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(54) Titre : FORMULATIONS D'OXYCODONE A ADMINISTRATION QUOTIDIENNE UNIQUE
(54) Title: ONCE-A-DAY OXYCODONE FORMULATIONS

(57) Abrégé/Abstract:
The invention is directed to sustained release formulations containing oxycodone or a pharmaceutically acceptable salt thereof which provide a mean C_{24}/C_{max} oxycodone ratio of 0.6 to 1.0 or 0.7 to 1 after oral administration at steady state to patients and methods thereof.

ABSTRACT OF THE DISCLOSURE

The invention is directed to sustained release formulations containing oxycodone or a pharmaceutically acceptable salt thereof which provide a mean C_{24}/C_{max} oxycodone ratio of 0.6 to 1.0 or 0.7 to 1 after oral administration at steady state to patients and methods thereof.

ONCE-A-DAY OXYCODONE FORMULATIONS

This application is a divisional application of co-pending application Serial No. 2,474,904, filed May 2, 2002.

FIELD OF THE INVENTION

The invention is directed to sustained release formulations containing oxycodone or a pharmaceutically acceptable salt thereof which is suitable for administration to a patient.

BACKGROUND OF THE INVENTION

Once-a-day sustained release opioid formulations are disclosed in U.S. Patent Nos. 5,478,577; 5,672,360; 5,958,459; 6,103,261; 6,143,332; 5,965,161; 5,958,452 and 5,968,551.

SUMMARY AND OBJECTS OF THE INVENTION

It is an object of the present invention to provide an oxycodone formulation suitable for once daily administration for effective pain management.

It is an object of preferred embodiments of the present invention to provide a pharmaceutically acceptable dosage form for orally administering oxycodone to provide analgesic therapy beyond its relatively short half-life over an extended period of time, and having a duration of pain relief of at least 24-hours.

The above objects and others are attained by the present invention, which is directed to a dosage form comprising an analgesically effective amount of oxycodone or a pharmaceutically acceptable salt thereof and a sustained release material, the dosage form providing an analgesic effect for at least about 24 hours after oral administration at steady state to human patients; and the dosage form providing a mean C_{24}/C_{max} oxycodone ratio of 0.6 to 1.0 after oral administration at steady state to the patients.

In certain embodiments of the invention, the dosage form after administration to patients provides a mean T_{max} of oxycodone in-vivo which occurs at about 2 to about 17 hours (e.g., about 2 to about 8 hours) after administration at steady state of the dosage form.

In certain embodiments of the invention, the mean T_{max} of oxycodone in-vivo occurs at about 6.5 hours to about 17 hours, at about 8 to about 16 hours, at about 10 to about 16 hours, or at about 12 to about 16 hours after administration at steady state of the dosage form.

In certain embodiments of the invention, the dosage form provides an analgesic effect for at least about 24 hours after administration of the dosage form to human patients at steady state; and provides a mean C_{24}/C_{max} oxycodone ratio of 0.60 to 1.0 after administration at steady state to patients.

In certain embodiments of the invention, the dosage form provides an analgesic effect for at least about 24 hours after administration at steady state to human patients; and provides a mean C_{24}/C_{max} oxycodone ratio of 0.60 to 1.0 or 0.7 to 1.0 after administration at steady state to patients. In certain embodiments of the invention, the dosage form provides an in-vitro release rate, of oxycodone or a pharmaceutically acceptable salt thereof, when measured by the USP Basket Method at 100 rpm in 900 ml aqueous buffer at a pH of between 1.6 and 7.2 at 37°C of from 0% to about 40% at 1 hour, from about 8% to about 70% at 4 hours, from about 20% to about 80% at 8 hours, from about 30% to about 95% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 50% at 24 hours.

In certain preferred embodiments the sustained release oral dosage form of the present invention provides oxycodone plasma levels which are effective for 24 hourly dosing, characterized by a W_{50} for the oxycodone of between 4 and 24 hours after administration at steady state. In certain embodiments, the W_{50} is at least 4 hours, preferably at least 12 hours, and more preferably at least 18 hours, after administration at steady state.

In certain embodiments the sustained release oral dosage form of the present invention comprises a matrix which includes a sustained release material and oxycodone or a pharmaceutically acceptable salt thereof. In certain embodiments, the matrix is compressed into a tablet and may be optionally overcoated with a coating that in addition to the sustained release material of the matrix may control the release of the oxycodone or pharmaceutically acceptable salt thereof from the formulation, such that blood levels of active ingredient are maintained within the therapeutic range over an extended period of time. In certain alternate embodiments, the matrix is encapsulated.

In certain embodiments, the sustained release oral dosage form of the present invention comprises a plurality of pharmaceutically acceptable sustained release matrices comprising oxycodone or a pharmaceutically acceptable salt thereof, the dosage form

maintaining the blood plasma levels of oxycodone within the therapeutic range over an extended period of time when administered to patients.

Preferably, the formulations prepared in accordance with the present invention can be presented in tablet, capsule, or in any other suitable unit dosage form.

In certain embodiments the sustained release oral dosage form of the present invention is an osmotic dosage form which comprises a single layer or bilayer core comprising oxycodone or a pharmaceutically acceptable salt thereof; an expandable polymer; a semipermeable membrane surrounding the core; and a passageway disposed in the semipermeable membrane for sustained release of the oxycodone or pharmaceutically acceptable salt thereof, such that blood levels of active ingredient are maintained within the therapeutic range over an extended period of time when administered to patients.

In certain embodiments the sustained release oral dosage form of the present invention comprises a substantially homogenous core comprising oxycodone or a pharmaceutically acceptable salt thereof and an expandable polymer; a semipermeable membrane surrounding the core; and a passageway disposed in the semipermeable membrane for sustained release of the oxycodone or pharmaceutically acceptable salt thereof, such that blood levels of active ingredient are maintained within the therapeutic range over an extended period of time when administered to a patients.

In certain embodiments of the present invention, there is provided a method of treating pain associated conditions in patients requiring such treatment which method includes administering to a patient an effective amount of oxycodone or a pharmaceutically acceptable salt thereof in a sustained release dosage form as described herein.

In certain embodiments, the invention is directed to the use of a sustained release dosage form comprising a pharmaceutically acceptable matrix comprising oxycodone or a pharmaceutically acceptable salt thereof and a sustained release material in the production of an analgesic preparation for oral administration to human patients on a once a day basis, to provide an analgesic effect for at least about 24 hours and a mean C_{24}/C_{max} oxycodone ratio of 0.6 to 1.0 after administration at steady state to said patients.

In certain embodiments, the invention is directed to the use of a sustained release oral dosage form comprising a bilayer core comprising a drug layer comprising an analgesically effective amount of oxycodone or a pharmaceutically acceptable salt thereof; and a

displacement layer comprising an osmopolymer; and a semipermeable wall surrounding the bilayer core having a passageway disposed therein for the release of said oxycodone or pharmaceutically acceptable salt thereof; in the production of an analgesic preparation for oral administration to human patients to provide an analgesic effect at least about 24 hours after oral administration at steady state to human patients; and to provide a mean C_{24}/C_{max} oxycodone ratio of 0.6 to 1.0 after administration at steady state to said patients.

In certain embodiments, the invention is directed to the use of a sustained release dosage form comprising a plurality of sustained release matrices comprising oxycodone or a pharmaceutically acceptable salt thereof and a sustained release material, in the production of an analgesic preparation for oral administration to a patient on a once-a-day basis, to provide an analgesic effect for at least 24 hours after oral administration at steady state to human patients; and to provide a mean C_{24}/C_{max} oxycodone ration of 0.6 to 1.0 after oral administration at steady state to said patients.

The term "C_{max}" as it is used herein is the highest plasma concentration of the drug attained within the dosing interval.

The term "C_{24}" as it is used herein is the plasma concentration of the drug at 24 hours after administration.

The term "T_{max}" as it is used herein is the time period which elapses after administration of the dosage form until the plasma concentration of the drug attains the highest plasma concentration within the dosing interval.

