purified neutral acrylic polymer,
 - from about 1% (w/w) to about 50% (w/w) active agent and
 - from about 5% (w/w) to about 60% (w/w) polyethylene oxide;
- 15 or are admixed in amounts such that the oral solid dosage form comprises
 - from about 40% (w/w) to about 90% (w/w) purified neutral acrylic polymer,
 - from about 5% (w/w) to about 50% (w/w) active agent and
 - from about 5% (w/w) to about 50% (w/w) polyethylene oxide;
- 20 or are admixed in amounts such that the oral solid dosage form comprises
 - from about 50% (w/w) to about 90% (w/w) purified neutral acrylic polymer,
 - from about 5% (w/w) to about 50% (w/w) active agent and
 - from about 5% (w/w) to about 40% (w/w) polyethylene oxide.
- 25

64. The method of any one of claims 42 to 63, wherein in step c) the blend is further processed by subjecting it to a direct compression step, an extrusion step, a

wet granulation step, a dry granulation step, a hot molding step, or a heat compression step.

65. The method of claim 64, wherein in step c) the blend is further processed by
5 subjecting it to a direct compression step, preferably by subjecting it to a direct compression step and a subsequent curing step.

66. The method of any one of claims 42 to 65, wherein the oral solid dosage form is in the form of a unitary dosage form, preferably in the form of a tablet.

10

67. The method of any one of claims 42 to 65, wherein the oral solid dosage form is in the form of multiparticulates.

15

68. The method of claim 64, wherein in step c) the blend is further processed by subjecting it to an extrusion step to obtain an extrudate.

69. The method of claim 68, wherein the extrusion step is a melt-extrusion step.

20

70. The method of claim 68 or 69, wherein the extrudate obtained in step c) is subsequently divided into unitary dosage forms, preferably in the form of a tablet.

71. The method of claim 68 or 69, wherein the extrudate obtained in step c) is subsequently divided into multiparticulates, preferably in the form of pellets or spheres.

25

72. The method of claim 71, wherein the multiparticulates are filled into a pharmaceutically acceptable capsule.

30

73. The method of claim 71, wherein the multiparticulates are compressed into a tablet.

74. The method of any one of claims 42 to 73, wherein the oral solid dosage form comprises a matrix formulation comprising the purified neutral acrylic polymer and the active agent.

5

75. The method of claim 74, wherein the matrix formulation is a controlled release matrix formulation.

76. The method of any one of claims 42 to 75, wherein the active agent is selected from the group consisting of ACE inhibitors, adenohypophoseal hormones, adrenergic neuron blocking agents, adrenocortical steroids, inhibitors of the biosynthesis of adrenocortical steroids, alpha-adrenergic agonists, alpha-adrenergic antagonists, selective alpha-two-adrenergic agonists, analgesics, antipyretics, anti-inflammatory agents, androgens, local and general anesthetics, antiaddictive agents, antiandrogens, antiarrhythmic agents, antiasthmatic agents, anticholinergic agents, anticholinesterase agents, anticoagulants, antidiabetic agents, antidiarrheal agents, antidiuretic, antiemetic and prokinetic agents, antiepileptic agents, antiestrogens, antifungal agents, antihypertensive agents, antimicrobial agents, antimigraine agents, antimuscarinic agents, antineoplastic agents, antiparasitic agents, antiparkinson's agents, antiplatelet agents, antiprogestins, antischizophrenia agents, antithyroid agents, antitussives, antiviral agents, atypical antidepressants, azaspirodecanediones, barbituates, benzodiazepines, benzothiadiazides, beta-adrenergic agonists, beta-adrenergic antagonists, selective beta-one-adrenergic antagonists, selective beta-two-adrenergic agonists, bile salts, agents affecting volume and composition of body fluids, butyrophенones, agents affecting calcification, calcium channel blockers, cardiovascular drugs, catecholamines and sympathomimetic drugs, cholinergic agonists, cholinesterase reactivators, contraceptive agents, dermatological agents, diphenylbutylpiperidines, diuretics, ergot alkaloids, estrogens, ganglionic blocking agents, ganglionic stimulating agents, hydantoins, agents for control of gastric acidity and treatment of peptic ulcers, hematopoietic agents, histamines, histamine

