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(54) **Oxikodont tartalmazó szabályozott hatóanyag-leadású orális adagolási forma**

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(54) **CONTROLLED RELEASE ORAL DOSAGE FORM COMPRISING OXYCODONE**

FORMULIERUNG MIT KONTROLLIERTER FREIGABE, OXYCODON ENTHALTEND

FORME ORALE PHARMACEUTIQUE À LIBÉRATION CONTRÔLÉE CONTENANT OXYCODONE

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EP 2 726 064 B1

## Description

**[0001]** The present invention relates to a controlled release oral dosage form for administration of oxycodone once a day and a method of preparing a controlled release oral dosage form for administration of oxycodone once a day.

**[0002]** Oxycodone is an opioid analgesic that is deemed particularly effective in the treatment of chronic pain. Currently, twice daily immediate release and twice daily extended release formulations are available on the market for oral administration. However, no controlled formulation for once daily administration is available as yet. Therefore, there is an ongoing need to provide a controlled release oral dosage form for administration of oxycodone once a day that has advantages such as reduced dosing intervals, provision of stable plasma levels and consistent pain relief over 24 hours.

**[0003]** Sustained release formulations containing oxycodone or opioids in general, have been the subject of numerous patent applications. A common feature to these patent applications is the requirement that the *in vitro* release rate of oxycodone from the controlled release formulations containing should be independent of pH. Just by way of example, it is referred to EP 0 631 781. Furthermore, it is common general knowledge that the differences between peak and trough levels of active ingredient in blood should ideally be as low as possible. Again, just by way of example, it is referred to WO 02/087512 which discloses a sustained release dosage form comprising oxycodone for oral administration to a patient on a once-a-day basis, which provides a mean ratio of the values of the plasma concentration 24 hours after administration ($C_{24}$) and the highest plasma concentration of the drug attained within the dosing interval ($C_{max}$) of 0.6 to 1.0.

**[0004]** WO 03/101384 A2 is directed to novel means for delivering varying doses of oxycodone using drug composition having only oxycodone, a polymer carrier and varying amounts of salt to provide a particular viscosity of the hydrated drug core for delivery of the drug at the desired release rate.

**[0005]** WO 03/092648 A1 is directed to dosage forms for the controlled release of oxycodone over a prolonged period of time. The sustained release dosage forms provide therapeutically effective average steady-state plasma oxycodone concentrations when administered once a day.

**[0006]** WO 02/087512 A2 is directed to sustained release formulations containing oxycodone which provide a mean $C_{24}/C_{max}$ oxycodone ratio of 0.6 to 1.0 after oral administration at steady state to patients.

**[0007]** US 2005/0074493 A1 relates to extended release formulations for the delivery of opioid agonists which exhibit low peak to trough plasma concentration fluctuations and sufficiently high plasma concentrations over an extended period of time to provide a once a day dosage administration.

**[0008]** The inventors of the present invention have now surprisingly found that, contrary to common presumptions, very advantageous *in vivo* properties can be achieved by a controlled release oral dosage form for administration of oxycodone once a day, wherein at steady state the oral dosage form provides a mean $C_{24}/C_{max}$ of less than 0.6 after oral administration.

**[0009]** Hence, the present invention provides a controlled release oral dosage form for administration of oxycodone once a day, comprising

a plurality of substrates comprising oxycodone or a pharmaceutically acceptable salt or solvate thereof,

each substrate comprising a release control substance for controlling the release of oxycodone or the salt or solvate thereof,

wherein each substrate comprises an oxycodone-containing core and a release-control layer containing the release-control substance for controlling the release of oxycodone from the substrate,

wherein at steady state the oral dosage form provides a mean $C_{24}/C_{max}$ of between 0.30 and 0.56 after oral administration,

wherein the core comprises a layer comprising oxycodone coated on an inert core and/or wherein the release control substance is a hydrophobic polymer,

wherein the plurality of substrates is contained in an external phase of at least one pharmaceutically acceptable excipient.

**[0010]** In an embodiment, the amount of oxycodone released by the controlled release oral dosage form at pH 1.6 or 2.0 after a time $t_1$ differs by 10.1% to 30%, in particular 10.5% to 30%, from an amount of oxycodone released at pH 4.5 or pH 7.2 after the same time $t_1$, when measured according to the USP Paddle Method in 900 ml aqueous buffer at 100 rpm and preferably 37°C. Alternatively, the amount of oxycodone released by the controlled release oral dosage form at pH 1.6 or 2.0 after a time $t_1$ differs by 10.1% to 25%, in particular 10.5% to 20%, from an amount of oxycodone released at pH 4.5 or pH 7.2 after the same time $t_1$, when measured according to the USP Paddle Method in 900 ml aqueous buffer at 100 rpm and preferably 37°C. The term "differs" preferably refers to an absolute difference. That means, if for example the dissolution at pH 1.6 is 10 %, then the difference of 8 % results in a dissolution at pH 7.2 of 18 %.

**[0011]** The value $C_{max}$ designates the highest plasma concentration of oxycodone attained within the dosing interval and $C_{24}$ designates the plasma concentration 24 hours after administration, each under steady state conditions. For purposes of the present invention, the steady state is regarded as being reached between 72.0 hours and 96.0 hours after administration of a first oxycodone once daily dosage form, with dosage forms being taken every 24 hours.

**[0012]** Time $t_1$ generally is a point in time more than 5 minutes and less than 24 hours after starting of the dissolution test, preferably more than 15 minutes and less than 12 hours. Further preferred, $t_1$ can be a point in time

between 30 minutes and 10 hours, in particular 60 minutes and 8 hours after starting of the dissolution test. Preferably, the $C_{24}$, $C_{max}$ and dissolution values referred to herein are based on at least three, for instance five and more preferably 12 measurements, *i.e.* patients in case of $C_{24}$, $C_{max}$ and measurement runs in case of dissolution values. The mean $C_{24}/C_{max}$ ratio is preferably based on 12 measurements (patients) or more (with the ratio being calculated for each patient, and then a mean of the ratios of the respective number of patients being taken, of course). As customary in the art, the mean value designates the arithmetic mean value of the ratios of the tested patient population.

**[0013]** Naturally, plasma oxycodone concentrations will vary from patient to patient due to individual differences in their response due to variability in terms of absorption, distribution, metabolism and excretion. It is for this reason that the mean $C_{24}/C_{max}$ ratio values are based on the at least three, for instance five and more preferably 12 measurements (patients).

**[0014]** The controlled release oral dosage form according to the invention is a so-called multi-particulate dosage form comprising a plurality of substrates comprising oxycodone or a pharmaceutically acceptable salt or solvate thereof, each substrate comprising a substance for controlling the release of oxycodone or the salt or solvate thereof.

**[0015]** From the above, it is clear that the oral dosage form according to the present invention is not an osmotic dosage form, *i.e.* does not utilize the principle of osmotic pressure for the delivery of the drug. Drug release from osmotic systems is typically independent of pH and thus quite in contrast to the above laid out aspect of the present invention.

**[0016]** Each substrate comprises an oxycodone containing core and a release control layer containing the release control substance for controlling the release of oxycodone from the substrate. Preferably, the release control layer is (physically) separate from the oxycodone containing core. The oxycodone containing core may be a core which contains oxycodone and excipients. In those embodiments, the excipients preferably do not substantially retard or delay the release of the oxycodone.

**[0017]** Preferably, the core comprises a layer of oxycodone on an inert core. The inert core (also referred to as seed core or neutral pellet) may be granules or beads, preferably spherical, and further preferably made from sugar or cellulose or other suitable materials. By way of example, spherical inert cores based on saccharose, such as those commercially available under the trade name Suglets®, or those based on cellulose, such as those commercially available under the trade name Celphere® or Cellets® may be mentioned. Saccharose-based inert cores are particularly preferred. Inert cores may preferably have a particle size in the range of 100 to 500 μm and more preferably in the range of 200 to 400 μm, with the particle size range indicating the size range for 90% of the particles as determined by sieve analysis.

**[0018]** Preferably, oxycodone is provided by coating an oxycodone-containing layer directly onto the inert cores. The oxycodone-containing layer preferably does not delay release of oxycodone, i.e. is an immediate-release layer.

**[0019]** Preferably, a suitable oxycodone-containing core comprises

10 to 50 wt.%, preferably 20 to 40 wt.%, more preferably 25 to 35 wt.% neutral pellets, 20 to 90 wt.%, preferably 35 to 80 wt.%, more preferably 50 to 70 wt.% oxycodone, in particular oxycodone hydrochloride,
0.1 to 20 wt.%, preferably 1 to 15 wt.%, more preferably 3 to 8 wt.% binder, and optionally
0 to 20 wt.% , preferably 1 to 15 wt.%, more preferably 3 to 8 wt.% glidant,

based on the total weight of the oxycodone containing core.