The term "W_{50}" for purposes of the present invention is the duration over which the plasma concentrations are equal to or greater than 50% of the peak concentration. The parameter is determined by linear interpolation of the observed data and represents the difference in time between the first (or only) upslope crossing and the last (or only) downslope crossing in the plasma profile.

The term "C_{24}/C_{max} ratio" is defined for purposes of the present invention as the ratio of the plasma concentration of the drug at 24 hours after administration to the highest plasma concentration of the drug attained within the dosing interval.

The term "USP Basket Method" is the Basket Method described in U.S. Pharmacopoeia XXII (1990).

The term "steady state" means that the amount of the drug reaching the system is approximately the same as the amount of the drug leaving the system. Thus, at "steady-state", the patient's body eliminates the drug at approximately the same rate that the drug becomes available to the patient's system through absorption into the blood stream.

The term "semipermeable wall" for purposes of the present invention means that the wall is permeable to the passage of an exterior fluid, such as aqueous or biological fluid, in the environment of use, including the gastrointestinal tract, but impermeable to drug.

The term "expandable polymer" for purposes of the present invention means a polymer which upon exposure to an aqueous or biological fluid, absorbs the fluid resulting in a greater mass.

The term "mean" for purposes of the present invention, when used to define a pharmacokinetic value (e.g., T_{max}) represents the arithmetic mean value measured across a patient population.

The phrase "pharmaceutically acceptable salt" includes, but is not limited to, metal salts such as sodium salt, potassium salt, cesium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, maleate, fumarate, tartrate and the like; sulfonates such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like; amino acid salts such as arginate, asparginate, glutamate and the like.

DESCRIPTION OF THE INVENTION

In certain embodiments of the present invention, the sustained release dosage form provides an in-vitro release rate of oxycodone or a pharmaceutically acceptable salt thereof, when measured by the USP Basket Method at 100 rpm in 900 ml aqueous buffer at a pH of

between 1.6 and 7.2 at 37°C of from 0% to about 40% at 1 hour, from about 8% to about 70% at 4 hours, from about 20% to about 80% at 8 hours, from about 30% to about 95% at 12 hours, from about 35% to about 95% at 18 hrs, and greater than about 50% at 24 hours.

In certain embodiments of the present invention the time period during which oxycodone blood levels (after administration at steady state) are greater than or equal to 75% of the maximum blood level ($T_{\geq 0.75Cmax}$) may be 4 hours or greater, preferably 6 hours or greater.

In certain embodiments, the time at which oxycodone blood levels reach their maximum concentration (T_{max}) is about 2 to about 17 hours, preferably about 6.5 hours to about 17 hours, more preferably about 8 to about 16 hours, and even more preferably about 10 to about 16 or about 12 to about 16 hours after administration at steady state of the dosage form.

In certain embodiments of the present invention, the dosage form provides a C_{24}/C_{max} ratio after administration at steady state of 0.6 to 1.0, a ratio 0.7 to 0.99 or a ratio of 0.8 to 0.95. In other embodiments of the present invention, the dosage form provides a C_{24}/C_{max} ratio after administration at steady state of 0.7 to 1.0, a ratio 0.72 to 0.99 or a ratio of 0.74 to 0.95.

In certain embodiments of the present invention, the dosage form provides a C_{24}/C_{max} ratio after administration at steady state of 0.6 to 1.0, a ratio 0.7 to 0.99 or a ratio of 0.8 to 0.95 and a (T_{max}) of about 6.5 hours to about 17 hours, about 8 to about 16 hours, about 10 to about 16 hours or about 12 hours to about 16 hours. In other embodiments of the present invention, the dosage form provides a C_{24}/C_{max} ratio after administration at steady state of 0.7 to 1.0, a ratio 0.72 to 0.99 or a ratio of 0.74 to 0.95 and a (T_{max}) in about 2 to about 17 hours.

In certain embodiments of the present invention, the co-administration of food will not significantly increase or decrease the extent of oxycodone absorption.

The sustained release oral dosage form of the present invention includes from about 1 to about 640 mg of oxycodone or a pharmaceutically acceptable salt thereof (e.g., oxycodone hydrochloride). Preferably the sustained release oral dosage form of the present invention includes from about 5 to about 500 mg oxycodone or a pharmaceutically acceptable salt thereof, more preferably from about 10 to about 320 mg oxycodone or a pharmaceutically acceptable salt thereof and even more preferably from about 10 to about 160 mg oxycodone or a pharmaceutically acceptable salt thereof.

In other preferred embodiments, the sustained release dosage form of the present invention comprises from about 10 to about 160 mg oxycodone hydrochloride or an equivalent amount of oxycodone or a pharmaceutically acceptable salt thereof other than the hydrochloride salt.

The present invention includes a method for administering from about 1 to about 640 mg of oxycodone or a pharmaceutically acceptable salt thereof on a once-a-day basis to a patient in need of relief of pain, in accordance with the pharmacokinetic parameters disclosed herein. Preferably, the method includes administering from about 5 to about 500 mg oxycodone or a pharmaceutically acceptable salt thereof.

The method of administration according to the present invention is particularly applicable to the treatment of acute and chronic pain, particularly pain associated with terminal disease such as cancer; chronic backpain; and post-operative pain.

DOSAGE FORMS

In certain embodiments the oral dosage form includes a sustained-release material which is incorporated into a matrix along with the oxycodone or pharmaceutically acceptable salt thereof to provide for the sustained release of the oxycodone. The sustained-release material may be hydrophobic or hydrophilic as desired. The oral dosage form of the present invention may be prepared as granules, spheroids, matrix multiparticulates, etc. which comprise oxycodone or a pharmaceutically acceptable salt thereof in a sustained release matrix, which may be compressed into a tablet or encapsulated. The oral dosage form of the present invention may optionally include other pharmaceutically acceptable ingredients (e.g., diluents, binders, colorants, lubricants, etc.).

In certain embodiments, the oral dosage form of the present invention may be an osmotic dosage form having a push or displacement composition as one of the layers of a bilayer core for pushing oxycodone or a pharmaceutically acceptable salt thereof from the dosage form, and a semipermeable wall composition surrounding the core, wherein the wall has at least one exit means or passageway for delivering the oxycodone from the dosage form. Alternatively, the core of the osmotic dosage form may comprise a single layer core including a controlled release polymer and oxycodone or a pharmaceutically acceptable salt thereof.

Preferably the dosage forms of the present invention provide an analgesic effect for at least about 24 hours after administration.

SUSTAINED-RELEASE MATRIX FORMULATIONS

In one preferred embodiment of the present invention, the sustained release carrier may be incorporated into a matrix with the oxycodone or pharmaceutically acceptable salt thereof which matrix provides for the sustained release of the oxycodone.

A non-limiting list of suitable sustained-release materials which may be included in a sustained-release matrix according to the invention include hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials, waxes, shellac, and oils such as hydrogenated castor oil and hydrogenated vegetable oil. However, any pharmaceutically acceptable hydrophobic or hydrophilic sustained-release material which is capable of imparting sustained-release of the oxycodone or pharmaceutically acceptable salt thereof may be used in accordance with the present invention. Preferred sustained-release polymers include alkylcelluloses such as ethylcellulose, acrylic and methacrylic acid polymers and copolymers; and cellulose ethers, especially hydroxyalkylcelluloses (especially hydroxypropylmethylcellulose) and carboxyalkylcelluloses. Preferred acrylic and methacrylic acid polymers and copolymers include methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, ethyl acrylate, trimethyl ammonioethyl methacrylate, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. Certain preferred embodiments utilize mixtures of any of the foregoing sustained-release materials in the matrix of the invention.

The matrix also may include a binder. In such embodiments, the binder preferably contributes to the sustained-release of the oxycodone or pharmaceutically acceptable salt thereof from the sustained-release matrix.

If an additional hydrophobic binder material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive. In certain preferred embodiments, a combination of two or more hydrophobic binder materials are included in the matrix formulations.

Preferred hydrophobic binder materials which may be used in accordance with the present invention include digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils, natural and synthetic waxes and polyalkylene glycols.