antagonists, hormones, 5-hydroxytryptamine antagonists, drugs for the treatment of hyperlipoproteinemia, hypnotics, sedatives, immunosuppressive agents, laxatives, methylxanthines, monamine oxidase inhibitors, neuromuscular blocking agents, organic nitrates, opioid agonists, opioid antagonists, pancreatic enzymes, 5 phenothiazines, progestins, prostaglandins, agents for the treatment of psychiatric disorders, retinoids, sodium channel blockers, agents for spasticity and acute muscle spasms, succinimides, testosterone, thioxanthines, thrombolytic agents, thyroid agents, tricyclic antidepressants, inhibitors of tubular transport of organic compounds, drugs affecting uterine motility, vasodilators, vitamins, and mixtures 10 thereof.

77. The method of any one of claims 42 to 75, wherein the active agent is an opioid agonist, wherein the opioid agonist is preferably selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, 15 bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diamprodime, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, 20 hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, 25 phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof.

78. The method of claim 77, wherein the opioid agonist is selected from the 30 group consisting of codeine, fentanyl, hydromorphone, hydrocodone, oxycodone,

dihydrocodeine, dihydromorphine, morphine, tramadol, oxymorphone, pharmaceutically acceptable salts thereof, and mixtures thereof.

79. The method of claim 77, wherein the opioid agonist is oxycodone or a 5 pharmaceutically acceptable salt thereof, preferably oxycodone hydrochloride.

80. The method of any one of claims 42 to 79, wherein the active agent further comprises an opioid antagonist, wherein the opioid antagonist is preferably selected from the group consisting of amiphenazole, naltrexone, methylnaltrexone, naloxone, 10 nalbuphine, nalorphine, nalorphine dinicotinate, nalmefene, nadide, levallorphan, cyclozocine, pharmaceutically acceptable salts thereof and mixtures thereof.

81. The method of any one of claims 42 to 75, wherein the active agent is a non- 15 opioid analgesic, wherein the non-opioid analgesic is preferably a non-steroidal anti-inflammatory agent selected from the group consisting of aspirin, celecoxib, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, 20 fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, pharmaceutically acceptable salts thereof and mixtures thereof.

82. The method of preparing an oral solid dosage form according to any one of 25 claims 42 to 81 comprising at least the following steps: (i) mixing in an extruder the purified neutral acrylic polymer and the active agent; (ii) extruding the mixture as a strand; (iii) cooling the strand; and (iv) dividing the strand into unit doses.

83. The method of preparing an oral solid dosage form according to any one of 30 claims 42 to 82 comprising at least the following steps: (i) mixing in an extruder the

purified neutral acrylic polymer, the active agent; and the polyethylene oxide (ii) extruding the mixture as a strand; (iii) cooling the strand; and (iv) dividing the strand into unit doses.

5 84. An oral solid dosage form obtainable by a method according to any one of claims 42 to 83.

85. Purified neutral acrylic polymer.

10 86. The purified neutral acrylic polymer according to claim 85, obtained by vacuum drying an aqueous dispersion comprising a neutral acrylic polymer.

87. The purified neutral acrylic polymer according to claim 85, obtained by oven drying an aqueous dispersion comprising a neutral acrylic polymer.

15 88. The purified neutral acrylic polymer according to claim 85, obtained by freeze drying an aqueous dispersion comprising a neutral acrylic polymer.

89. A bulk powder comprising (i) a purified neutral acrylic polymer and (ii) an 20 active agent.

90. The bulk powder according to claim 89, wherein the purified neutral acrylic polymer is obtained by vacuum drying an aqueous dispersion comprising a neutral acrylic polymer.

