

(19) **DANMARK**



Patent- og
Varemærkestyrelsen

(12)

Oversættelse af europæisk patentskrift

(10) **DK/EP 2281555 T3**

(51)	Int.Cl.:	A 61 K 9/20 (2006.01)	A 61 K 9/16 (2006.01)	A 61 K 9/22 (2006.01)
		A 61 K 9/48 (2006.01)	A 61 K 31/485 (2006.01)	

(45) Oversættelsen bekendtgjort den: **2016-06-06**

(80) Dato for Den Europæiske Patentmyndigheds
bekendtgørelse om meddelelse af patentet: **2016-03-23**

(86) Europæisk ansøgning nr.: **10178548.3**

(86) Europæisk indleveringsdag: **2002-05-02**

(87) Den europæiske ansøgnings publiceringsdag: **2011-02-09**

(30) Prioritet: **2001-05-02 US 288211 P**

(62) Stamansøgningsnr: **08151238.6**

(84) Designerede stater: **AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR**

(73) Patenthaver: **EURO-CELTIQUE S.A., 1, rue Jean Piret, 2350 Luxembourg, Luxembourg**

(72) Opfinder: **Oshlack, Benjamin, 350 South Ocean Boulevard Apt. 3D, Boca Raton, FL 33432, USA**
Wright, Curtis, 21 Summit Avenue, Rockport, MO 01966-1430, USA
Prater, Derek Allan, 28 Pearson Close Milton, Cambridge, Cambridgeshire CB24 6Ys, Storbritannien

(74) Fuldmægtig i Danmark: **Zacco Denmark A/S, Arne Jacobsens Allé 15, 2300 København S, Danmark**

(54) Benævnelse: **Oxycodonformuleringer til administration én gang dagligt**

(56) Fremdragne publikationer:

WO-A-93/10765

WO-A-95/14460

WO-A1-03/092648

WO-A2-97/33566

US-A- 5 284 662

DESCRIPTION

FIELD OF THE INVENTION

[0001] 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

[0002] 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.

WO 95/14460, and WO 93/10765 describe oxycodone sustained release dosage forms.

WO 97/33566 describes a composition comprising an opioid antagonist and an opioid

WO 03/092648 describes dosage forms and methods for the controlled release of oxycodone over a prolonged period of time.

US 5,284,662 relates to an oral sustained release composition for slightly soluble pharmaceutically active agents comprising a core, a wall around said core, and a bore to said wall connecting said core and the environment outside of said wall; wherein said core comprises a slightly soluble active agent, optionally a crystal habit modifier, at least two osmotic driving agents, at least two different (or two different grades of) hydroxyalkylcelluloses, and optionally lubricants, wetting agents and carriers; said wall being substantially impermeable to said core components and permeable to water and gastrointestinal fluids.

SUMMARY AND OBJECTS OF THE INVENTION

[0003] It is an object of the present invention to provide an oxycodone formulation suitable for once daily administration for effective pain management.

[0004] 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.

[0005] The above objects and others are attained by the present invention, which is directed to a sustained-release oral dosage form for once daily administration comprising

1. (a) a bilayer core comprising:
 1. (i) a drug layer comprising from 5 to 640 mg of oxycodone or a pharmaceutically acceptable salt thereof and at least one polymer hydrogel; and
 2. (ii) a displacement layer comprising an osmopolymer; and
2. (b) a semipermeable wall surrounding the bilayer core having a passageway disposed therein for the release of said oxycodone or pharmaceutically acceptable salt thereof,

wherein 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; and said oxycodone or pharmaceutically acceptable salt thereof is the only drug in the dosage form.

[0006] In certain embodiments the dosage form after administration to patients provides a mean T_{max} of oxycodone in-vivo which occurs at 2 to 17 hours (e.g., 2 to 8 hours) after administration at steady state of the dosage form.

[0007] In certain embodiments, the mean T_{max} of oxycodone in-vivo occurs at 6.5 hours to 17 hours, at 8 to 16 hours, at 10 to 16 hours, or at 12 to 16 hours after administration at steady state of the dosage form.

[0008] In certain embodiments, the dosage form provides an analgesic effect for at least 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.

[0009] In certain embodiments, the dosage form provides an analgesic effect for at least 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, 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 40% at 1 hour, from 8% to 70% at 4 hours, from 20% to 80% at 8 hours, from 30% to 95% at 12 hours, from 35% to 95% at 18 hours, and greater than 50% at 24 hours.