**[0020]** Generally, binders as described below can be used. In particular, HPMC is used as binder in the oxycodone-containing core. Preferably, said HPMC has a methoxy content of 25 % to 35 %, more preferably 28 % to 30 %. Further, preferably said HPMC has a hydroxypropoxy content of about 5 % to 15 %, more preferably 7 % to 12 %. Preferably, a 2% by weight (aqueous) solution of said HPMC has a viscosity of 0.5 to 100 mPa•s, preferably 1 to 50 mPas, more preferably 2 to 10 mPa•s, in particular 3 to 8 mPa•s, measured at 20°C, preferably by means of a Brookfield-Synchro-Lectric LVF viscosimeter.

**[0021]** Generally, glidants as described below can be used. In particular, talcum is used as glidant in the oxycodone-containing core.

**[0022]** The release control layer may be disposed in direct vicinity, *i.e.* in immediate contact with and surrounding the oxycodone containing core, which is preferred. In other exemplary embodiments, an intermediate layer may be disposed between the oxycodone containing core and the release control layer. This intermediate layer may further control the release of oxycodone from the core. However, it is preferred that, if present, the intermediate layer does not substantially influence the release from the core.

**[0023]** The release control substance may be any substance known in the art as suitable to control the release of an active substance. Exemplary embodiments of suitable control release substances include cellulose esters, such as cellulose acetate phthalate, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, polyvinyl chloride, nylon, polyamide, polyethylene oxide, polylactide-co-glycolide and mixtures thereof. Preferably, the release control substance is a hydrophobic polymer. Suitable hydrophobic polymers include those selected from alkylcelluloses, in particular cellulose ethers, polymers and copolymers based on acrylate or methacrylate, pol-

ymers and copolymers based on acrylic or methacrylic esters and mixtures thereof. Preferably, the release control substance is an alkyl cellulose. More preferably, the alkyl cellulose is ethyl cellulose.

**[0024]** In exemplary embodiments of the present invention wherein the release control substance is a polymer, said polymer has a weight average molecular weight of from 5,000 to 500,0000 g/mol, preferably 50,000 to 900,000 g/mol, more preferably from 100,000 to 400,000 g/mol, for instance from 140,000 to 300,000 g/mol. The weight average molecular weight is preferably determined by gel permeation chromatography.

**[0025]** In further embodiments, and in addition or in the alternative to one or more of the properties mentioned above, the release control substance preferably has a solubility in water of less than 20 mg/l preferably less than 15 mg/l preferably between 0.001 to 10.0 mg/l The solubility in water is preferably determined in accordance with European Regulation RL67-548 EWG, Annex V, Chapter A6 (German version referred to and referenced herein).

**[0026]** In further embodiments where a polymer is used as or as part of the release control substance, and in addition or in the alternative to one or more of the properties mentioned above, the polymer has a glass transition temperature of 20 to 220°C, for instance 60 to 150°C or 90 to 140°C. The glass transition temperature is preferably measured by means of differential scanning calorimetry DSC, preferably using a Mettler Toledo instrument and a preferably applying a heating/cooling rate of 10°C per minute.

**[0027]** In a particular preferred embodiment the release-control substance is ethylcellulose having an ethoxyl content of about 35 to 65 %, more preferred of about 45 to 55%. Preferably, a 2% by weight (aqueous) solution of ethylcellulose has a viscosity of 5 to 500 mPa•s, preferably 10 to 100 mPa•s, in particular 25 to 55 mPa•s measured at 25°C, preferably by means of a Brookfield-Synchro-Lectric LVF viscosimeter.

**[0028]** In exemplary embodiments, the release control substance is contained in an amount of from 0.1 to 80% by weight of the total weight of the plurality of substrates in the dosage form, more preferably in amounts from 0.5 to 60% by weight, 10 to 50% by weight, 15 to 40% by weight, 20 to 30% by weight of the total weight of the plurality of substrates in the dosage form.

**[0029]** Control of the release rate can be adapted by appropriate selection of the control release substance or mixture of such substances, its/their amount, coating thickness, inclusion of further excipients, such as pore formers and/or plasticizers or others.

**[0030]** In accordance with one aspect of the present invention, the release control substance or mixture thereof and/or the release control layer and/or an external phase wherein the plurality of substrates may be contained, optionally in combination with additional release control layers, is chosen and adapted such that the pH dependence of the controlled release oral dosage form is in the indicated range, in particular wherein an amount of oxycodone released by the controlled release oral dosage form at pH 1.6 after a time $t_1$ differs by 8% to 30%, preferably 10.1% to 30%, more preferably 10.5% to 30% from an amount of oxycodone released at pH 7.2 after the same time $t_1$, when measured according to the USP Paddle Method in 900 ml aqueous buffer at 100 rpm and at 37°C. As mentioned above, alternatively, the difference in dissolution may also be determined at pH 2.0 (as the lower pH) and 4.5 (as the higher pH).

**[0031]** In a particularly preferred embodiment, the overall pH dependence (measured according to the conditions set out before) of the oral dosage form is due to (or substantially, respectively predominantly due to) at least one excipient in the external phase of the oral dosage form, in particular tablet, wherein the plurality of substrates is contained, whereas a dissolution profile (measured according to the conditions set out before) of the plurality of substrates is substantially independent of pH, *i.e.* shows less than 8%, more preferably less than 7, 6, 5, 4, 3, 2 or even 1% deviation at any point in time between the weight percentage of oxycodone dissolved at pH 1.6 or 2.0 compared to the weight percentage dissolved at the same time at pH 4.5 or 7.2.

**[0032]** Further to the release control substance, one or more additional excipients may be used, in particular in a release control layer. A preferred excipient for use with the release control substance, in particular a polymeric release control substance, is a plasticizer and/or a pore builder.

**[0033]** A plasticizer, as the term is used herein, is a substance that typically lowers the glass transition temperature of the polymer it is used in admixture with by at least 2°C, preferably at least 5°C, for instance between 5 and 30°C, as compared to the polymer alone. A preferred plasticizer is propylene glycol, in particular for use with ethylcellulose.

**[0034]** A pore former usually is a substance having a water-solubility which is higher than the water solubility of the release-control substance. Preferably, the pore former has a solubility in water of more than 20 mg/l preferably 50 mg/l to 5000 mg/l more preferably 100 to 1000 mg/l. The solubility in water is preferably determined as described above. In particular, hydroxypropyl cellulose (HPC) is used as pore former. Preferably, said HPC has a hydroxypropoxy content of about 50 to 95%, more preferably 70 to 80%. Preferably, a 10% by weight (aqueous) solution of said HPC has a viscosity of 10 to 3000 mPa•s, preferably 100 to 1000 mPa•s, in particular 300 to 600 mPa•s, measured at 25°C, preferably by means of a Brookfield-Synchro-Lectric LVF viscosimeter.

**[0035]** In a preferred embodiment, the release control layer comprises 20 to 95 wt.%, preferably 40 to 80 wt.%, more preferably 50 to 70 wt.% release control substance, preferably as described above,

0.1 to 30 wt.%, preferably 1 to 25 wt.%, more preferably 5 to 20 wt.% pore builder, preferably as de-

scribed above,
0.1 to 30 wt.%, preferably 1 to 25 wt.%, more preferably 5 to 20 wt.% plasticiser, preferably as described above, and optionally
0 to 40 wt.% , preferably 5 to 30 wt.%, more preferably 10 to 25 wt.% glidant, preferably as described above,

based on the total weight of the release control layer.

**[0036]** The release control layer may be a single layer or a plurality of layers. For ease of fabrication, embodiments with a single release control layer are preferred.

**[0037]** The plurality of substrates may be used as a pharmaceutical formulation in granular form, for instance, without any further processing. For this kind of administration, the substrates are preferably filled into sachets. In the alternative, they may be incorporated into capsules, optionally together with one or more excipients, or other suitable ingestible pharmaceutical dosage forms.

**[0038]** Most preferably, the plurality of substrates is contained in an external phase of at least one pharmaceutically acceptable excipient. Furthermore, the controlled release oral dosage form is preferably a tablet.

**[0039]** As evident from what has been set out before, most preferably, the oral dosage form according to the present invention does not contain any oxycodone in immediate-release form, *i.e.* does not contain oxycodone the release of which is not controlled by the release-control substance(s). For instance, a tablet comprising the plurality of controlled-release oxycodone substrates does not comprise any further oxycodone in the external phase.