Hydrocarbons having a melting point of between 25° and 90°C are preferred. Of the long-chain hydrocarbon binder materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 80% (by weight) of at least one digestible, long chain hydrocarbon.

In certain embodiments, the hydrophobic binder material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic acid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about 30 to about 100°C. In certain preferred embodiments, the dosage form comprises a sustained release matrix comprising oxycodone or a pharmaceutically acceptable salt thereof and at least one water soluble hydroxyalkyl cellulose, at least one C_{12}-C_{36}, preferably C_{14}-C_{22}, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The hydroxyalkyl cellulose is preferably a hydroxy (C_1 to C_6) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and, especially, hydroxyethyl cellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form may be determined, inter alia, by the precise rate of oxycodone or oxycodone salt release required. The aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the aliphatic alcohol in the present oral dosage form may be determined, as above, by the precise rate of oxycodone or oxycodone salt release required. It may also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between about 20% and about 50% (by wt) of the aliphatic alcohol. When a polyalkylene glycol is present in the oral dosage form, then the combined weight of the aliphatic alcohol and the polyalkylene glycol preferably constitutes between about 20% and about 50% (by wt) of the total dosage form.

In one preferred embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the oxycodone or oxycodone salt from the formulation. In certain embodiments, a ratio of the hydroxyalkyl cellulose to the aliphatic alcohol/polyalkylene glycol of between 1:1 and 1:4 is preferred, with a ratio of between 1:2 and 1:3 being particularly preferred.

In certain embodiments, the polyalkylene glycol may be, for example, polypropylene glycol, or polyethylene glycol which is preferred. The average molecular weight of the at least one polyalkylene glycol is preferably between 1,000 and 15,000, especially between 1,500 and 12,000.

Another suitable sustained-release matrix comprises an alkylcellulose (especially ethylcellulose), a C_{12} to C_{36} aliphatic alcohol and, optionally, a polyalkylene glycol.

In addition to the above ingredients, a sustained-release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

In order to facilitate the preparation of a solid, sustained-release oral dosage form according to this invention there is provided, in a further aspect of the present invention, a process for the preparation of a solid, sustained-release oral dosage form according to the present invention comprising incorporating oxycodone or a salt thereof in a sustained-release matrix. Incorporation in the matrix may be effected, for example, by:

(a) forming granules comprising at least one hydrophobic and/or hydrophilic material as set forth above (e.g., a water soluble hydroxyalkyl cellulose) together with the oxycodone or pharmaceutically acceptable salt thereof;

(b) mixing the at least one hydrophobic and/or hydrophilic material- containing granules with at least one C_{12}-C_{36} aliphatic alcohol, and

(c) optionally, compressing and shaping the granules.

The granules may be formed by any of the procedures well-known to those skilled in the art of pharmaceutical formulation. For example, in one preferred method, the granules may be formed by wet granulating hydroxyalkyl cellulose/oxycodone or oxycodone salt with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the oxycodone or oxycodone salt.

A sustained-release matrix can also be prepared by, e.g., melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic binder material, e.g., a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate a hydrophobic sustained-release material, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic binder material. Examples of sustained-release formulations prepared via melt-granulation techniques are found, e.g., in U.S. Patent No. 4,861,598.

The additional hydrophobic binder material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve sustained release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like binder substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the oxycodone or pharmaceutically acceptable salt thereof, together with a sustained release material and preferably a binder material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded, e.g., using a twin-screw extruder, to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The matrix multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and provides sustained release of the oxycodone or pharmaceutically acceptable salt thereof for a time period of at least about 24 hours.

An optional process for preparing the melt extruded formulations of the present invention includes directly metering into an extruder a hydrophobic sustained release material, the oxycodone or salt thereof, and an optional binder material; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into matrix multiparticulates having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

Plasticizers, such as those described above, may be included in melt-extruded matrices. The plasticizer is preferably included as from about 0.1 to about 30% by weight of the matrix. Other pharmaceutical excipients, e.g., talc, mono or poly saccharides, colorants, flavorants, lubricants and the like may be included in the sustained release matrices of the present invention as desired. The amounts included will depend upon the desired characteristic to be achieved.

The diameter of the extruder aperture or exit port can be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be

oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

A melt extruded matrix multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For purposes of the present invention, the terms "melt-extruded matrix multiparticulate(s)" and "melt-extruded matrix multiparticulate system(s)" and "melt-extruded matrix particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic sustained release material as described herein. Preferably the melt-extruded matrix multiparticulates will be of a range of from about 0.1 to about 12 mm in length and have a diameter of from about 0.1 to about 5 mm. In addition, it is to be understood that the melt-extruded matrix multiparticulates can be any geometrical shape within this size range. In certain embodiments, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

In one preferred embodiment, oral dosage forms are prepared that include an effective amount of melt-extruded matrix multiparticulates within a capsule. For example, a plurality of the melt-extruded matrix multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastrointestinal fluid.

In another embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tableting equipment using standard techniques. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980).

In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Patent No. 4,957,681 (Klimesch, et. al.).

Optionally, the sustained-release matrix multiparticulate systems, tablets, or capsules can be coated with a sustained release coating such as the sustained release coatings described herein. Such coatings preferably include a sufficient amount of hydrophobic and/or hydrophilic sustained-release material to obtain a weight gain level from about 2 to about 25 percent, although the overcoat may be greater depending upon, e.g., the desired release rate.

The dosage forms of the present invention may further include combinations of melt-extruded matrix multiparticulates containing oxycodone or pharmaceutically acceptable salt thereof. Furthermore, the dosage forms can also include an amount of an immediate release therapeutically active oxycodone or pharmaceutically acceptable salt thereof for prompt therapeutic effect. The immediate release oxycodone or pharmaceutically acceptable salt thereof may be incorporated, e.g., as separate multiparticulates within a gelatin capsule, or may be coated on the surface of, e.g., melt extruded matrix multiparticulates.

The sustained-release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of sustained-release material, by varying the amount of plasticizer relative to other matrix constituents, by varying the amount of hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

In other embodiments of the invention, melt-extruded formulations are prepared without the inclusion of the oxycodone or pharmaceutically acceptable salt thereof, which is added thereafter to the extrudate. Such formulations typically will have the oxycodone or pharmaceutically acceptable salt thereof blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation. Such formulations may be advantageous, for example, when the therapeutically active agent included in the formulation is sensitive to temperatures needed for softening the hydrophobic material and/or the retardant material.

Typical melt-extrusion production systems suitable for use in accordance with the present invention include a suitable extruder drive motor having variable speed and constant torque control, start-stop controls, and ammeter. In addition, the production system will include a temperature control console which includes temperature sensors, cooling means and temperature indicators throughout the length of the extruder. In addition, the production system will include an extruder such as a twin-screw extruder which consists of two counter-rotating intermeshing screws enclosed within a cylinder or barrel having an aperture or die at the exit thereof. The feed materials enter through a feed hopper and are moved through the barrel by the screws and are forced through the die into strands which are thereafter conveyed such as by a continuous movable belt to allow for cooling and being directed to a pelletizer or other suitable device to render the extruded ropes into the matrix multiparticulate system. The pelletizer can consist of rollers, fixed knife, rotating cutter and the like. Suitable instruments and systems are available from distributors such as C.W. Brabender Instruments, Inc. of South Hackensack, New Jersey. Other suitable apparatus will be apparent to those of ordinary skill in the art.

A further aspect of the invention is related to the preparation of melt-extruded matrix multiparticulates as set forth above in a manner which controls the amount of air included in the extruded product. By controlling the amount of air included in the extrudate, the release rate of the oxycodone or therapeutically acceptable salt thereof may be altered.