[0010] 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.

[0011] Preferably, the formulations prepared in accordance with the present invention can be presented in tablet, capsule, or in any other suitable unit dosage form.

[0012] The sustained release oral dosage form of the present invention is an osmotic dosage form which comprises a 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.

[0013] The dosage form of the present invention can be used for treating pain associated conditions in patients requiring such treatment which 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.

[0014] 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 for at least 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.

[0015] The term " $C_{\max}$ " as it is used herein is the highest plasma concentration of the drug attained within the dosing interval.

[0016] The term " C_{24} " as it is used herein is the plasma concentration of the drug at 24 hours after administration.

[0017] 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.

[0018] 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.

[0019] 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.

[0020] The term "USP Basket Method" is the Basket Method described in U.S. Pharmacopoeia XXII (1990).

[0021] 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.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] 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, aspartate, glutamate and the like.

DESCRIPTION OF THE INVENTION

[0026] 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 40% at 1 hour, from 8% to 70% at 4 hours, from 20% to 80% at 8 hours, from 30% to 95% at 12 hours, from 35% to 95% at 18 hrs, and greater than 50% at 24 hours.

[0027] 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 ($T_{\geq 0.75C_{max}}$) may be 4 hours or greater, preferably 6 hours or greater.

[0028] In certain embodiments, the time at which oxycodone blood levels reach their maximum concentration (T_{max}) is 2 to 17 hours, preferably 6.5 hours to 17 hours, more preferably 8 to 16 hours, and even more preferably 10 to 16 or 12 to 16 hours after administration at steady state of the dosage form.

[0029] 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 of 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 of 0.72 to 0.99 or a ratio of 0.74 to 0.95.

[0030] 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 of 0.7 to 0.99 or a ratio of 0.8 to 0.95 and a (T_{max}) of 6.5 hours to 17 hours, 8 to 16 hours, 10 to 16 hours or 12 hours to 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 of 0.72 to 0.99 or a ratio of 0.74 to 0.95 and a (T_{max}) in 2 to 17 hours.

[0031] In certain embodiments of the present invention, the co-administration of food will not significantly increase or decrease the extent of oxycodone absorption.

[0032] The sustained release oral dosage form of the present invention includes from 1 to 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 5 to 500 mg oxycodone or a pharmaceutically acceptable salt thereof, more preferably from 10 to 320 mg oxycodone or a pharmaceutically acceptable salt thereof and even more preferably from 10 to 160 mg oxycodone or a pharmaceutically acceptable salt thereof.

[0033] In other preferred embodiments, the sustained release dosage form of the present invention comprises from 10 to 160 mg oxycodone hydrochloride or an equivalent amount of oxycodone or a pharmaceutically acceptable salt thereof other than the hydrochloride salt.

[0034] The present specification describes a method for administering from 1 to 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 5 to 500 mg oxycodone or a pharmaceutically

acceptable salt thereof.

[0035] 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

[0036] The oral dosage form of the present invention may optionally include other pharmaceutically acceptable ingredients (e.g., diluents, binders, colorants, lubricants, etc.).

[0037] The oral dosage form of the present invention is 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.

[0038] Preferably the dosage forms of the present invention provide an analgesic effect for at least 24 hours after administration.

SUSTAINED RELEASE OSMOTIC DOSAGE

[0039] Sustained release dosage forms according to the present invention are prepared as osmotic dosage formulations. The osmotic dosage forms include a bilayer core comprising a drug layer and a delivery or push layer, wherein the bilayer core is surrounded by a semipermeable wall having at least one passageway disposed therein.

[0040] 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.

[0041] The bilayer core comprises a drug layer with oxycodone or a salt thereof and a displacement or push layer. The drug layer also comprises at least one polymer hydrogel. The polymer hydrogel may have an average molecular weight of between 500 and 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula $(C_6H_{12}O_5)_n \cdot H_2O$, 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.

[0042] 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.

[0043] 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.

[0044] 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 hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropylcellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose.

[0045] 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.

[0046] 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, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiary butylphenol, alphanatocopherol, and propylgallate.

[0047] 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 alkynylates. The poly(cellulose) used for the present invention comprises a number-average molecular weight of 20,000 to 7,500,000.