**[0040]** In particularly preferred embodiments, the plurality of substrates is contained in a so-called "external phase". The external phase preferably comprises carboxymethyl cellulose, in particular sodium carboxymethyl cellulose, as a pharmaceutically acceptable excipient. Carboxymethyl cellulose may be used as such or in the form of one of its salts, for instance sodium salt, calcium salt or a combination thereof. Carboxymethyl cellulose sodium salts are particularly preferred, in particular those designated "Carmellose sodium" or "low substituted carmellose sodium" according to Ph.Eur. 6.0. Preferably, the sodium content is in the range of 1 to 15 % by weight, based on the total weight of the carmellose sodium salt. Enzymatically hydrolysed carboxymethyl cellulose (E 469) shall be equally encompassed by the term carboxymethyl cellulose. In the following, it will be simply referred to carboxymethyl cellulose, with the salts being included in the meaning of the term, for ease of reference.

**[0041]** Preferably, the carboxymethyl cellulose is not cross-linked. Further preferably, a 2% by weight (aqueous) solution of carboxymethyl cellulose has a viscosity of 50 to 4500 mPa•s, preferably 100 to 3000 mPa•s, in particular 120 to 2000 mPa•s and in further embodiments 150 to 1500 mPa•s, measured at 25°C, preferably by means of a Brookfield-Synchro-Lectric LVF viscosimeter. For instance, a grade CMC 400 to 800 cPs or equivalent may be used, *i.e.* a carboxymethyl cellulose having a viscosity (2% by weight aqueous solution) of 200 to 1500 mPas, more preferably 400 to 800 mPa•s (measured as set our before).

**[0042]** In other embodiments, the carboxymethyl cellulose may have a degree of substitution of 0.6 to 1.5, preferably 0.7 to 1.3.

**[0043]** Carboxymethyl cellulose may be present in an amount of from 0.1 to 80 % by weight, preferably 1.0 to 60 % by weight, in further embodiments 5.0 to 50.0 % by weight and in further embodiments 15 to 40% by weight, based on the total weight of the controlled release dosage form.

**[0044]** The dosage forms of the present invention have proven advantageous to avoid the effect of so-called dose dumping. Dose dumping is a phenomenon that occurs, for instance, when patients do no comply with the advice to avoid the intake of alcohol concomitantly with the administration of the controlled release pharmaceutical dosage form. The intake of alcohol can accelerate the release of the dose of the active ingredient, thus leading to potentially very harmful consequences for the patient, in particular in case of analgesics and opioid analgesics. It has been found that the use of the dosage forms of the present invention in a very effective mean to avoid or at least significantly reduce the risk of dose dumping upon ingestion of alcohol.

**[0045]** In accordance with what has been said above, the controlled release oral dosage forms described herein are characterized by a difference of no more than 20%, preferably no more than 15% and preferably no more than 12.5 % between an *in vitro* release rate of oxycodone at 37 °C in a solution containing 20% by weight ethanol and an *in vitro* release rate at 37 °C in an ethanol-free aqueous solution, when measured according to the USP Paddle Method (preferably as described in USP 34) in 900 ml aqueous buffer at 900 rpm.

**[0046]** Preferably, an *in vitro* release rate at 37°C in an aqueous solution containing 10% by weight ethanol, and/or in an aqueous solution containing 20% by weight ethanol, and/or in an aqueous solution containing 40% by weight ethanol, has a fit factor of between 50 and 100 compared to an ethanol-free aqueous solution. The fit factor is defined as follows:

$$f_2 = 50 \cdot \log\left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}\left[\overline{R}(t) - \overline{T}(t)\right]^2}{n}}}\right]$$

**[0047]** In this equation, $f_2$ is the similarity factor, n is the number of (measurement) time points, R(t) is the

mean percent reference drug dissolved at time t after initiation of the study (*i.e.* oxycodone in the aqueous solution without ethanol), T(t) is the mean percent test drug dissolved at time t after initiation of the study *(i.e.* oxycodone in ethanol containing solution). For both test and reference formulations percent dissolution should be determined.

**[0048]** The evaluation of the $f_2$ factor is based on the following conditions:

- A minimum of three time points (zero excluded)
- The time points should be the same for the two formulations
- Twelve individual values for every time point for each formulation
- Not more than one mean value of >85% dissolved for any of the formulations.
- The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point.

**[0049]** Preferably, the amount of substrates in the controlled release oral dosage form ranges from 1% to 100% by weight, based on the total weight of the controlled release dosage form. In preferred embodiments, the substrates are comprised in an amount of 20% to 90% by weight, more preferably 30% to 80% by weight, based on the total weight of the controlled release dosage form.

**[0050]** The controlled release oral dosage forms according to the present invention, in particular when present as tablets, may further comprise one or more pharmaceutically acceptable excipients, such as fillers, binding agents, disintegrants, plasticizers, and glidants. These excipients may be included in a coating or the external phase of the tablet, in particular.

**[0051]** Fillers are normally used to dilute a pharmaceutical composition and provide bulk. Fillers are preferably used in tablets. Examples for preferred fillers include lactose, starch, calcium phosphate, calcium carbonate, saccharose, sugar alcohols such as mannitol, sorbitol, xylitol, and or microcrystalline cellulose. Microcrystalline cellulose is particularly preferred. Vivapur®102 or Avicel®102 are suitable commercially available examples.

**[0052]** In a preferred embodiment a filler mixture comprising sodium carboxymethyl cellulose and microcrystalline cellulose, preferably in a weight ratio of 3:1 to 1:3, more preferably 2:1 to 1:2 is used. A filler or mixture of fillers may be used in an amount of from 0 to 60% by weight, preferably 1 to 50% by weight, and in particular 5 to 40% by weight, based on the total weight of the controlled release oral dosage form, preferably the tablet.

**[0053]** Binders generally serve to enhance the integrity and stability of tablets. In addition, they may improve the suitability of pharmaceutical compositions for granulation. Binders are commonly also used for the preparation of films, such as active agent containing layers, around an inert core. Exemplary binders include synthetic polymers, such as polyvinyl pyrrolidone, vinyl pyrrolidone-vinyl acetate-copolymer, modified celluloses, such as hydroxy alkyl celluloses and mixtures thereof. A binder is typically used in an amount of 0 to 25% by weight, preferably 0.1 to 15% by weight and in further embodiments 1 to 10% by weight of the controlled release oral dosage form. Preferably hydroxypropyl methyl cellulose (HPMC) is used as binder.

**[0054]** A disintegrant enhances the disintegration of a dosage form, in particular a tablet, after its immersion in water or gastric juices. Suitable disintegrants include carrageenan, cro-spovidone and mixtures thereof. Disintegrants may be used in amounts of 0 to 25% by weight, preferably 1.0 to 20% by weight and in further embodiments 3 to 15% by weight of the controlled release oral dosage form, preferably the tablet.

**[0055]** The controlled release oral dosage forms may further include a glidant, such as disperse silica, such as Aerosil®, or talc. A glidant (or mixture thereof) may be comprised in an amount of from 0 to 5 % by weight, for instance 0.1 to 4% by weight of the controlled release oral dosage form, preferably the tablet.

**[0056]** The oral controlled release dosage form may further comprise a lubricant, in particular in tablets prepared by compression. Suitable lubricants include stearic acid, magnesium stearate, adipic acid and sodium stearyl fumarate (Pruv®).

**[0057]** In a preferred embodiment the external phase (without coated pellets) comprises

85 to 99,9%, preferably 90 to 98% by weight filler,
0 to 5%, preferably 0.1 to 1.0% by weight lubricant and
0.1 to 10%, preferably 1.0 to 5% by weight glidant,

based on the total weight of the external phase.

**[0058]** Optionally, the controlled release oral dosage form according to the present invention, particularly when present in the form of a tablet, can comprise an external film for improved ease of swallowing, for protection, for colouring, for taste-masking or other purposes. Preferably, this external film does not influence the release of oxycodone to any significant extent. The external film may comprise the usual excipients known in this art for this purpose. A combination of hypromellose, talc, a colouring agent, such as titanium dioxide, and/or a polymer, such as polyethylene glycol is a preferred embodiment herein. This optional film is not counted towards the total weight of the controlled release oral dosage form herein. Expressed differently, any amount of an ingredient expressed as weight percent herein refers to the controlled release oral dosage form without this optional external film. As evident from the above, the external film is free of oxycodone in any form.

**[0059]** The multi-particulate controlled-release oral dosage form according to the present invention has the advantage that it may be divided into two or more units without impairing the controlled release of oxycodone.

The controlled release oral dosage form, and in particular the tablet, may therefore comprise means facilitating its division into two or more units, such as a break-line, each of said units providing controlled release of oxycodone. The dosage form according to the present invention therefore provides for the possibility to adjust the dosage, for instance halve the dosage by breaking the tablet in two.