Thus, in a further aspect of the invention, the melt-extruded product is prepared in a manner which substantially excludes air during the extrusion phase of the process. This may be accomplished, for example, by using a Leistritz extruder having a vacuum attachment. The extruded matrix multiparticulates prepared according to the invention using the Leistritz extruder under vacuum provides a melt-extruded product having different physical characteristics. In particular, the extrudate is substantially non-porous when magnified, e.g., using a scanning electron microscope which provides an SEM (scanning electron micrograph). Such substantially non-porous formulations may provide a faster release of the therapeutically active agent, relative to the same formulation prepared without vacuum. SEMs of the matrix multiparticulates prepared using an extruder under vacuum appear very smooth, and the multiparticulates tend to be more robust than those multiparticulates prepared without vacuum. It has been observed that in at least certain formulations, the use of extrusion under vacuum provides an extruded matrix multiparticulate product which is more pH-dependent than its counterpart formulation prepared without vacuum.

Alternatively, the melt-extruded product is prepared using a Werner-Pfleiderer twin screw extruder.

In certain embodiments, a spheronizing agent is added to a granulate or matrix multiparticulate and then spheronized to produce sustained release spheroids. The spheroids are then optionally overcoated with a sustained release coating by methods such as those described above.

Spheronizing agents which may be used to prepare the matrix multiparticulate formulations of the present invention include any art-known spheronizing agent. Cellulose derivatives are preferred, and microcrystalline cellulose is especially preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (TradeMark, FMC Corporation). The spheronizing agent is preferably included as about 1 to about 99% of the matrix multiparticulate by weight.

In certain embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water

soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxy propyl cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose.

In certain embodiments, a sustained release coating is applied to the sustained release spheroids, granules, or matrix multiparticulates. In such embodiments, the sustained-release coating may include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein. The coating is preferably derived from an aqueous dispersion of the hydrophobic sustained release material.

In certain embodiments, it is necessary to overcoat the sustained release spheroids, granules, or matrix multiparticulates comprising the oxycodone or pharmaceutically acceptable salt thereof and sustained release carrier with a sufficient amount of the aqueous dispersion of, e.g., alkylcellulose or acrylic polymer, to obtain a weight gain level from about 2 to about 50%, e.g., about 2 to about 25%, in order to obtain a sustained-release formulation. The overcoat may be lesser or greater depending upon, e.g., the desired release rate, the inclusion of plasticizer in the aqueous dispersion and the manner of incorporation of the same. Cellulosic materials and polymers, including alkylcelluloses, are sustained release materials well suited for coating the sustained release spheroids, granules, or matrix multiparticulates according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

One commercially–available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pennsylvania, U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water–immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pennsylvania, U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous

mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly to the sustained release spheroids, granules, or matrix multiparticulates.

In other preferred embodiments of the present invention, the sustained release material comprising the sustained-release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in the National Formulary (NF) XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth) acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from Röhm GMBH and Co. Kg Darmstadt, Germany. There are several different types of Eudragit®. For example, Eudragit E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit L is a methacrylic acid copolymer which does not swell at about pH < 5.7 and is soluble at about pH > 6. Eudragit S does not swell at about pH < 6.5 and is soluble at about pH > 7. Eudragit RL and Eudragit RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent; however, dosage forms coated with Eudragit RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are

copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained-release formulation having a desirable dissolution profile. Desirable sustained-release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS, and 10% Eudragit® RL:Eudragit® 90% RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L. In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic sustained release material, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained-release coating. For example, because ethyl-cellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing sustained-release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2–propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol,

diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

In certain embodiments, the uncoated/coated sustained release spheroids, granules, or matrix multiparticulates containing the oxycodone or oxycodone salt are cured until an endpoint is reached at which the sustained release spheroids, granules, or matrix multiparticulates provide a stable dissolution. The curing endpoint may be determined by comparing the dissolution profile (curve) of the dosage form immediately after curing to the dissolution profile (curve) of the dosage form after exposure to accelerated storage conditions of, e.g., at least one month at a temperature of 40°C and a relative humidity of 75%. Cured formulations are described in detail in U.S. Patent Nos. 5,273,760; 5,286,493; 5,500,227; 5,580,578; 5,639,476; 5,681,585; and 6,024,982. Other examples of sustained-release formulations and coatings which may be used in accordance with the present invention include U.S. Patent Nos. 5,324,351; 5,356,467; and 5,472,712.

In addition to the above ingredients, the spheroids, granules, or matrix multiparticulates may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the formulation if desired. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986).

It has further been found that the addition of a small amount of talc to the sustained release coating reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

SUSTAINED RELEASE OSMOTIC DOSAGE

Sustained release dosage forms according to the present invention may also be prepared as osmotic dosage formulations. The osmotic dosage forms preferably include a bilayer core comprising a drug layer and a delivery or push layer, wherein the bilayer core is surrounded by a semipermeable wall and optionally having at least one passageway disposed therein.

The expression "passageway" as used for the purpose of this invention, includes aperture, orifice, bore, pore, porous element through which oxycodone or oxycodone salt can be pumped, diffuse or migrate through a fiber, capillary tube, porous overlay, porous insert, microporous member, or porous composition. The passageway can also include a compound that erodes or is leached from the wall in the fluid environment of use to produce at least one passageway. Representative compounds for forming a passageway include erodible poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable compounds such as fluid-removable pore-forming polysaccharides, acids, salts or oxides. A passageway can be formed by leaching a compound from the wall, such as sorbitol, sucrose, lactose, maltose, or fructose, to form a sustained-release dimensional pore-passageway. The passageway can have any shape, such as round, triangular, square and elliptical, for assisting in the sustained metered release of oxycodone or oxycodone salt from the dosage form. The dosage form can be manufactured with one or more passageways in spaced-apart relation on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are disclosed in U.S. Patent Nos. 3,845,770; 3,916,899; 4,063,064 and 4,088,864. Passageways comprising sustained-release dimensions sized, shaped and adapted as a releasing-pore formed by aqueous leaching to provide a releasing-pore of a sustained-release rate are disclosed in U.S. Patent Nos. 4,200,098 and 4,285,987.

In certain embodiments, the bilayer core comprises a drug layer with oxycodone or a salt thereof and a displacement or push layer. In certain embodiments the drug layer may also comprise at least one polymer hydrogel. The polymer hydrogel may have an average molecular weight of between about 500 and about 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula $(C_6 H_{12} O_5)_n \cdot H_2O$, wherein n is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) represented by, e.g., a poly(ethylene oxide) and a poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000 or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium or potassium, the alkyl is methyl, ethyl, propyl, or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 500,000 number-average molecular weight.

In certain embodiments of the present invention, the delivery or push layer comprises an osmopolymer. Examples of an osmopolymer include but are not limited to a member selected from the group consisting of a polyalkylene oxide and a carboxyalkylcellulose. The

polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. The polyalkylene oxide may be a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 average molecular weight, polyethylene oxide comprising a 5,000,000 average molecular weight, polyethylene oxide comprising a 7,000,000 average molecular weight, cross-linked polymethylene oxide possessing a 1,000,000 average molecular weight, and polypropylene oxide of 1,200,000 average molecular weight. Typical osmopolymer carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkylcellulose, sodium carboxymethylcellulose, potassium carboxymethylcellulose, sodium carboxyethylcellulose, lithium carboxymethylcellulose, sodium carboxyethylcellulose, carboxyalkylhydroxyalkylcellulose, carboxymethylhydroxyethyl cellulose, carboxyethylhydroxyethylcellulose and carboxymethylhydroxypropylcellulose. The osmopolymers used for the displacement layer exhibit an osmotic pressure gradient across the semipermeable wall. The osmopolymers imbibe fluid into dosage form, thereby swelling and expanding as an osmotic hydrogel (also known as osmogel), whereby they push the oxycodone or pharmaceutically acceptable salt thereof from the osmotic dosage form.

The push layer may also include one or more osmotically effective compounds also known as osmagents and as osmotically effective solutes. They imbibe an environmental fluid, for example, from the gastrointestinal tract, into dosage form and contribute to the delivery kinetics of the displacement layer. Examples of osmotically active compounds comprise a member selected from the group consisting of osmotic salts and osmotic carbohydrates. Examples of specific osmagents include but are not limited to sodium chloride, potassium chloride, magnesium sulfate, lithium phosphate, lithium chloride, sodium phosphate, potassium sulfate, sodium sulfate, potassium phosphate, glucose, fructose and maltose.