[0048] Additional semipermeable polymers for the purpose of this invention comprise acetaldehyde dimethylcellulose 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 2.5×10^{-8} to 2.5×10^{-2} ($\text{cm}^2 / \text{hr} \cdot \text{atm}$) 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.

[0049] 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 laurate, and vinyl stearate. Other binders include for example, acacia, starch, gelatin, and hydroxypropylalkylcellulose of 9,200 to 250,000 average molecular weight.

[0050] 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.

[0051] 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.

[0052] The present specification further describes 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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 (Reference example)

[0058] Oxycodone sustained release matrix tablets are produced with the formula set forth in Table 1 below.

Table 1

<i>Ingredient</i>	<i>Amt/unit (mg)</i>	<i>Amt/batch (gram)</i>
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.		

[0059] 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

[0060] Oxycodone sustained release osmotic tablets are produced with the formula set forth in Table 2 below:

TABLE 2

<i>Ingredient</i>	<i>Amt/unit (mg)</i>
<i>Drug Layer:</i>	
Oxycodone HCl	35.20
Polyethylene oxide	130.24
Povidone	8.8
Magnesium Stearate	1.76
<i>Displacement Layer:</i>	
Polyethylene oxide	85.96
Sodium chloride	40.50

<i>Displacement Layer:</i>	
Hydroxypropylmethylcellulose	6.75
Ferric Oxide	1.35
Magnesium Stearate	0.34
BHT	0.10
<i>Semipermeable Wall:</i>	
Cellulose acetate	38.6

[0061] 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.

[0062] 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.

[0063] 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 43EC and air flow 4300 m³/hr. At the end of solution spraying, 45,033 g, the resultant coated granulated particles are subjected to a drying process for 35 minutes.

[0064] 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.

[0065] 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.

[0066] 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 45EC and 45% humidity. Next, the osmotic dosage systems are dried for 4 hours at 45EC to remove excess moisture. The dosage forms produced by this manufacture comprise 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

[0067] Oxycodone sustained release osmotic tablets are produced with the formula set forth in Table 3 below:

TABLE 3

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

[0068] 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.

[0069] 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 hydroxypropylmethylcellulose/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 hydroxytoluene/alcohol solution, again with continuous mixing.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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 50EC and 50% humidity. Next, the osmotic dosage forms are dried for 4 hours at 50EC to remove excess moisture. The dosage form produced by this manufacture comprises 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.

[0075] 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.

[0076] 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 (Reference example)

[0077] Oxycodone 10 mg sustained release capsules were prepared with the formula set forth in Table 4 below:

Table 4

<i>Ingredient</i>	<i>Amt/unit (mg)</i>
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. 4. Allow the strands to cool on the conveyor.
5. 5. Cut the strands into 1 mm pellets using a pelletizer.
6. 6. Screen the pellets for fines and oversized pellets to an acceptable range of about 0.8 - 1.4 mm in size.
7. 7. Fill into capsules with a fill weight of 120 mg/capsule (fill into size 2 capsules).

[0078] 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

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

Example 5 (Reference example)

[0079] Oxycodone 160 mg sustained release capsules were prepared with the formula set forth in Table 5 below:

Table 5

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

DISSOLUTION METHOD:

[0080] 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.

[0081] The dissolution parameters for the above formulation are set forth in Table 5A below.

Table 5A

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

[0082] The present invention is also supported by the following items:

1. 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. 2. The dosage form of item 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. 3. The dosage form of item 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. 4. The dosage form of item 1, which provides a mean W_{50} for the oxycodone of between 4 and 24 hours after administration at steady state to said patients.
5. 5. The dosage form of item 4, which provides a mean W_{50} for the oxycodone of at least 12 hours after administration at steady state to said patients.
6. 6. The dosage form of item 1, wherein the matrix is substantially homogeneous.
7. 7. The dosage form of item 1, wherein said matrix is contained within a gelatin capsule.
8. 8. The dosage form of item 1, wherein said matrix is formulated into a tablet.
9. 9. The dosage form of item 1, which provides a mean T_{max} at about 12 to about 16 hours after administration at steady state to said patients.
10. 10. The dosage form of item 1, wherein said oxycodone or pharmaceutically acceptable salt thereof is an amount from about 5 to about 640 mg.
11. 11. The dosage form of item 1, wherein said pharmaceutically acceptable salt of oxycodone is oxycodone hydrochloride.
12. 12. The dosage form of item 1, which provides a mean C_{24}/C_{max} ratio of 0.7 to 0.99 after administration at steady state to said patients.
13. 13. The dosage form of item 1, which provides a mean C_{24}/C_{max} ratio of 0.8 to 0.95 after administration at steady state to said patients.
14. 14. The dosage form of item 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 37EC 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.
15. 15. 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.