**[0060]** In preferred embodiments according to the present invention, the oxycodone salt is oxycodone hydrochloride. The dosage form may contain oxycodone in amounts of from 5 to 160 mg. If oxycodone is used as free base, the amount of 5 to 160 mg refers to the weight of the free base. If oxycodone is used in the form of a pharmaceutical acceptable salt, the amount of 5 to 160 mg refers to the weight of the salt. Preferably, the dosage form of the present invention comprises 10 mg oxycodone, 20 mg oxycodone, 40 mg oxycodone or 80 mg oxycodone, more preferably 10 mg oxycodone hydrochloride, 20 mg oxycodone hydrochloride, 40 mg oxycodone hydrochloride or 80 mg oxycodone hydrochloride.

**[0061]** Preferably, the dosage form of the present invention provides the following *in vitro* release of oxycodone, when measured according to the USP Paddle Method in 900 ml aqueous buffer at 100 rpm, 37 °C and pH 2: between 1 and 20% by weight after 2 hours, between 10 and 35% by weight after 4 hours and/or between 40 and 70% by weight after 8 hours.

**[0062]** As mentioned before, the dosage forms according to the present invention have surprisingly been found to have very advantageous *in vivo* properties despite a mean $C_{24}/C_{max}$ ratio of less than 0.6. At steady state the oral dosage form according to the present invention provides a mean $C_{24}/C_{max}$ of between 0.30 and 0.56, for instance between 0.35 and 0.55 or 0.54 after oral administration. Preferably, *in vivo* parameters are determined as described in Bauer, Frömming, Führer, "Lehrbuch der Pharmazeutischen Technologie", 8th edition, chapter 4.2.1 "Grundlagen und Methoden".

**[0063]** The controlled release oral dosage forms according to the present invention are preferably for the treatment of severe and very severe pain, more preferably of severe and very severe pain according to the VAS scale. In particular, the controlled release oral dosage form is suitable for patients who need continuous treatment over an extended period of time.

**[0064]** A controlled release oral dosage form as described above can be formed by a method comprising:

a) coating each of a plurality of inert cores with a layer comprising oxycodone or a pharmaceutically acceptable salt or solvent thereof,

b) coating each of the plurality of coated inert cores with a release control layer comprising a release control substance for controlling the release of oxycodone, thus forming a plurality of substrates,

c) mixing the plurality of substrates with at least one pharmaceutically acceptable excipient,

d) forming a tablet from the mixture comprising the plurality of substrates and the at least one pharmaceutically acceptable excipient.

**[0065]** For preferred embodiments of inert cores, preferred oxycodone forms, release controlling substances, further excipients, the substrates etc., it is referred to the explanations concerning embodiments of the dosage forms of the present invention above, which naturally equally apply to the method for preparing a controlled release dosage form according to the present invention.

**[0066]** Step a) may further include dissolving or suspending oxycodone or a salt thereof in a suitable solvent or solvent mixture, optionally together with a binder, such as a hydrox-yalkyl cellulose, such as hydroxy propylmethyl cellulose. The solvent is preferably water, an alcohol, such as ethanol, or mixtures thereof. Preferably, the pH of the solvent is adjusted to a value which enables a complete dissolution of the oxycodone. More preferably, the pH is adjusted to a value of 2 to 6, in particular 3 to 5.

**[0067]** Preferably, the inert cores are sugar spheres. Preferably, oxycodone hydrochloride is used. Further preferably, the coating step a) is a coating step in a fluid bed processor wherein preferably a solution or suspension (in particular solution) of oxycodone hydrochloride and one or more excipients, such as hypromellose, are sprayed onto the inert cores. The coating solution or suspension usually comprises respectively consists of water and/or an alcohol. Preferably, the process temperature is between 30 and 60°C.

**[0068]** Preferably, step b) involves coating by spraying a coating solution containing the release control substance onto the coated inert cores from step a). The spraying step is preferably performed in a fluid bed processor. The fluid bed processor is preferably suitable for coating of powders, particles, inert spheres, pellets and tablets, and/or simultaneous drying. Preferably, the process temperature is between 30 and 60°C.

**[0069]** The solvent of the coating solution or suspension from step b) predominantly contains alcohol, *i.e.* the solvent used for dissolving the release controlling agent and optional further excipients contains preferably 60% or more by weight, more preferably 70% or more by weight of alcohol. A mixture of ethanol and water is particularly preferred. Furthermore, preferably ethylcellulose is used as the release controlling agent. Additional excipients may include hydroxypropyl cellulose, talc and other pharmaceutical suitable excipients.

**[0070]** The substrates preferably have a weight average particle diameter ($d_{50}$) of 50 to 1000 μm, in preferred embodiments 100 to 800 μm, in further embodiments 150 to 600 μm, as measured by sieve analysis, such as by means of a Retsch Siebmaschine AS 300 control. The thickness of the release control layer is preferably in a range of from 0.1 to 200 μm, preferably 0.5 to 100 μm, and most preferably 1.0 to 50 μm.

**[0071]** A particularly preferred embodiment of the present invention comprises one or more of the following

features:

- controlled-release tablet for administration of oxycodone once a day, which is a multi-particulate dosage form,
- a plurality of substrates,
- each substrate comprises a core containing oxycodone or a pharmaceutically acceptable salt or solvate thereof and a release-control layer containing a release-control substance for controlling the release of oxycodone from the substrate comprising oxycodone,
- wherein the oxycodone containing core comprises a layer comprising oxycodone disposed on an inert core,
- the inert cores preferably being saccharose cores,
- 90% of the inert cores having a particle size in the range of 200 to 400 μm,
- the oxycodone-comprising layer comprising oxycodone in the form of its HCl salt,
- the oxycodone-comprising layer comprising at least one of HPMC (binder) and talc (glidant),
- the HPMC having a viscosity < 100 mPa•s, more preferably < 50 mPa•s and most preferably < 10 mPa•s (measurement conditions as before),
- the oxycodone-comprising layer having a thickness in the range of 10 to 400 μm, more preferably 100 to 300 μm (90% of the particles, as determined by sieve analysis),
- wherein the release control substance is a hydrophobic polymer, preferably an alkyl cellulose, most preferably ethyl cellulose,
- wherein the release-control layer further comprises at least one of hydroxypropyl cellulose, propylene glycol and talc,
- the hydroxypropyl cellulose having a viscosity (10% aqueous solution, 25°C) of 10 to 3000 mPa•s, more preferably 100 to 1000 mPa•s, for instance 300 to 600 mPa•s,
- the release-control layer preferably having a (mean) thickness of less than 500 μm, more preferably less than 250 μm, such as less than 150 μm (90%, determined by sieve analysis relative to the oxycodone-coated inert cores)
- the plurality of substrates being contained in an external phase,
- the external phase comprising at least one of carmellose sodium, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate,
- carmellose sodium having a viscosity (2% aqueous solution, 25°C) of 400 to 800 mPa•s (measured as set our before),
- microcrystalline cellulose having a particle size distribution, as determined by air jet sieving, of at most 25, 15 or 10 % > 250 μm and/or at least 30, 40 or 45% > 75 μm and/or at least 50, 60 or 70% > 30 μm.

**[0072]** It is further preferred that the tablet of the present invention comprises:

oxycodone-containing cores comprising

1 to 30 wt.%, preferably 2 to 20 wt.%, more preferably 3 to 10 wt.% neutral pellets,
1 to 40 wt.%, preferably 5 to 20 wt.%, more preferably 10 to 15 wt.% oxycodone, in particular oxycodone hydrochloride,
0.01 to 10 wt.%, preferably 0.1 to 5 wt.%, more preferably 0.5 to 3 wt.% binder, and
0 to 10 wt.%, preferably 0.1 to 5 wt.%, more preferably 0.5 to 3 wt.% glidant, said cores being coated with a release-control layer comprising
1 to 40 wt.%, preferably 3 to 20 wt.%, more preferably 7 to 15 wt.% release-control substance,
0.01 to 10 wt.%, preferably 0.1 to 6 wt.%, more preferably 1 to 4 wt.% pore builder,
0 to 10 wt.%, preferably 0.1 to 6 wt.%, more preferably 1 to 4 wt.% plasticiser,
0 to 15 wt.%, preferably 0.1 to 10 wt.%, more preferably 2 to 5 wt.% glidant, and
an external phase comprising

20 to 85%, preferably 40 to 75%, more preferably 50 to 65% filler,
0 to 3 wt.%, preferably 0.001 to 2.0 wt.%, more preferably 0.1 to 0.5 wt.% lubricant and
0 to 5 wt.%, preferably 0.1 to 5 wt.%, more preferably 0.5 to 2.0 wt.% glidant,

wherein all wt.% are based on the total weight of the tablet (without film coating).