The push layer may optionally include a hydroxypropylalkylcellulose possessing a 9,000 to 450,000 number-average molecular weight. The hydroxypropylalkylcellulose is represented by a member selected from the group consisting of hydroxypropyl-methylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose.

The push layer optionally may comprise a nontoxic colorant or dye. Examples of colorants or dyes include but are not limited to Food and Drug Administration Colorant (FD&C), such as FD&C No. 1 blue dye, FD&C No. 4 red dye, red ferric oxide, yellow ferric oxide, titanium dioxide, carbon black, and indigo.

The push layer may also optionally comprise an antioxidant to inhibit the oxidation of ingredients. Some examples of antioxidants include but are not limited to a member selected from the group consisting of ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaretic acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiary butylphenol, alphatocopherol, and propylgallate.

In certain alternative embodiments, the dosage form comprises a homogenous core comprising oxycodone or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable polymer (e.g., polyethylene oxide), optionally a disintegrant (e.g., polyvinylpyrrolidone), optionally an absorption enhancer (e.g., a fatty acid, a surfactant, a chelating agent, a bile salt, etc.). The homogenous core is surrounded by a semipermeable wall having a passageway (as defined above) for the release of the oxycodone or pharmaceutically acceptable salt thereof.

In certain embodiments, the semipermeable wall comprises a member selected from the group consisting of a cellulose ester polymer, a cellulose ether polymer and a cellulose ester-ether polymer. Representative wall polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkenylates, and mono-, di- and tricellulose alkinylates. The poly(cellulose) used for the present invention comprises a number-average molecular weight of 20,000 to 7,500,000.

Additional semipermeable polymers for the purpose of this invention comprise acetaldehyde dimethycellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose diacetate, propylcarbamate, cellulose acetate diethylaminoacetate; semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable cross-linked polymer formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Patent Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,876; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Patent No. 3,133,132; semipermeable crosslinked polystyrenes; semipermeable cross-linked poly(sodium styrene sulfonate); semipermeable crosslinked poly(vinylbenzyltrimethyl ammonium chloride); and semipermeable polymers possessing a fluid permeability of $2.5x10^{-8}$ to $2.5x10^{-2}$ (cm^2 /hr·atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. Other polymers useful in the present invention are known in the art in U.S. Patent Nos. 3,845,770; 3,916,899 and 4,160,020; and

in Handbook of Common Polymers, Scott, J. R. and W. J. Roff, 1971, CRC Press, Cleveland, Ohio.

In certain embodiments, preferably the semipermeable wall is nontoxic, inert, and it maintains its physical and chemical integrity during the dispensing life of the drug. In certain embodiments, the dosage form comprises a binder. An example of a binder includes, but is not limited to a therapeutically acceptable vinyl polymer having a 5,000 to 350,000 viscosity-average molecular weight, represented by a member selected from the group consisting of poly-n-vinylamide, poly-n-vinylacetamide, poly(vinyl pyrrolidone), also known as poly-n-vinylpyrrolidone, poly-n-vinylcaprolactone, poly-n-vinyl-5-methyl-2-pyrrolidone, and poly-n-vinyl-pyrrolidone copolymers with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laureate, and vinyl stearate. Other binders include for example, acacia, starch, gelatin, and hydroxypropylalkylcellulose of 9,200 to 250,000 average molecular weight.

In certain embodiments, the dosage form comprises a lubricant, which may be used during the manufacture of the dosage form to prevent sticking to die wall or punch faces. Examples of lubricants include but are not limited to magnesium stearate, sodium stearate, stearic acid, calcium stearate, magnesium oleate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, and magnesium palmitate.

In certain preferred embodiments, the present invention includes a therapeutic composition comprising 1 to 640 mg of the oxycodone or pharmaceutically acceptable salt thereof, 25 to 500 mg of poly(alkylene oxide) having a 150,000 to 500,000 average molecular weight, 1 to 50 mg of poly(vinylpyrrolidone) having a 40,000 average molecular weight, and 0 to about 7.5 mg of a lubricant.

In certain embodiments, the invention also provides a method for administering 1 to 640 mg of oxycodone or a pharmaceutically acceptable salt thereof by admitting orally 1 to 640 mg of oxycodone or pharmaceutically acceptable salt thereof to a patient administered from a dosage form comprising a semipermeable wall permeable to aqueous-biological fluid and impervious to the passageway of oxycodone or pharmaceutically acceptable salt thereof, which semipermeable wall surrounds an internal space comprising an oxycodone drug composition and a push composition, said oxycodone drug composition comprising 1 to 640 mg of oxycodone or pharmaceutically acceptable salt thereof, 25 to 500 mg of a poly(alkylene oxide) having a 150,000 to 500,000 average molecular weight, 1 to 50 mg of a poly(vinylpyrrolidone) having a 40,000 average molecular weight, and 0 to 7.5 mg of a lubricant, said push composition comprising 15 to 250 mg of a poly(alkylene oxide) of

3,000,000 to 7,500,000 average molecular weight, 0 to 75 mg of an osmagent, 1 to 50 mg of a hydroxyalkylcellulose, 0 to 10 mg of ferric oxide, 0 to 10 mg of a lubricant, and 0 to 10 mg of antioxidant; and a passageway in the semipermeable wall for delivering the oxycodone or pharmaceutically acceptable salt thereof from the dosage form, by imbibing fluid through the semipermeable wall into the dosage form causing the oxycodone or oxycodone salt composition to become dispensable and the push composition to expand and push the oxycodone or oxycodone salt composition through the passageway, whereby through the combined operations of the dosage form, the oxycodone or oxycodone salt is delivered at a therapeutically effective dose at a rate controlled over a sustained period of time.

The dosage forms of the present invention may optionally be coated with one or more coatings suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal (GI) fluid. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. Other preferred embodiments include a pH-dependent coating that releases the oxycodone or pharmaceutically acceptable salt thereof in desired areas of the GI tract, e.g., the stomach or small intestine, such that an absorption profile is provided which is capable of providing at least about twelve hours and preferably about twenty-four hours or more of analgesia to a patient. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

Formulations according to the invention that utilize pH-dependent coatings may also impart a repeat-action effect whereby unprotected drug is coated over an enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent and may be used in accordance with the present invention include a sustained release material such as, e.g., shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain embodiments of the present invention, an effective amount of oxycodone or pharmaceutically acceptable salt thereof in immediate release form is included in the formulation. The immediate release form of the oxycodone or oxycodone salt is included in an amount which is effective to reduce the time to maximum concentration of the oxycodone in the blood (e.g., plasma), such that the T_{max} is reduced. By including such an effective

amount of immediate release oxycodone or oxycodone salt in the unit dose, the experience of relatively higher levels of pain in patients may be reduced. In such embodiments, an effective amount of the oxycodone or oxycodone salt in immediate release form may be coated onto the tablet of the present invention. For example, where the extended release oxycodone or oxycodone salt from the formulation is due to a sustained release coating, the immediate release layer would be overcoated on top of the sustained release coating. On the other hand, the immediate release layer may be coated onto the surface of tablets wherein the oxycodone or oxycodone salt is incorporated in a sustained release matrix. One skilled in the art would recognize still other alternative manners of incorporating the immediate release oxycodone or oxycodone salt portion into the formulation. Such alternatives are deemed to be encompassed by the appended claims.

In yet further embodiments, the sustained release dosage forms of the present invention in addition to oxycodone or oxycodone salt may further include a non-opioid drug which may or may not act synergistically with the oxycodone or oxycodone salt. Such non-opioid drugs would preferably provide additional analgesia, and include, for example, aspirin; acetaminophen; non-steroidal anti-inflammatory drugs ("NSAIDS"), e.g., ibuprofen, ketoprofen, etc.; N-methyl-D-aspartate (NMDA) receptor antagonists, e.g., a morphinan such as dextromethorphan or dextrorphan, or ketamine; cyclooxygenase-II inhibitors ("COX-II inhibitors"); and/or glycine receptor antagonists.