16. 16. The method of item 15 which provides a mean T_{max} of oxycodone at about 2 to about 17 hours after administration at steady state to said patients.
17. 17. The method of item 15 which provides a mean T_{max} of oxycodone at about 8 to about 16 hours after administration at steady state to said patients.
18. 18. The method of item 15, which provides a mean W_{50} of the oxycodone of between 4 and 24 hours after administration at steady state to said patients.
19. 19. The method of item 18, which provides a mean W_{50} of the oxycodone of at least 12 hours after administration at steady state to said patients.
20. 20. The method of item 15, which provides a mean C_{24}/C_{max} ratio of 0.7 to 0.99 after administration at steady state to said patients.
21. 21. The method of item 15, which provides a mean C_{24}/C_{max} ratio of 0.8 to 0.95 after administration at steady state to said patients.
22. 22. The method of item 15, 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 37EC 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.
23. 23. A sustained release oral dosage form comprising:
 1. (a) a bilayer core comprising:
 1. (i) a drug layer comprising an analgesically effective amount of oxycodone or a pharmaceutically acceptable salt thereof; and
 2. (ii) a displacement layer comprising an osmopolymer; and
 2. (b) a semipermeable wall surrounding the bilayer core having a passageway disposed therein for the release of said oxycodone or pharmaceutically acceptable salt thereof;

said dosage form providing an analgesic effect for at least about 24 hours after steadystate oral administration to human patients; and

said dosage form providing a mean C_{24}/C_{max} oxycodone ratio of 0.6 to 1.0 after oral administration at steady state to said patients.
24. 24. The dosage form of item 23, which provides a mean T_{max} of oxycodone in about 2 to about 17 hours after administration at steady state to said patients.
25. 25. The dosage form of item 23, which provides a mean T_{max} of oxycodone in about 8 to about 16 hours after administration at steady state to said patients.
26. 26. The dosage form of item 23, which provides a mean W_{50} of the oxycodone of between 4 and 24 hours after administration at steady state to said patients.
27. 27. The dosage form of item 23, which provides a W_{50} of the oxycodone of at least 12 hours after administration at steady state to said patients.
28. 28. The dosage form of item 23, wherein said displacement layer further comprises an osmagent.
29. 29. The dosage form of item 28, wherein said osmagent is selected from the group consisting of osmotic salts and osmotic carbohydrates.
30. 30. The dosage form of item 23, wherein said pharmaceutically acceptable salt of oxycodone is oxycodone hydrochloride.
31. 31. The dosage form of item 23, wherein said oxycodone or pharmaceutically acceptable salt thereof is in an amount of from about 5 to about 640 mg.
32. 32. The dosage form of item 23, which provides a mean T_{max} of oxycodone which occurs at about 12 to about 16 hours after administration at steady state to said patients.
33. 33. The dosage form of item 23, which provides a mean C_{24}/C_{max} ratio of 0.7 to 0.99 after administration at steady state to said patients.
34. 34. The dosage form of item 23, which provides a mean C_{24}/C_{max} ratio of 0.8 to 0.95 after administration at steady state to said patients.
35. 35. The dosage form of item 23, 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 37EC 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.
36. 36. A method of treating pain in patients comprising:

orally administering to human patients a sustained release oral dosage form comprising

1. (a) a bilayer core comprising:
 1. (i) a drug layer comprising an analgesically effective amount of oxycodone or a pharmaceutically acceptable salt thereof; and
 2. (ii) a displacement layer comprising an osmopolymer; and
2. (b) a semipermeable wall surrounding the bilayer core having a passageway disposed therein for the release of said oxycodone or pharmaceutically acceptable salt thereof;

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 oral administration at steady state to said patients.