**[0073]** The tablets of the present invention preferably have a tablet height of from 2 to 5 mm, more preferably 3 to 4 mm. Preferably, the tablets have a hardness of 40 to 300 N, more preferably of 50 to 200 N.

**[0074]** Tablets with a combination of several of the above features have been found to be particularly advantageous: They provide good clinical efficacy, not least due to providing an advantageous dissolution profile without the need to include an immediate release portion of oxycodone. They can be broken or divided without affecting the release of drug from the tablet. Dose dumping phenomena do not occur.

**[0075]** The invention will be further described by way of exemplary embodiments with reference to the Figures wherein

**Figure 1a** shows the dissolution profile of a 20 mg containing oxycodone tablet at pH 2 and pH 4.5,

**Figure 1b** shows the dissolution profile of a 20 mg containing oxycodone tablet at pH 1.6 and pH 7.2,

**Figure 2a** shows the dissolution profile of a 40 mg

containing oxycodone tablet at pH 2 and pH 4.5,

**Figure 2b** shows the dissolution profile of a 40 mg containing oxycodone tablet at pH 1.6 and pH 7.2,

**Figure 3** shows the dissolution profile of a 10 mg containing oxycodone tablet at pH 2 and pH 4.5,

**Figure 4** represents a table listing the $C_{max}$ and $C_{24}$ values as well as their ratios in 36 subjects taking part in a steady state study involving tablets containing 10 mg oxycodone according to the invention,,

**Figure 5** illustrates the efficacy of dosage forms according to the present invention administered once a day in comparison to commercially available tablets administered twice a day.

## EXAMPLES

**Example 1:** Preparation of tablets containing 10 mg oxycodone

**Step 1:**

**[0076]** A spraying suspension is prepared from the following ingredients:

| | |
|---|---|
| Purified water | 20.00 kg |
| Ethanol 96% | 6.80 kg |
| Hypromellose | 0.40 kg |
| Talc | 0.40 kg |
| Hydrochloric acid 0.1 N | q.s. |
| Oxycodone hydrochloride | 4.00 kg |

**[0077]** A spraying suspension is prepared by successively dissolving hypromellose and oxycodone hydrochloride in a large part of the preheated purified water. Ethanol 96% is added to this solution under stirring. Talc is suspended in the remaining part of water, homogenized, and added to the oxycodone containing solution. The pH of the resulting suspension is adjusted using HCl in order to keep the oxycodone hydrochloride in solution.

**[0078]** 2.00 kg sugar spheres (saccharose, particle size range (90%) 200 to 400 μm are filled into a fluid-bed processor with a bottom-spray nozzle and pre-heated. The spraying suspension is then sprayed onto the sugar spheres in the fluid-bed processor, thus preparing a plurality of sugar spheres having a layer of oxycodone coated thereupon. The coated sugar spheres are then sieved through a 0.6 mm sieve (vibration sieve or equivalent).

**Step 2:**

**[0079]** A coating solution is prepared from the following ingredients:

| | |
|---|---|
| Ethanol 96% | 45.55 kg |
| Water, purified | 13.19 kg |
| Ethylcellulose | 2.33 kg |
| Hydroxypropyl cellulose (Klucel® EF) | 0.49 kg |
| Propylene glycol | 0.48 kg |
| Talc | 0.70 kg |

**[0080]** Hydroxypropyl cellulose is added to the purified water and mixed until the solution is clear. Ethylcellulose and ethanol are then added to the solution. The solution is stirred and becomes opalescent. Finally, propylene glycol is added and the solution is continuously stirred until it is clear.

**[0081]** The coated sugar spheres from Step 1 are filled into a fluid-bed processor and preheated. The coated solution prepared as indicated above is sprayed onto the coated sugar spheres. The substrates obtained thereby as then sieved through a 0.710 mm sieve.

Step 3:

**[0082]** The following ingredients are dry mixed to a blend:

| | |
|---|---|
| Substrates from Step 2 | 10.80 kg |
| Carmellose sodium (CMC 400-800 cPs) | 9.60 kg |
| Microcrystalline cellulose | 9.350 kg |
| Colloidal anhydrous silica | 0.35 kg |
| Magnesium stearate | 0.30 kg |

**[0083]** The resulting dry blend is then compressed to tablets.

**Step 4 (optional):**

**[0084]** A tablet coating suspension is made from the following ingredients:

| | |
|---|---|
| Titanium dioxide | 0.42 kg |
| Hypromellose | 1.16 kg |
| Macrogol 6000 | 0.26 kg |
| Talc | 0.16 kg |
| Water, purified | 14.50 kg |

34.0 kg tablets are film coated with the tablet coating suspension.

**[0085]** The dissolution profiles of the 10 mg tablets are in accordance with the present invention, as apparent from Figure 3. Figure 4 shows the $C_{max}$ and $C_{24}$ values as well as their ratios from 36 subjects taking part in a steady state study involving tablets containing 10 mg oxycodone according to Example 1.

**Example 2:** Preparation of tablets containing 20 mg oxycodone

**[0086]** The tablets of Example 2 are prepared in the same manner as those in Example 1. Except, in the 20 mg tablets, double the amount of oxycodone hydrochloride and excipients (including in this context release controlling layer, solvents etc.) is employed.

**[0087]** The dissolution profiles of the 20 mg tablets according to Example 2 are shown in Figures 1a and b. The dissolution profiles were measured using the USP Paddle Method at 37°C.

**Example 3:** Preparation of tablets containing 40 mg oxycodone

**[0088]** The tablets of Example 3 are prepared in the same manner as those in Example 1. Except, in the 40 mg tablet, four times the amount of oxycodone hydrochloride and excipients (including in this context release controlling layer, solvents etc.) is used.

**[0089]** The dissolution profiles of the 40 mg tablets according to Example 3 are shown in Figures 2a and b. The dissolution profiles were measured using the USP Paddle Method at 37°C.

**[0090]** Figure 5 illustrates results of a randomized, double-blind cross-over Phase III study to investigate the efficacy and safety of oxycodone tablets according to the present invention administered once a day (designated "test" in Figure 5) in comparison to twice daily administration of Oxygesic® 20 - 120 mg tablets (designated "reference" in Figure 5) in patients with chronic cancer pain/chronic pain. As apparent from Figure 5, which illustrates the mean current pain intensity score (on a 0 - 100 mm VAS scale), the pain relief provided by the dosage forms according to the present invention when administered once a day closely resembles that obtained by twice daily administration of conventional oxycodone tablets.

## Claims

1. A multi-particulate controlled-release oral dosage form for use in the treatment of chronic pain by administration of oxycodone once a day,
comprising
a plurality of substrates comprising oxycodone or a pharmaceutically acceptable salt or solvate thereof,
each substrate comprising a release-control substance for controlling the release of oxycodone of the salt or solvate thereof,
wherein each substrate comprises an oxycodone-containing core and a release-control layer containing the release-control substance for controlling the release of oxycodone from the substrate,
wherein at steady state the oral dosage form provides a mean $C_{24}/C_{max}$ of between 0.30 and 0.56 after oral administration,
wherein the core comprises a layer comprising oxycodone coated on an inert core and/or wherein the release control substance is a hydrophobic polymer,
wherein the plurality of substrates is contained in an external phase of at least one pharmaceutically acceptable excipient.

2. The controlled-release oral dosage form according to claim 1, wherein the external phase comprises carboxymethyl cellulose, optionally in the form of a salt, as a pharmaceutically acceptable excipient.

3. The controlled-release oral dosage form according to claim 1 or 2, which is a tablet.

4. The controlled-release oral dosage form according to one of the preceding claims, comprising means facilitating division into two or more units, each of said units providing controlled-release of oxycodone.

5. The controlled-release oral dosage form according to one of the preceding claims, wherein the oxycodone salt is oxycodone hydrochloride.

6. The controlled release oral dosage form according to one of the preceding claims, providing an in vitro release of oxycodone, when measured according to the USP Paddle Method in 900 ml aqueous buffer at 100 rpm and pH 2 of between 1 and 20% by weight after 2 hours, between 10 and 35% by weight after 4 hours and/or between 40 and 70% by weight after 8 hours.

7. The controlled-release oral dosage form according to one of the preceding claims **characterized by** a difference of no more than 20% between an in vitro release rate at 37°C in a solution containing 20% by weight ethanol and an in vitro release rate at 37°C in an ethanol-free aqueous solution, when measured according to the USP Paddle Method in 900 ml aqueous buffer at 100 rpm.