25 91. The bulk powder according to claim 89, wherein the purified neutral acrylic polymer is obtained by oven drying an aqueous dispersion comprising a neutral acrylic polymer.

92. The bulk powder according to claim 89, wherein the purified neutral acrylic polymer is obtained by freeze drying an aqueous dispersion comprising a neutral acrylic polymer.

5 93. Use of a purified neutral acrylic polymer in the preparation of an oral solid dosage form.

94. Use of a blend comprising a purified neutral acrylic polymer and an active agent in the preparation of an oral solid dosage form.

10

95. Use according to claim 94, wherein the blend further comprises a polyethylene oxide.

15

96. Use according to any one of claims 94 to 95, wherein the blend is in the form of a bulk powder.

97. Use according to any one of claims 94 to 96, wherein the blend comprises less than 20% (w/w) water or less than 15% (w/w) water, and preferably comprises less 10% (w/w) water or less than 5 % (w/w) water or less than 3% (w/w) water.

20

98. Use according to claim 97, wherein the blend further comprises less than 10% (w/w) organic solvents, preferably comprises less than 5 % (w/w) organic solvents, most preferably comprises less than 3% (w/w) or less than 1% (w/w) organic solvents.

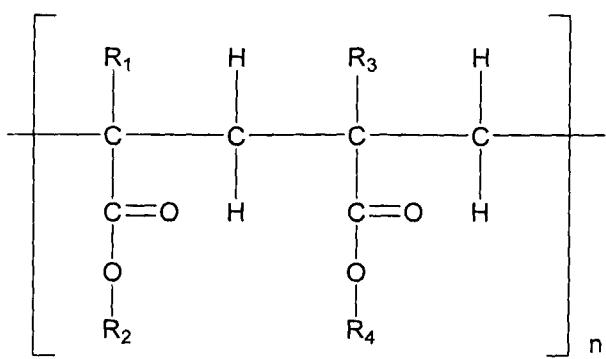
25

99. Purified neutral acrylic polymer, bulk powder or use according to any one of claims 85 to 98, wherein the neutral acrylic polymer is a copolymer or homopolymer of acrylic acid (C₁-C₈) alkyl esters and/or methacrylic acid (C₁-C₈) alkyl esters, preferably a copolymer or homopolymer of acrylic acid (C₁-C₄) alkyl esters and/or methacrylic acid (C₁-C₄) alkyl esters.

30

- 110 -

100. Purified neutral acrylic polymer, bulk powder or use according to any one of claims 85 to 98, wherein the neutral acrylic polymer is a copolymer having the structural formula I



5

I

wherein R₁ and R₃ are independently selected from H and methyl, R₂ and R₄ are independently selected from methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl or octyl,

10 and n is selected such that the copolymer has a mean relative molecular mass of at least about 100,000, preferably of at least about 300,000, most preferably of from about 600,000 to about 1,000,000.

15 101. Use according to any one of claims 93 to 100 in the preparation of an oral solid dosage form according to any one of claims 1 to 41 and 84.

102. A method of treating a disease or condition comprising administering an oral solid dosage form according to any one of claims 1 to 41 and 84 to a patient in need thereof.