37. 37. The method of item 36, which provides a mean T_{max} of oxycodone at about 2 to about 17 hours after administration at steady state to said patients.
38. 38. The method of item 36, which provides a mean T_{max} of oxycodone at about 8 to about 16 hours after administration at steady state to said patients.
39. 39. The method of item 36, which provides a W_{50} of the oxycodone of between 4 and 24 hours after administration at steady state to said patients.
40. 40. The method of item 39, which provides a W_{50} of the oxycodone of at least 12 hours after administration at steady state to said patients.
41. 41. The method of item 36, which provides a mean C_{24}/C_{max} ratio of 0.7 to 0.99 after administration at steady state to said patients.
42. 42. The method of item 36, which provides a mean C_{24}/C_{max} ratio of 0.8 to 0.95 after administration at steady state to said patients.
43. 43. The method of item 36, 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 37EC 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.
44. 44. A sustained-release oral dosage form for once-a-day administration comprising:

a plurality of pharmaceutically acceptable matrices comprising an analgesically effective amount of oxycodone or a 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 oral administration at steady state to said patients.
45. 45. The dosage form of item 44, which provides a mean T_{max} of oxycodone at about 2 to about 17 hours after administration at steady state to said patients.
46. 46. The dosage form of item 44, which provides a mean T_{max} of oxycodone at about 8 to about 16 hours after administration at steady state to said patients.
47. 47. The dosage form of item 44, which provides a W_{50} of the oxycodone of between 4 and 24 hours after administration at steady state to said patients.
48. 48. The dosage form of item 47, which provides a W_{50} of the oxycodone of at least 12 hours after administration at steady state to said patients.
49. 49. The dosage form of item 44, wherein said plurality of matrices is contained within a gelatin capsule.
50. 50. The dosage form of item 44, wherein said plurality of matrices is formulated into a tablet.
51. 51. The dosage form of item 44, which provides a mean T_{max} at about 12 to about 16 hours after administration at steady state to said patients.
52. 52. The dosage form of item 44, wherein said oxycodone or pharmaceutically acceptable salt thereof is an amount from about 5 to about 640 mg.
53. 53. The dosage form of item 44, wherein said pharmaceutically acceptable salt of oxycodone is oxycodone hydrochloride.
54. 54. The dosage form of item 44, which provides a mean C_{24}/C_{max} ratio of 0.7 to 0.99 after administration at steady state to said patients.

55. 55. The dosage form of item 44, which provides a mean C_{24}/C_{max} ratio of 0.8 to 0.95 after administration at steady state to said patients.
56. 56. The dosage form of item 44, 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 37EC 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.
57. 57. A method of treating pain in a patient comprising:

orally administering to a patient on a once-a-day basis 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,

to provide an analgesic effect for 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 oral administration at steady state to said patients.
58. 58. The method of item 57, which provides a mean T_{max} of oxycodone at about 2 to about 17 hours after administration at steady state to said patients.
59. 59. The method of item 57, which provides a mean T_{max} of oxycodone at about 8 to about 16 hours after administration at steady state to said patients.
60. 60. The method of item 57, which provides a W_{50} of the oxycodone of between 4 and 24 hours after administration at steady state to said patients.
61. 61. The method of item 57, which provides a W_{50} of the oxycodone of at least 12 hours after administration at steady state to said patients.
62. 62. The method of item 57, which provides a mean C_{24}/C_{max} ratio of 0.7 to 0.99 after administration at steady state to said patients.
63. 63. The method of item 57, which provides a mean C_{24}/C_{max} ratio of 0.8 to 0.95 after administration at steady state to said patients.
64. 64. The method of item 57, 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 37EC 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.
65. 65. 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 and a T_{max} of oxycodone at greater than 6 to about 17 hours after oral administration at steady state to said patients.
66. 66. 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 0.7 to 1.0 after oral administration at steady state to said patients.
67. 67. A sustained-release oral dosage form for once-a-day administration comprising:

a plurality of pharmaceutically acceptable matrices 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 and a T_{max} of oxycodone at greater than 6 to about 17 hours after oral administration at steady state to said patients.

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

a plurality of pharmaceutically acceptable matrices 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 0.7 to 1.0 after oral administration at steady state to said patients.

69. 69. 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.

70. 70. The use of a sustained release oral dosage form comprising

1. (a) a bilayer core comprising:

1. (i) a drug layer comprising an analgesically effective amount of oxycodone or a pharmaceutically acceptable salt thereof; and

2. (ii) a displacement layer comprising an osmopolymer; and

2. (b) 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.