8. The controlled-release oral dosage form according to one of the preceding claims, wherein the dosage forms comprises 10 mg, 20 mg, 40 mg or 80 mg oxycodone hydrochloride.

## Patentansprüche

1. Multipartikuläre orale Darreichungsform mit kontrollierter Freisetzung zur Verwendung in der Behandlung von chronischem Schmerz durch Verabreichung von Oxycodon einmal täglich, umfassend eine Vielzahl an Substraten, umfassend Oxycodon oder ein pharmazeutisch verträgliches Salz oder Solvat davon,
wobei jedes Substrat eine die Freisetzung kontrollierende Substanz zur Kontrolle der Freisetzung des Oxycodons oder des Salzes oder Solvats davon umfasst,
wobei jedes Substrat einen Oxycodon enthaltenden Kern und eine die Freisetzung kontrollierende Schicht enthaltend die die Freisetzung kontrollierende Substanz zur Kontrolle der Freisetzung des Oxycodons aus dem Substrat umfasst,
wobei im Steady-State-Zustand die orale Darreichungsform einen durchschnittlichen $C_{24}/C_{max}$-Wert von 0.30 bis 0.56 nach oraler Verabreichung liefert,
wobei der Kern eine Schicht umfasst, die auf einem inerten Kern beschichtetes Oxycodon umfasst, und/oder wobei die die Freisetzung kontrollierende Substanz ein hydrophobes Polymer ist,
wobei die Vielzahl an Substraten in einer externen Phase von mindestens einem pharmazeutisch verträglichen Hilfsstoff enthalten ist.

2. Orale Darreichungsform mit kontrollierter Freisetzung gemäß Anspruch 1,
wobei die externe Phase Carboxymethylcellulose, optional in Form eines Salzes, als pharmazeutisch verträglichen Hilfsstoff umfasst.

3. Orale Darreichungsform mit kontrollierter Freisetzung gemäß Anspruch 1 oder 2, welche eine Tablette ist.

4. Orale Darreichungsform mit kontrollierter Freisetzung gemäß einem der vorangegangenen Ansprüche, welche Mittel zur Erleichterung der Teilung in zwei oder mehrere Einheiten umfasst, wobei jede der Einheiten eine kontrollierte Freisetzung von Oxycodon liefert.

5. Orale Darreichungsform mit kontrollierter Freisetzung gemäß einem der vorangegangenen Ansprüche, wobei das Oxycodonsalz Oxycodonhydrochlorid ist.

6. Orale Darreichungsform mit kontrollierter Freisetzung gemäß einem der vorangegangenen Ansprüche, welche eine in vitro Freisetzung von Oxycodon von zwischen 1 und 20 Gew.% nach 2 Stunden, zwischen 10 und 35 Gew.% nach 4 Stunden und/oder zwischen 40 und 70 Gew.% nach 8 Stunden liefert, wenn gemäß der USP Paddle Methode in 900 mL wässrigem Puffer bei 100 rpm und pH 2 gemessen.

7. Orale Darreichungsform mit kontrollierter Freisetzung gemäß einem der vorangegangenen Ansprüche, welche durch einen Unterschied von nicht mehr als 20% zwischen einer in vitro Freisetzungsrate bei 37°C in einer Lösung enthaltend 20 Gew.% Ethanol und einer in vitro Freisetzungsrate bei 37°C in einer Ethanol-freien wässrigen Lösung gekennzeichnet ist, wenn gemäß der USP Paddle Methode in 900 mL wässrigem Puffer bei 100 rpm gemessen.

8. Orale Darreichungsform mit kontrollierter Freisetzung gemäß einem der vorangegangenen Ansprüche, wobei die orale Darreichungsform 10 mg, 20 mg, 40 mg oder 80 mg Oxycodonhydrochlorid umfasst.

## Revendications

1. Une forme de dosage orale à libération contrôlée multi-particulaire pour usage dans le traitement de la douleur chronique par administration d'oxycodone une fois par jour, comprenant
une pluralité de substrats comprenant de l'oxycodone ou un sel ou un solvate pharmaceutiquement acceptable de celui-ci,
chaque substrat comprenant une substance de contrôle de libération pour contrôler la libération d'oxycodone du sel ou du solvate de celui-ci,
dans laquelle chaque substrat comprend un noyau contenant de l'oxycodone et une couche de contrôle de libération contenant la substance de contrôle de libération pour contrôler la libération d'oxycodone du substrat,
dans laquelle à l'état d'équilibre la forme de dosage orale fourni une moyenne $C_{24}/C_{max}$ d'entre 0,30 et 0,56 après administration orale,
dans laquelle le noyau comprend une couche comprenant de l'oxycodone revêtue sur un noyau inerte et/ou dans laquelle la substance de contrôle de libération est un polymère hydrophobique, laquelle la pluralité des substrats est contenue dans un phase externe d'au moins un excipient pharmaceutiquement acceptable.

2. La forme de dosage orale à libération contrôlée selon la revendication 1, dans laquelle la phase externe comprend de la carboxyméthylcellulose, facultativement en forme d'un sel, en tant qu'un excipient pharmaceutiquement acceptable.

3. La forme de dosage orale à libération contrôlée selon la revendication 1 ou 2, qui est un comprimé.

4. La forme de dosage orale à libération contrôlée selon

l'une quelconque des revendications précédentes, comprenant des moyens facilitant la division en deux unités ou plus, chacune desdites unités fournissant de l'oxycodone à libération contrôlée.

5. La forme de dosage orale à libération contrôlée selon l'une quelconque des revendications précédentes, dans laquelle le sel d'oxycodone est de l'hydrochlorure d'oxycodone.

6. La forme de dosage orale à libération contrôlée selon l'une quelconque des revendications précédentes, fournissant une libération d'oxycodone in vitro, quand mesuré selon la méthode USP Paddle dans 900 ml d'un tampon aqueux a 100 tours par minute et a un pH 2, d'entre 1 and 20% en poids après 2 heures, d'entre 10 and 35% en poids après 4 heures et/ou d'entre 40 and 70% en poids après 8 heures.

7. La forme de dosage orale à libération contrôlée selon l'une quelconque des revendications précédentes, **caractérisée par** une différence non supérieure à 20% entre un taux de libération in vitro à 37°C dans une solution contenant 20% en poids d'éthanol et un taux de libération à 37°C dans un solution aqueuse sans éthanol, quand mesuré selon la méthode USP Paddle dans 900 ml d'un tampon aqueux a 100 tours par minute.

8. La forme de dosage orale à libération contrôlée selon l'une quelconque des revendications précédentes, dans laquelle la formes de dosage comprend 10 mg, 20 mg, 40 mg ou 80 mg d'hydrochlorure d'oxycodone.