20

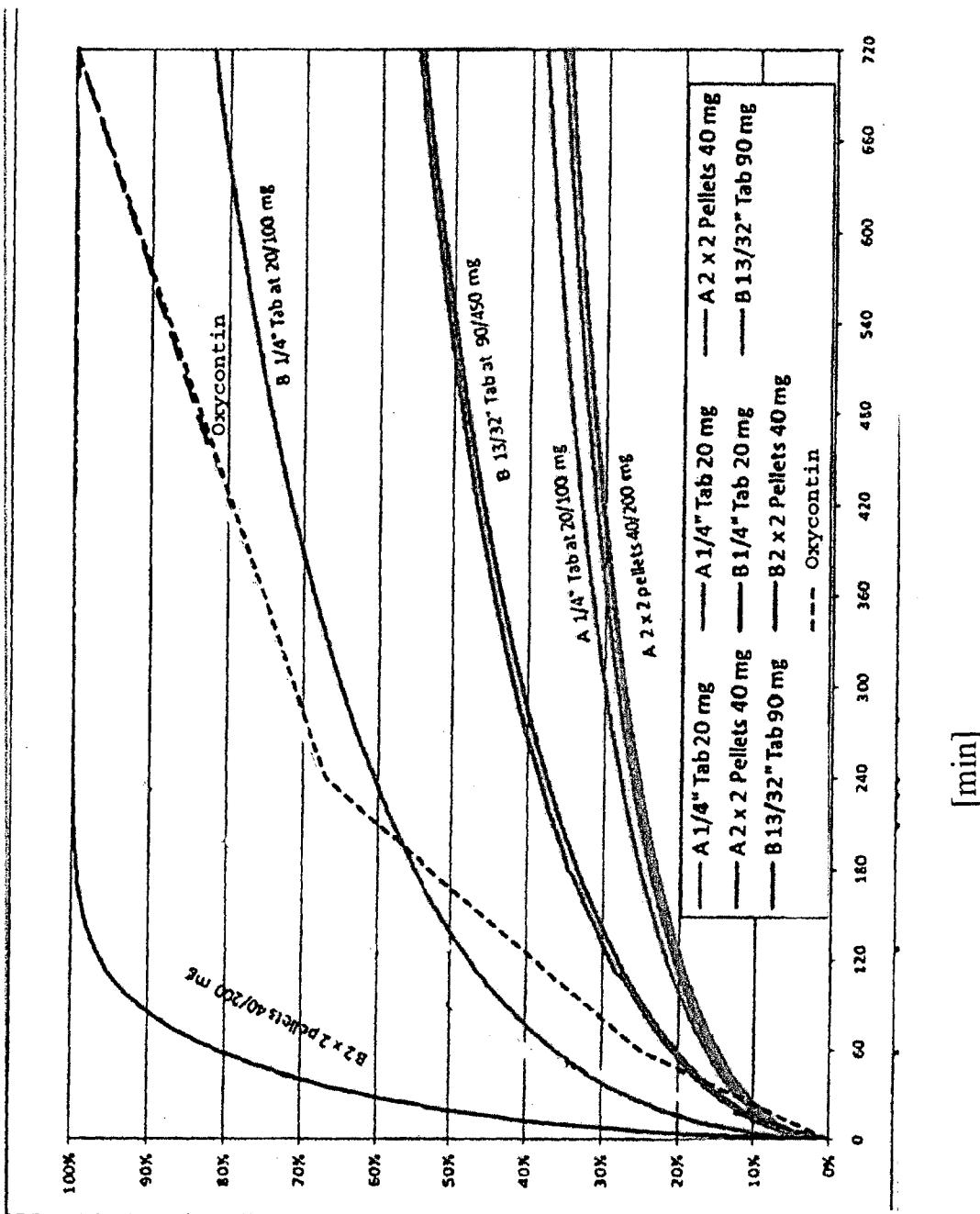
103. A method of treating pain comprising administering an oral solid dosage form according to any one of claims 1 to 41 and 84 to a patient in need thereof, wherein the oral solid dosage form comprises an opioid agonist.

- 111 -

104. Use of an oral solid dosage form according to any one of claims 1 to 41 and 84 in the manufacture of a medicament for the treatment of pain, wherein the oral solid dosage form comprises an opioid agonist.

5 105. An oral solid dosage form according to any one of claims 1 to 41 and 84 for use in the treatment of pain, wherein the oral solid dosage form comprises an opioid agonist.