In certain embodiments of the present invention, the invention allows for the use of lower doses of oxycodone or oxycodone salt by virtue of the inclusion of an additional non-opioid analgesic, such as an NSAID or a COX-2 inhibitor. By using lower amounts of either or both drugs, the side effects associated with effective pain management in humans may be reduced.

Suitable non-steroidal anti-inflammatory agents, include 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, mixtures thereof, and the like. Useful dosages of these drugs are well known to those skilled in the art.

N-methyl-D-aspartate (NMDA) receptor antagonists are well known in the art, and encompass, for example, morphinans such as dextromethorphan or dextrorphan, ketamine, or

pharmaceutically acceptable salts thereof. For purposes of the present invention, the term "NMDA antagonist" is also deemed to encompass drugs that at least partially inhibit a major intracellular consequence of NMDA-receptor activation, e.g. a ganglioside such as GM_1 or GT_{1b}, a phenothiazine such as trifluoperazine or a naphthalenesulfonamide such as N-(6-aminothexyl)-5-chloro-1-naphthalenesulfonamide. These drugs are stated to inhibit the development of tolerance to and/or dependence on addictive drugs, e.g., narcotic analgesics such as morphine, codeine, etc. in U.S. Patent Nos. 5,321,012 and 5,556,838 (both to Mayer, et al.), and to treat chronic pain in U.S. Patent No. 5,502,058 (Mayer, et al.). The NMDA antagonist may be included alone, or in combination with a local anesthetic such as lidocaine, as described in these Mayer, et al. patents.

The treatment of chronic pain via the use of glycine receptor antagonists and the identification of such drugs is described in U.S. Patent No. 5,514,680 (Weber, et al.).

COX-2 inhibitors have been reported in the art and many chemical structures are known to produce inhibition of cyclooxygenase-2. COX-2 inhibitors are described, for example, in U.S. Patent Nos. 5,616,601; 5,604,260; 5,593,994; 5,550,142; 5,536,752; 5,521,213; 5,475,995; 5,639,780; 5,604,253; 5,552,422; 5,510,368; 5,436,265; 5,409,944; and 5,130,311. Certain preferred COX-2 inhibitors include celecoxib (SC-58635), DUP-697, flosulide (CGP-28238), meloxicam, 6-methoxy-2 naphthylacetic acid (6-MNA), MK-966 (also known as Vioxx), nabumetone (prodrug for 6-MNA), nimesulide, NS-398, SC-5766, SC-58215, T-614; or combinations thereof. Dosage levels of COX-2 inhibitor on the order of from about 0.005 mg to about 140 mg per kilogram of body weight per day are therapeutically effective in combination with oxycodone or oxycodone salt. Alternatively, about 0.25 mg to about 7 g per patient per day of a COX-2 inhibitor is administered in combination with oxycodone or oxycodone salt.

In yet further embodiments, a non-opioid drug can be included which provides a desired effect other than analgesia, e.g., antitussive, expectorant, decongestant, antihistamine drugs, local anesthetics, and the like.

The additional (non-opioid) therapeutically active agent may be included in sustained release form or in immediate release form. The additional drug may be incorporated into the sustained release matrix along with the oxycodone or oxycodone salt, may be incorporated as a powder, granulation, etc. into the dosage form, or may be incorporated as a separated sustained release layer or immediate release layer.

The sustained-release oral solid dosage forms of the present invention may be opioid-sparing. It is possible that the sustained-release oral solid dosage forms of the present invention may be dosed at a substantially lower daily dosage in comparison to conventional immediate-release products, with no significant difference in analgesic efficacy. At comparable daily dosages, greater efficacy may result with the use of sustained-release oral solid dosage forms of the present invention in comparison to conventional immediate-release products.

The present invention will now be more fully described with reference to the accompanying examples. It should be understood, however, that the following description is illustrative only and should not be taken in any way as a restriction on the generality of the invention specified above.

Example 1

Oxycodone sustained release matrix tablets are produced with the formula set forth in Table 1 below:

Table 1

Ingredient	*Amt/unit (mg)*	*Amt/batch (gram)*
Oxycodone HCl	30.0	150.0
Spray Dried Lactose	50.0	250.0
Povidone	8.0	40.0
Eudragit RS30D (Solids)	50.0	250.0
Triacetin	6.0	30.0
Stearyl Alcohol	70.0	350.0
Talc	4.0	20.0
Magnesium Stearate	2.0	10.0
Opadry Red YS1-15597-A	10.0	50.0
Purified Water	*	*
Total	230.0	1150.0

*Used for processing and remains in product as residual moisture only.

According to the following procedure:

1. Granulation: Spray the Eudragit/Triacetin dispersion onto the Oxycodone HCl, Spray Dried Lactose and Povidone using a fluid bed granulator.
2. Milling: Discharge the granulation and pass through a mill with approximately 1 mm openings (18 mesh screen).
3. Waxing: Melt the stearyl alcohol at about 50 degrees C and add to the milled granulation using a high shear mixer. Allow to cool to room temperature on trays or a fluid bed.
4. Milling: Pass the cooled granulation through a mill with an approximately 18 mesh screen.
5. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.
6. Compression: Compress the granulation into tablets using a Kilian® Tablet press.
7. Film Coating: Apply an aqueous film coat to the tablets using a rotary pan.

Example 2

Oxycodone sustained release osmotic tablets are produced with the formula set forth in Table 2 below:

TABLE 2

Ingredient	***Amt/unit (mg)***
Drug Layer:	
Oxycodone HCl	35.20
Polyethylene oxide	130.24
Povidone	8.8
Magnesium Stearate	1.76
Displacement Layer:	
Polyethylene oxide	85.96
Sodium chloride	40.50
Hydroxypropylmethylcellulose	6.75
Ferric Oxide	1.35
Magnesium Stearate	0.34
BHT	0.10
Semipermeable Wall:	
Cellulose acetate	38.6

The dosage form having the above formulation is prepared according to the following procedure:

First, 175 g of oxycodone hydrochloride, 647.5 g of poly(ethylene oxide) possessing a 200,000 average molecular weight, and 43.75 g of poly(vinylpyrrolidone) having a 40,000 average molecular weight is added to a mixer and mixed for 10 minutes. Then, 331 g of denatured anhydrous alcohol is added to the blended materials with continuous mixing for 10 minutes. Then, the wet granulation is passed through a 20 mesh screen, allowed to dry at room temperature for 20 hours, and then passed through a 16 mesh screen. Next, the granulation is transferred to the mixer, mixed and lubricated with 8.75 g of magnesium stearate.

Then, the displacement or push composition for pushing the oxycodone HCl composition from the dosage form is prepared as follows: first 3910 g of hydroxypropylmethylcellulose possessing an 11,200 average molecular weight is dissolved in 45,339 g of water. Then, 101 g of butylated hydroxytoluene is dissolved in 650 g of denatured anhydrous alcohol. Next, 2.5 kg of the hydroxypropylmethylcellulose aqueous solution is added with continuous mixing to the butylated hydroxytoluene alcohol solution.

Then, binder solution preparation is completed by adding with continuous mixing the remaining hydroxypropylmethylcellulose aqueous solution to the butylated hydroxytoluene alcohol solution.

Next, 36,000 g of sodium chloride is sized using a Quadro Comil® mill equipped with a 21 mesh screen. Then, 1200 g of ferric oxide is passed through a 40 mesh screen. Then, the screened materials, 76,400 g of pharmaceutically acceptable poly(ethylene oxide) possessing a 7,500,000 average molecular weight, 2500 g of hydroxypropylmethylcellulose having a 11,200 average molecular weight are added to a Glatt® Fluid Bed Granulation's bowl. The bowl is attached to the granulator and the granulation process is initiated for effecting granulation. Next, the dry powders are air suspended and mixed for 10 minutes. Then, the binder solution is sprayed from 3 nozzles onto the powder. The granulating is monitored during the process as follows: total solution spray rate of 800 g/min; inlet temperature 43°C and air flow 4300 m^3/hr. At the end of solution spraying, 45,033 g, the resultant coated granulated particles are subjected to a drying process for 35 minutes.