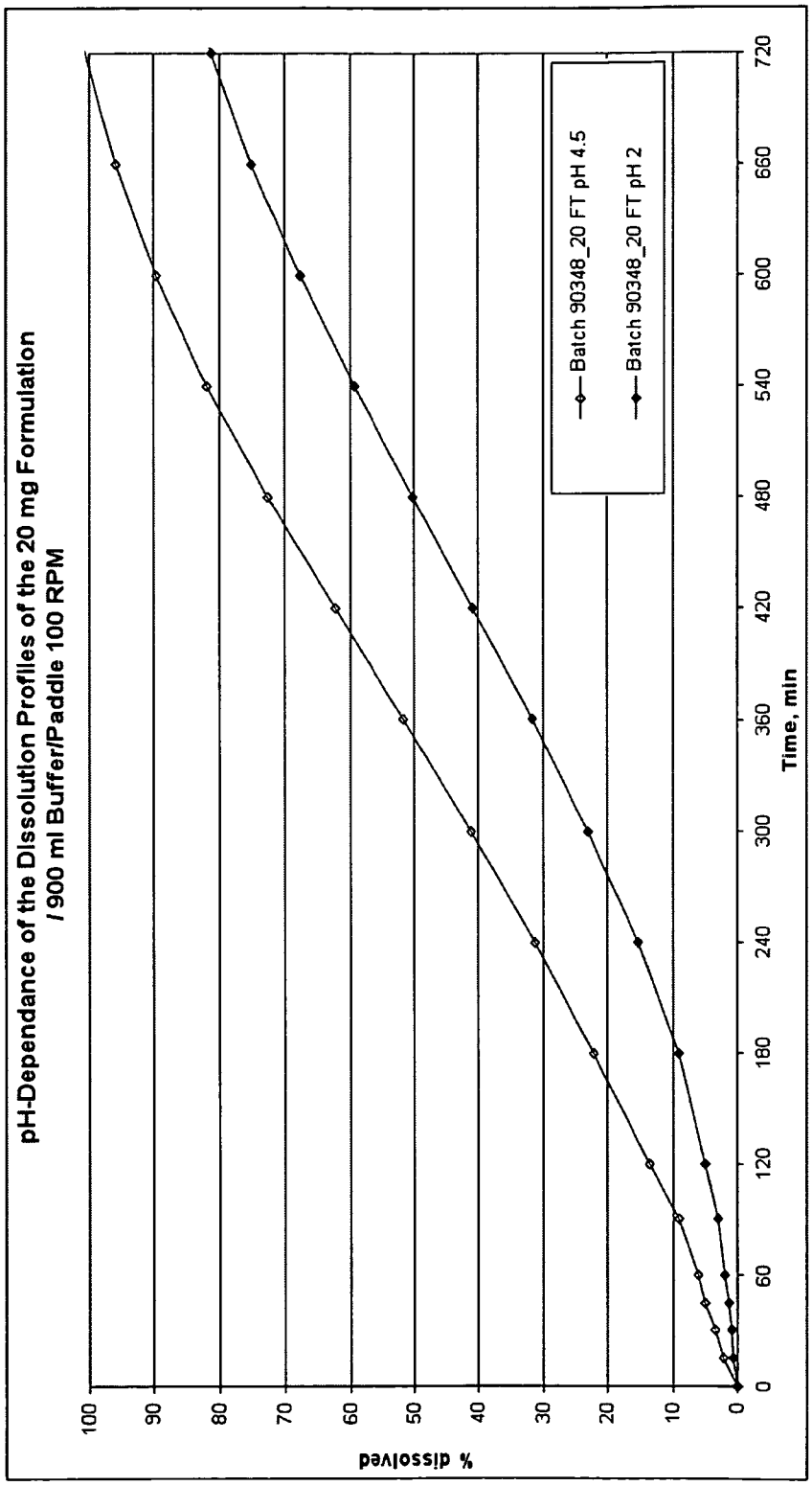



**Figure 1a** Dissolution profiles for tablets containing 20 mg oxycodone at pH 2 and 4.5

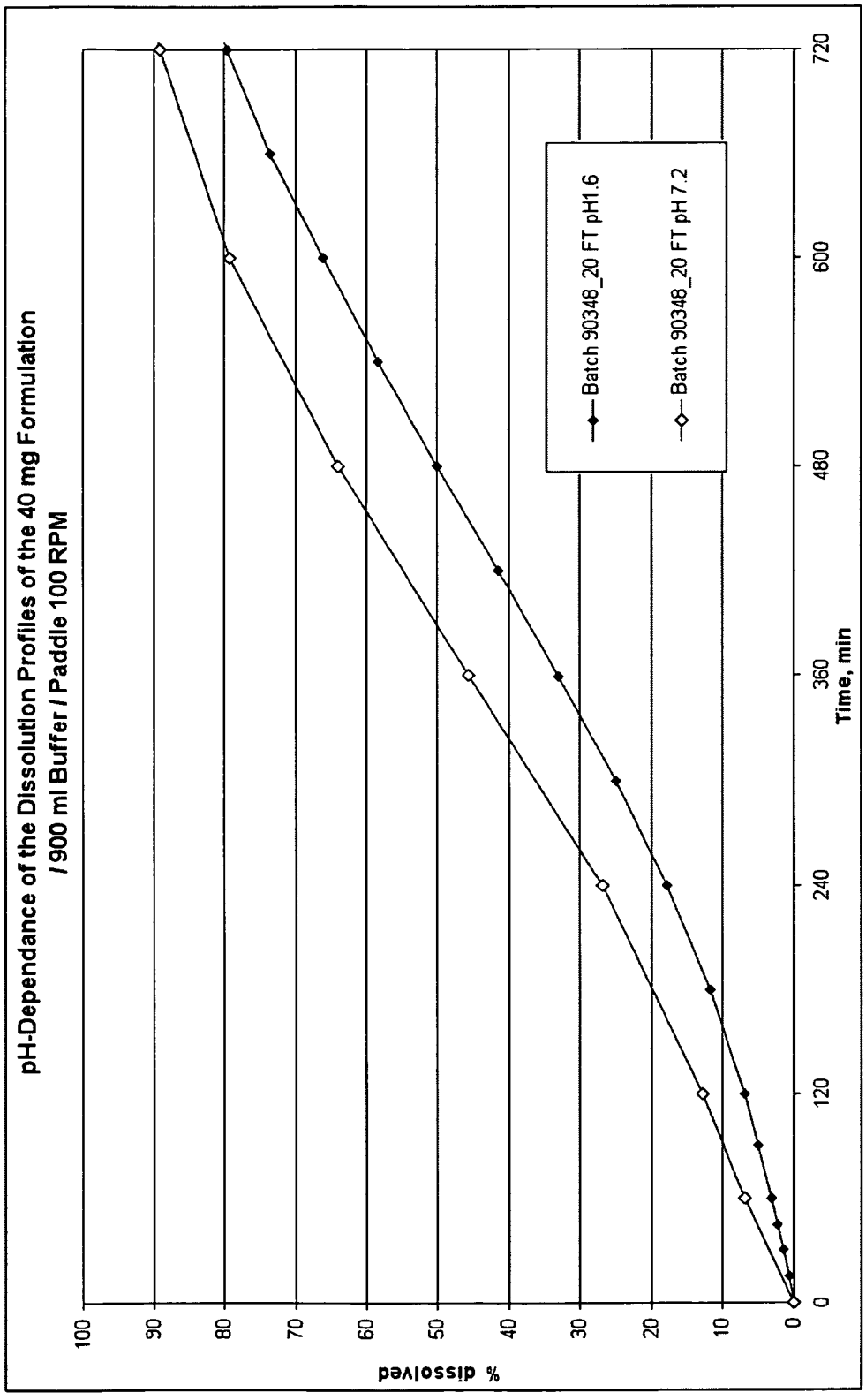



**Figure 1b** Dissolution profiles for tablets containing 20 mg oxycodone at pH 1.6 and 7.2

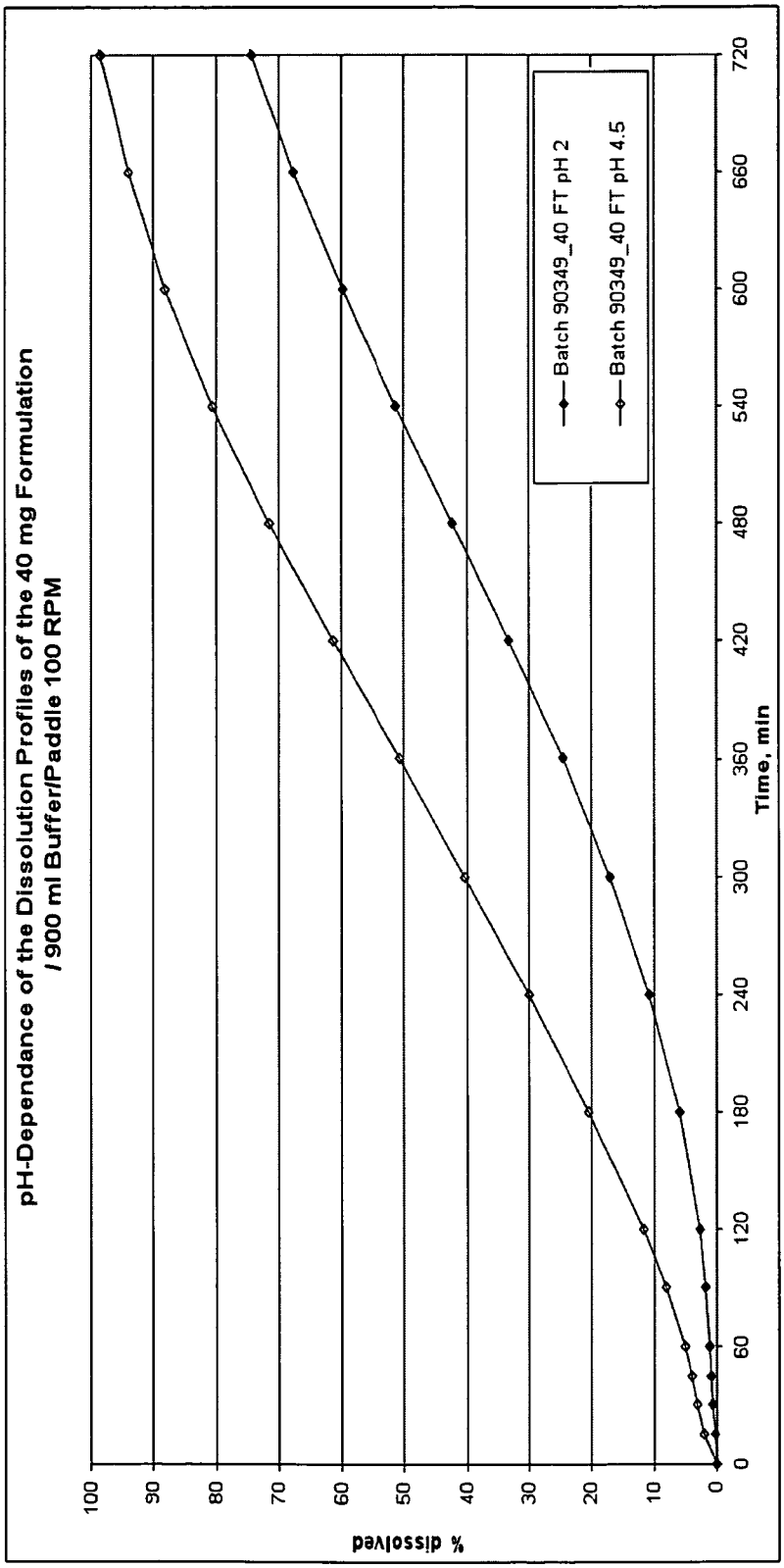