71. 71. 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 ratio of 0.6 to 1.0 after oral administration at steady state to said patients.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- [US5478577A \[0002\]](#)
- [US5672360A \[0002\]](#)
- [US5958459A \[0002\]](#)
- [US6103261A \[0002\]](#)
- [US6143332A \[0002\]](#)
- [US5965161A \[0002\]](#)
- [US5958452A \[0002\]](#)
- [US5968561A \[0002\]](#)
- [WO9514460A \[0002\]](#)
- [WO9310765A \[0002\]](#)

- WO9733566A [0002]
- WO03092648A [0002]
- US5284662A [0002]
- US3845770A [0040] [0048] [0075]
- US3916898A [0040] [0048] [0075]
- US4063064A [0040]
- US4088864A [0040]
- US4200096A [0040]
- US4285987A [0040]
- US3173876A [0048]
- US3276586A [0048]
- US3541005A [0048]
- US3541006A [0048]
- US3546876A [0048]
- US3133132A [0048]
- US4160020A [0048]
- US4008719A [0075]
- US4036226A [0075]
- US4111201A [0075]

Non-patent literature cited in the description

- USP Basket Method U.S. Pharmacopoeia, 1990, vol. XXI, [0020]
- SCOTT, J. R.W. J. ROFF Handbook of Common Polymers CRC Press 19710000 [0048]

Patentkrav

1. Oral depotdoseringsform til administration én gang dagligt, hvilken doseringsform omfatter
 - 5 (a) en tolagskerne omfattende:
 - (i) et lægemiddellag omfattende fra 5 til 640 mg oxycodon eller et farmaceutisk acceptabelt salt deraf og mindst én polymerhydrogel; og
 - (ii) et forskydningslag omfattende en osmopolymer; og
 - (b) en semipermeabel væg, der omgiver tolagskernen med en passage
- 10 tilvejebragt deri for frigørelse af oxycodon eller det farmaceutisk acceptable salt deraf;
hvor den semipermeable væg omfatter et element udvalgt fra gruppen bestående af en celluloseesterpolymer, en celluloseetherpolymer og en celluloseester-etherpolymer; og
- 15 oxycodon eller det farmaceutisk acceptable salt deraf er det eneste lægemiddel i doseringsformen.
2. Oral depotdoseringsform ifølge krav 1, hvor forskydningslaget endvidere omfatter en osmagent, der fortrinsvis er udvalgt fra gruppen bestående af osmotiske salte
- 20 og osmotiske carbohydrater.
3. Oral depotdoseringsform ifølge krav 1 eller 2, hvor doseringsformen tilvejebringer en in-vitro frigørelshastighed for oxycodon eller et farmaceutisk acceptabelt salt deraf; når den måles efter USP Basket Method
- 25 ved 100 o/m i 900 ml vandig buffer ved et pH på mellem 1,6 og 7,2 ved 37 °C, på fra 0 % til 40 % ved 1 time, fra 8 % til 70 % ved 4 timer, fra 20 % til 80 % ved 8 timer, fra 30 % til 95 % ved 12 timer, fra 35 % til 95 % ved 18 timer og over 50 % ved 24 timer.
- 30 4. Oral depotdoseringsform ifølge krav 1 eller 2, der omfatter fra 5 til 500 mg oxycodon.
5. Oral depotdoseringsform ifølge krav 1 eller 2, hvor det farmaceutisk acceptable salt af oxycodon er oxycodonhydrochlorid.
- 35 6. Oral depotdoseringsform ifølge krav 1 eller 2 til anvendelse ved behandling af smerte, hvor doseringsformen tilvejebringer en analgesisk effekt i mindst 24 timer.

7. Doseringsform ifølge et hvilket som helst af kravene 1 eller 2 i form af en tablet.
8. Doseringsform ifølge krav 1 eller 2, hvor osmopolymeren indbefatter et element udvalgt fra gruppen bestående af et polyalkylenoxid og en carboxyalkylcellulose.
9. Doseringsform ifølge krav 2, hvor osmagenten er udvalgt fra gruppen bestående af natriumchlorid, kaliumchlorid, magnesiumsulfat, lithiumphosphat, lithiumchlorid, natriumphosphat, kaliumsulfat, natriumsulfat, kaliumphosphat, glucose, fructose og maltose.

5

10