The coated granules are sized using a Quadro Comil® mill with an 8 mesh screen. The granulation is transferred to a Tote® Tumbler, mixed and lubricated with 281.7 g of magnesium stearate.

Next, the drug composition comprising the oxycodone hydrochloride and the push composition are compressed into bilayer tablets on a Kilian® Tablet press. First, 176 mg of the oxycodone hydrochloride composition is added to the die cavity and precompressed, then, 135 mg of the push composition is added and the layers are pressed under a pressure head of 3 metric tons into an 11/32 inch (0.873 cm) diameter contacting layer arrangement.

The bilayered arrangements are coated with a semipermeable wall. The wall forming composition comprises 100% cellulose acetate having a 39.8% acetyl content. The wall-forming composition is dissolved in acetone:water (95:5 wt:wt) cosolvent to make a 4% solid solution. The wall-forming composition is sprayed onto and around the bilayers in a 24 inch (60 cm) Vector® Hi-Coater. Next, one 20 mil (0.508 mm) exit passageway is drilled through the semipermeable wall to connect the drug oxycodone layer with the exterior of the dosage form. The residual solvent is removed by drying for 72 hours at 45°C and 45% humidity. Next, the osmotic dosage systems are dried for 4 hours at 45°C to remove excess moisture. The dosage forms produced by this manufacture comprises 35.20 mg of oxycodone HCl, 130.24 mg of poly(ethylene oxide) of 200,000 average molecular weight, 8.80 mg of poly(vinylpyrrolidone) of 40,000 average molecular weight, and 1.76 mg of magnesium stearate. The push composition comprises 85.96 mg of poly(ethylene oxide) of 7,500,000

average molecular weight, 40.50 mg of sodium chloride, 6.75 mg of hydroxypropylmethylcellulose, 1.35 mg of red ferric oxide, 0.34 mg of magnesium stearate, and 0.10 mg of butylated hydroxytoluene. The semipermeable wall comprises 38.6 mg of cellulose acetate comprising a 39.8% acetyl content. The dosage form comprises one passageway, 20 mil (0.508 mm).

EXAMPLE 3

Oxycodone sustained release osmotic tablets are produced with the formula set forth in Table 3 below:

TABLE 3

Ingredient	***Percentage***
Drug Layer:	Percentage of Drug Layer
Oxycodone HCL	28.8
Polyethylene oxide	64.2
Povidone	6
Magnesium Stearate	1
Displacement Layer:	Percentage of Displacement Layer
Polyethylene oxide	63.675
Sodium chloride	30
Hydroxypropylmethylcellulose	5
Ferric Oxide	1
Magnesium Stearate	0.25
BHT	0.075
Semipermeable Wall:	Percentage of Semipermeable Wall
Cellulose acetate	95
Polyethylene glycol	5

The dosage form having the above formulation is prepared according to the following procedure:

First, 1728 g of oxycodone HCl, 3852 g of poly(ethylene oxide) possessing a 200,000 average molecular weight, and 360 g of poly(vinyl pyrrolidone) having an average molecular weight of 40,000 are added to a planetary mixing bowl. Next, the dry materials are mixed for ten minutes. Then, 1616 g of denatured anhydrous ethyl alcohol is slowly added to the blended materials with continuous mixing for 15 minutes. Next, the freshly prepared wet

granulation is passed through a 20 mesh screen, allowed to dry at room temperature for 20.5 hours, and passed through a 16 mesh screen. Next, the granulation is transferred to a planetary mixer, mixed and lubricated with 59.8 g of magnesium stearate.

Next, a push composition is prepared as follows: first, a binder solution is prepared by dissolving 3910 g of hydroxypropylmethylcellulose possessing an average molecular weight of 11,200 in 45,339 g of water. Next, 101 g of butylated hydroxytoluene is dissolved in 650 g of denatured anhydrous alcohol. Approximately 2.5 kg of the hydroxypropyl-methylcellulose/water solution is added to the butylated hydroxytoluene/alcohol solution with continuous mixing. Next, the binder solution preparation is completed by adding the remaining hydroxypropyl-methylcellulose/water solution to the butylated hydroxyl-toluene/alcohol solution, again with continuous mixing.

Next, 36,000 g of sodium chloride is sized using a Quadro Comil® mill, used to reduce the particle size of the sodium chloride. A fluid air mill is another mill used to size materials with a 21 mesh screen. Next, 1200 g of ferric oxide is passed through a 40 mesh screen. Then, all the screened materials, 76,400 g of pharmaceutically acceptable poly(ethylene oxide) comprising a 7,000,000 average molecular weight, 2520 g of hydroxypropylmethylcellulose comprising an average molecular weight of 11,200 is added to a Glatt Fluid Bed Granulator bowl. The bowl is attached to the granulator and the granulation process is initiated for effecting granulation. Next, the dry powders are air suspended and mixed for 10 minutes. Then, the binder solution is sprayed from 3 nozzles onto the powder.

While spraying the binder solution, the filter bags are shaken for 10 seconds every 1.5 minutes to unglue any possible powder deposits. At the end of the solution spraying, 45,033 g of the resultant coated granulated particles are subjected to a drying process for 35 minutes. The machine is turned off, and the coated granules are removed from the granulator. The coated granules are sized using a Quadro Comil with an 8 mesh screen. The granulation is transferred to Tote Tumbler, mixed and lubricated with 281.7 g of magnesium stearate. Please review second sentence and clarify.

Next, the oxycodone HCl drug composition and the push composition are compressed into bilayer tablets on the Kilian® Tablet Press. First, 434 mg of the oxycodone HCl composition is added to the die cavity and pre-compressed, then, 260 mg of the push

composition is added and the layers are pressed under a pressure head of approximately 3 metric tons into a 0.700" (1.78 cm) x 0.375" (0.95 cm) oval contacting layered arrangement.

The bilayered arrangement is coated with a semi-permeable wall. The wall forming composition comprises 95% cellulose acetate having a 39.8% acetyl content, and 5% polyethylene glycol having a molecular weight of 3350. The wall-forming composition is dissolved in an acetone:water (95:5 wt:wt) cosolvent to make a 4% solids solution. The wall-forming composition is sprayed onto and around the bilayers in a 24" Vector Hi® Coater.

Next, two 30 mil (0.762 mm) exit passageways are drilled through the semi-permeable wall to connect the drug layer with the exterior of the dosage system. The residual solvent is removed by drying for 48 hours at 50°C and 50% humidity. Next, the osmotic dosage forms are dried for 4 hours at 50°C to remove excess moisture. The dosage form produced by this manufacture provides 28.8% oxycodone HCl, 64.2% poly(ethylene oxide) possessing a 200,000 average molecular weight, 6% poly(vinyl pyrrolidone) possessing a 40,000 average molecular weight, and 1% magnesium stearate. The push composition comprises 63.675% poly(ethylene oxide) comprising a 7,000,000 average molecular weight, 30% sodium chloride, 5% hydroxypropylmethylcellulose comprising a 11,200 average molecular weight, 1% ferric oxide, 0.075% butylated hydroxytoluene, and 0.25% magnesium stearate. The semipermeable wall comprises 95 wt % cellulose acetate comprising a 39.8% acetyl content, and 5.0 wt % polyethylene glycol comprising a 3350 average molecular weight. The dosage form comprises two passageways, 30 mils (0.762 mm), and has an oxycodone hydrochloride mean release rate of about 5 mg/hr.