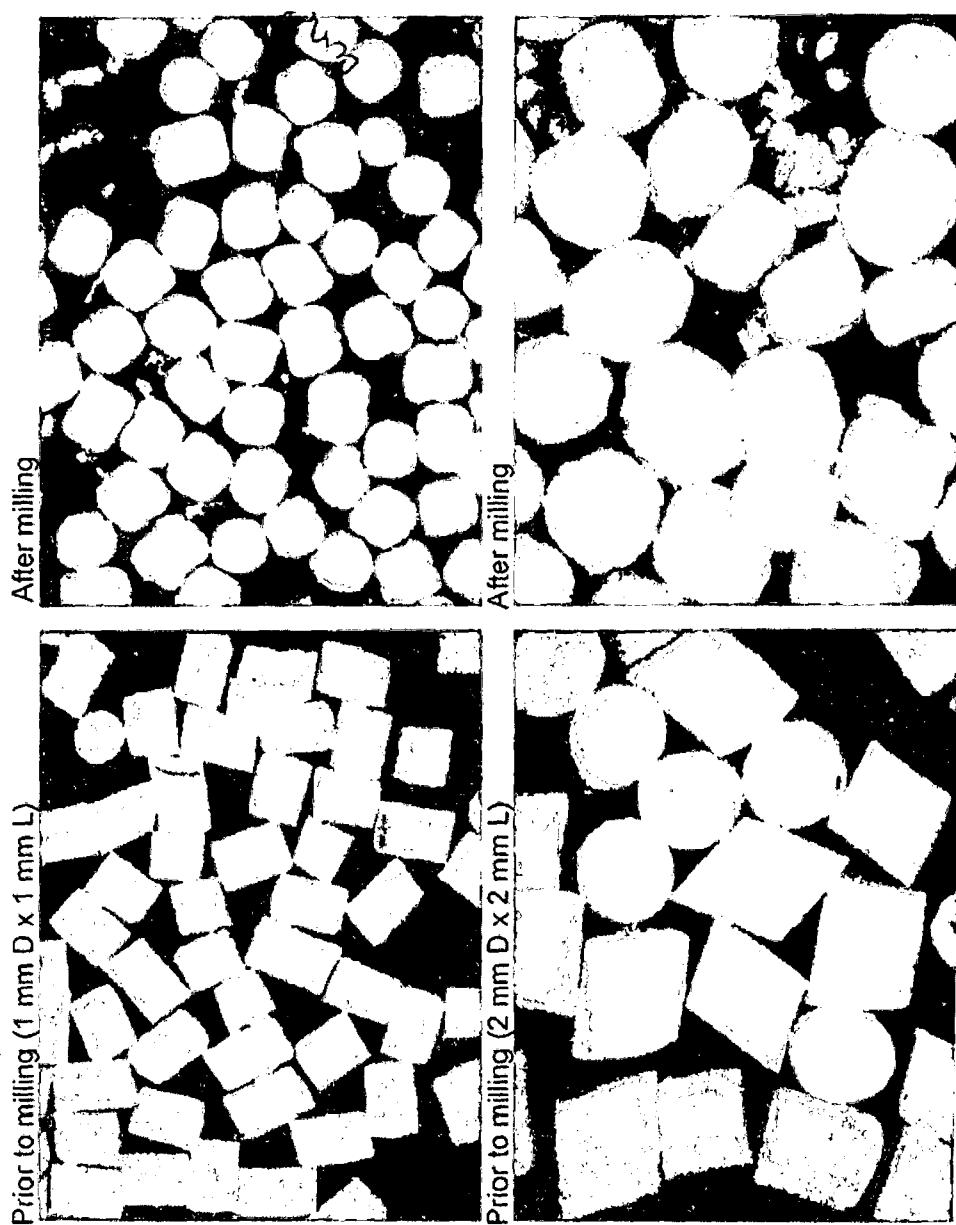
Figure 1



[min]

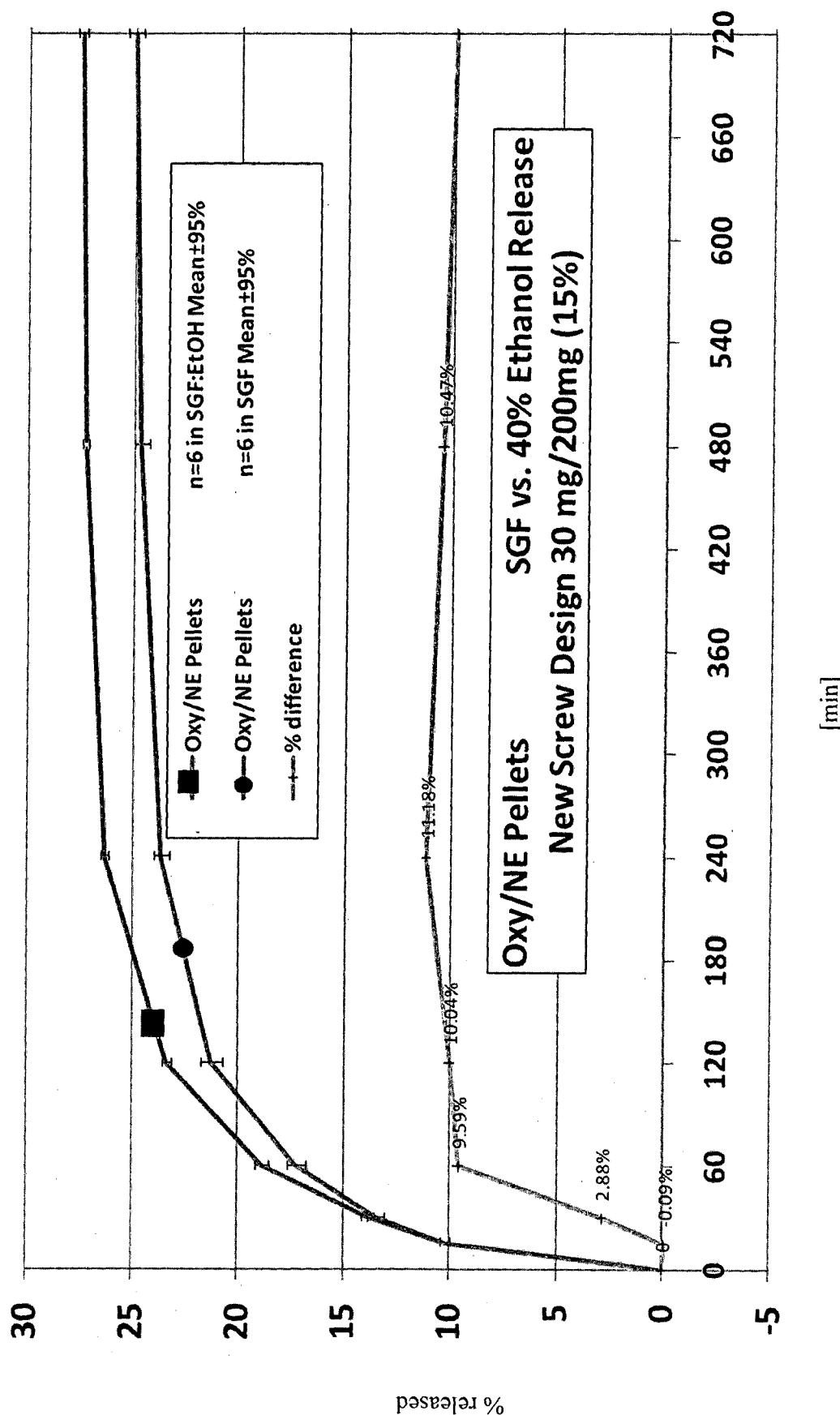
2 / 4

Figure 2



3 / 4

Figure 3



4 / 4

Figure 4