The dosage form in further embodiments can comprise 65 wt % to 100 wt % of a cellulose polymer which polymer comprises a member selected from the group consisting of a cellulose ester, cellulose diester, cellulose triester, cellulose ether, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacetate, cellulose acetate butyrate, and the like. The wall can also comprise from 0 wt % to 40 wt % of a cellulose ether member selected from the group consisting of hydroxypropylcellulose and hydroxypropylmethylcellulose and from 0 wt % to 20 wt % of polyethylene glycol. The total amount of all components comprising the wall is equal to 100 wt %. Semipermeable

polymers useful for manufacturing wall of the dosage form are disclosed in U.S. Patent Nos. 3,845,770; 3,916,899; 4,008,719; 4,036,228; and 4,111,201.

The wall in other preferred processes comprises the selectively permeable cellulose ether, ethyl cellulose. The ethyl cellulose comprises an ethoxy group with a degree of substitution, of about 1.4 to 3, equivalent to 40% to 50% ethoxy content, and a viscosity range of 7 to 100 centipoise, or higher. More specifically, the wall comprises 45 wt % to 80 wt % ethyl cellulose, from 5 wt % to 30 wt % hydroxypropylcellulose, and from 5 wt % to 30 wt % polyethylene glycol, with the total weight percent of all components comprising the wall equal to 100 wt %. In another embodiment the wall comprises 45 wt % to 80 wt % of ethylcellulose, from 5 wt % to 30 wt % hydroxypropylcellulose, from 2 wt % to 20 wt % of polyvinyl pyrrolidone, with the total amount of all components comprising the wall equal to 100 wt %.

EXAMPLE 4

Oxycodone 10 mg sustained release capsules were prepared with the formula set forth in Table 4 below:

Table 4

Ingredient	*Amt/unit (mg)*
Oxycodone HCl	10.0
Stearic Acid	8.25
Stearic Alcohol	24.75
Eudragit RSPO	77
Total	120

The formulation above was prepared according to the following procedure:

1. Pass the stearyl alcohol flakes through an impact mill.
2. Blend the Oxycodone HCl, stearic acid, stearyl alcohol and the Eudragit RSPO in a suitable blender/mixer.
3. Continuously feed the blended material into a twin screw extruder at elevated temperatures, and collect the resultant strands on a conveyor.
4. Allow the strands to cool on the conveyor.
5. Cut the strands into 1 mm pellets using a pelletizer.
6. Screen the pellets for fines and oversized pellets to an acceptable range of about 0.8 - 1.4 mm in size.
7. Fill into capsules with a fill weight of 120 mg/capsule (fill into size 2 capsules).

The pellets were then tested for dissolution using the following procedure: Fiber optic UV dissolution using USP apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid (SGF) and in 900 ml simulated intestinal fluid (SIF) monitoring at 282 nm.

The dissolution parameters are set forth in Table 4A below:

Table 4A

Time (hour)	*% Dissolved in SGF*	*% Dissolved in SIF*
1	15	10
2	22	15
4	32	22
8	44	29
12	53	34
18	62	40
24	66	44

Example 5

Oxycodone 160 mg sustained release capsules were prepared with the formula set forth in Table 5 below:

Table 5

Ingredient	*Amt/unit (mg)*
Oxycodone HCL	160
Stearic Acid	80
Stearyl Alcohol	20
Eudragit RSPO	140
Total	400

The formulation above was prepared according to the following procedure:

1. Pass the stearyl alcohol flakes through an impact mill.
2. Blend the Oxycodone HCl, stearic acid, stearyl alcohol and the Eudragit RSPO in a suitable lender/mixer.
3. Continuously feed the blended material into a twin screw extruder at elevated temperatures and collect the resultant strands on a conveyor.
4. Allow the strands to cool on the conveyor.
5. Cut the strands into 1 mm pellets using a pelletizer.
6. Screen the pellets for fines and oversized pellets to an acceptable range of about 0.8 - 1.4 mm in size.
7. Fill into capsules with a fill weight of 400 mg/capsule (Fill into size 00 capsules).

DISSOLUTION METHOD:

The pellets were then tested for dissolution using the following procedure:

Fiber optic UV dissolution using USP apparatus 1 (basket) at 100 rpm in 900 ml simulated gastric fluid (SGF) and in 900 ml simulated intestinal fluid (SIF) monitoring at 282 nm.

The dissolution parameters for the above formulation are set forth in Table 5A below: Please ensure Table 5A does not have error message.

Table 5A

Time (hour)	*% Dissolved in SGF*	*% Dissolved in SIF*
1	32	20
2	47	28
4	66	42
8	86	60
12	93	70
18	95	77
24	95	80

Many other variations of the present invention will be apparent to those skilled in the art and are meant to be within the scope of the claims appended hereto.

CLAIMS:

1. A sustained-release oral dosage form for once-a-day administration comprising:

a pharmaceutically acceptable matrix comprising an analgesically effective amount of oxycodone or a pharmaceutically acceptable salt thereof and a sustained release material, said dosage form providing an analgesic effect for at least about 24 hours after oral administration at steady state to human patients; and said dosage form providing a mean C_{24}/C_{max} oxycodone ratio of 0.6 to 1.0 after steady state oral administration to said patients.

2. The dosage form of claim 1, which provides a mean T_{max} of oxycodone at about 2 to about 17 hours after administration at steady state to said patients.

3. The dosage form of claim 1, which provides a mean T_{max} of oxycodone at about 8 to about 16 hours after administration at steady state to said patients.

4. The dosage form of claim 1, wherein the matrix is substantially homogeneous.

5. The dosage form of claim 1, wherein said matrix is contained within a gelatin capsule.

6. 6. The dosage form of claim 1, wherein said matrix is formulated into a tablet.

7. 7. The dosage form of claim 1, which provides a mean T_{max} at about 12 to about 16 hours after administration at steady state to said patients.

8. 8. The dosage form of claim 1, wherein said oxycodone or pharmaceutically acceptable salt thereof is an amount from about 5 to about 640 mg.

9. The dosage form of claim 1, wherein said pharmaceutically acceptable salt of oxycodone is oxycodone hydrochloride.

10. The dosage form of claim 1, which provides a mean C_{24}/C_{max} ratio of 0.7 to 0.99 after administration at steady state to said patients.

11. The dosage form of claim 1, which provides a mean C_{24}/C_{max} ratio of 0.8 to 0.95 after administration at steady state to said patients.

12. The dosage form of claim 1, which provides an in-vitro release rate, of oxycodone or a pharmaceutically acceptable salt thereof, when measured by the USP Basket Method at 100 rpm in 900 ml aqueous buffer at a pH of between 1.6 and 7.2 at 37°C of from 0% to about 40% at 1 hour, from about 8% to about 70% at 4 hours, from about 20% to about 80% at 8 hours, from about 30% to about 95% at 12 hours, from about 35% to about 95% at 18 hrs, and greater than about 50% at 24 hours.

13. A method of treating pain in patients comprising:

orally administering to human patients on a once a day basis, a sustained release dosage form comprising a pharmaceutically acceptable matrix comprising oxycodone or a pharmaceutically acceptable salt thereof and a sustained release material, to provide an analgesic effect for at least about 24 hours and a mean C_{24}/C_{max} oxycodone ratio of 0.6 to 1.0 after administration at steady state to said patients.

14. The method of claim 13 which provides a mean T_{max} of oxycodone at about 2 to about 17 hours after administration at steady state to said patients.

15. The method of claim 13, which provides a mean T_{max} of oxycodone at about 8 to about 16 hours after administration at steady state to said patients.

16. The method of claim 13, which provides a mean C_{24}/C_{max} ratio of 0.7 to 0.99 after administration at steady state to said patients.

17. The method of claim 13, which provides a mean C_{24}/C_{max} ratio of 0.8 to 0.95 after administration at steady state to said patients.

18. The method of claim 13, wherein said dosage form provides an in-vitro release rate, of oxycodone or a pharmaceutically acceptable salt thereof, when measured by the USP Basket Method at 100 rpm in 900 ml aqueous buffer at a pH of between 1.6 and 7.2 at 37°C of from 0% to about 40% at 1 hour, from about 8% to about 70% at 4 hours, from about 20% to about 80% at 8 hours, from about 30% to about 95% at 12 hours, from about 35% to about 95% at 18 hrs, and greater than about 50% at 24 hours.