**Figure 2a** Dissolution profiles for tablets containing 40 mg oxycodone at pH 2 and 4.5

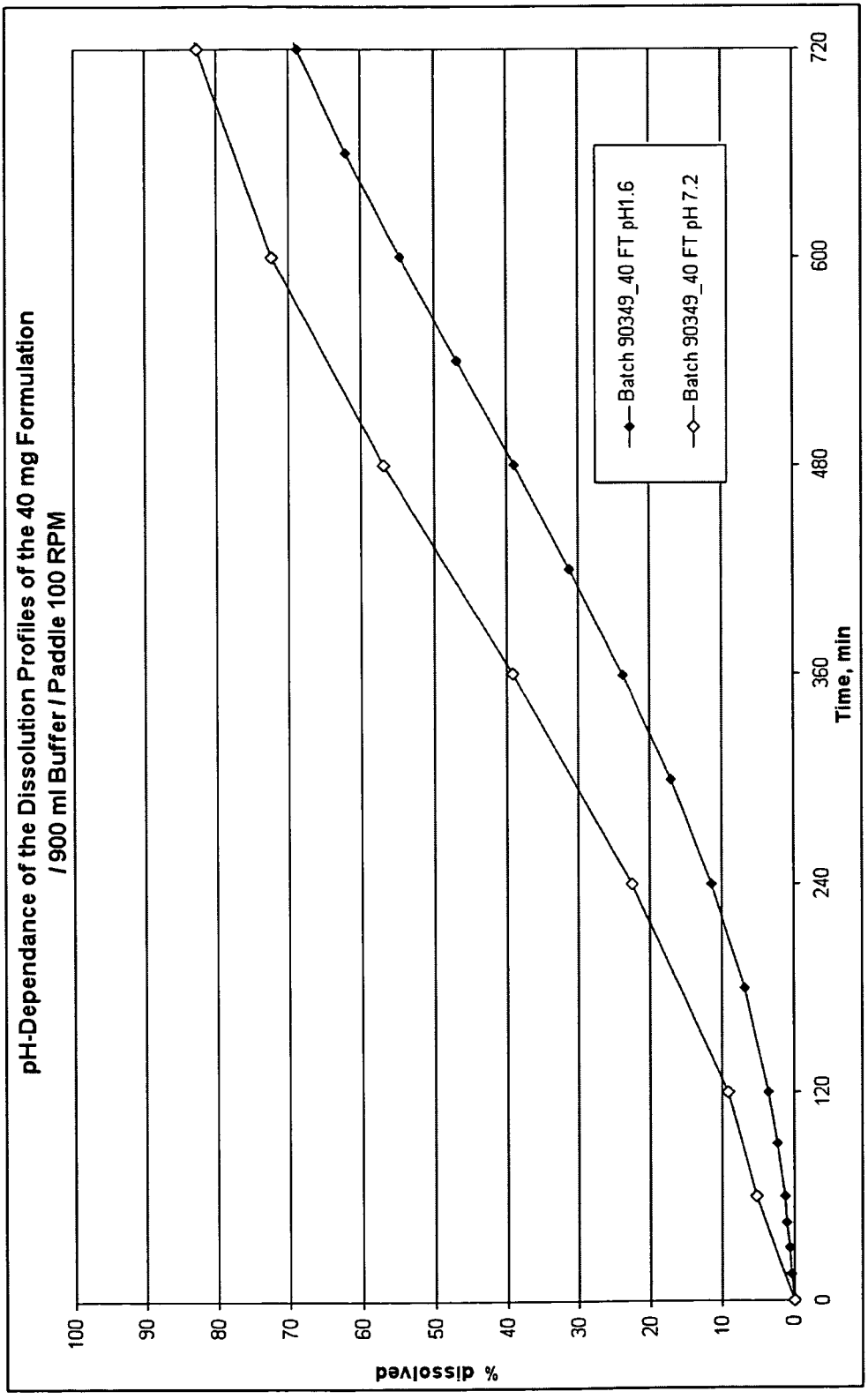



**Figure 2b** Dissolution profiles for tablets containing 40 mg oxycodone at pH 1.6 and 7.2

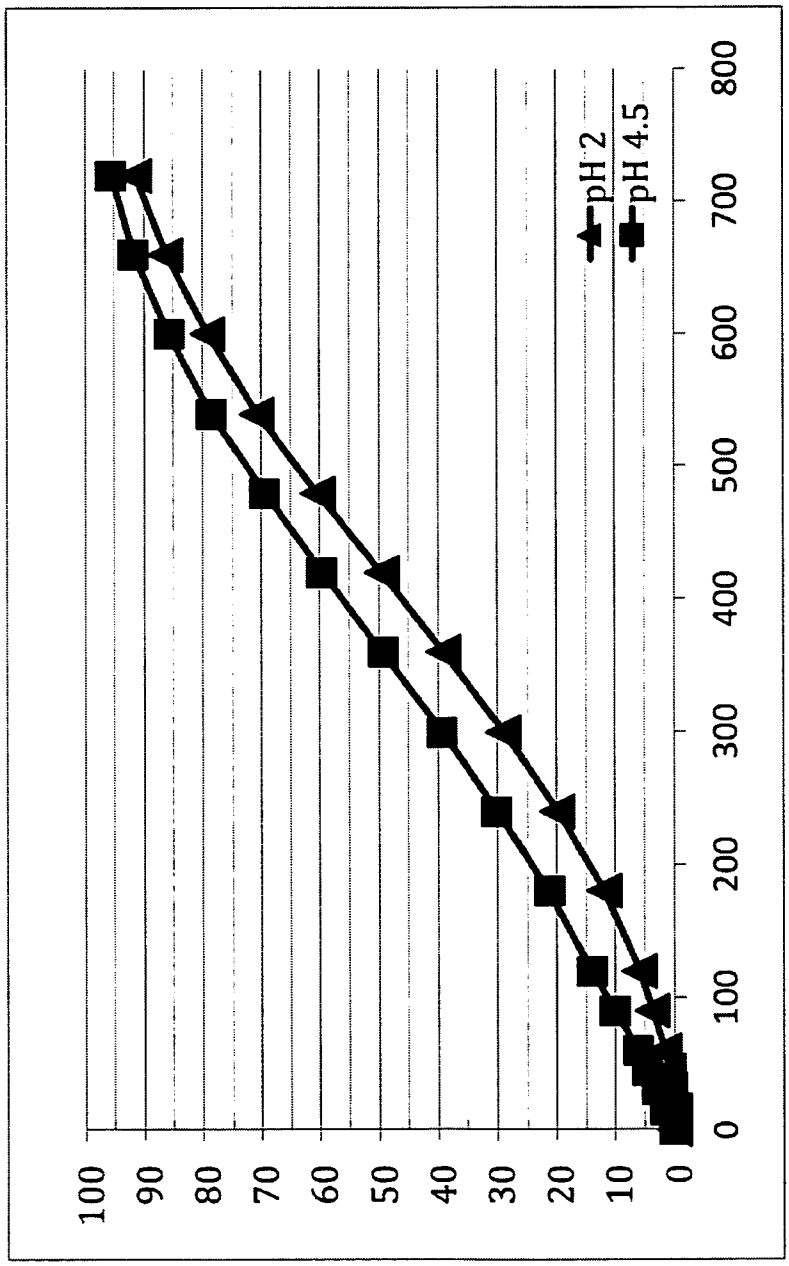
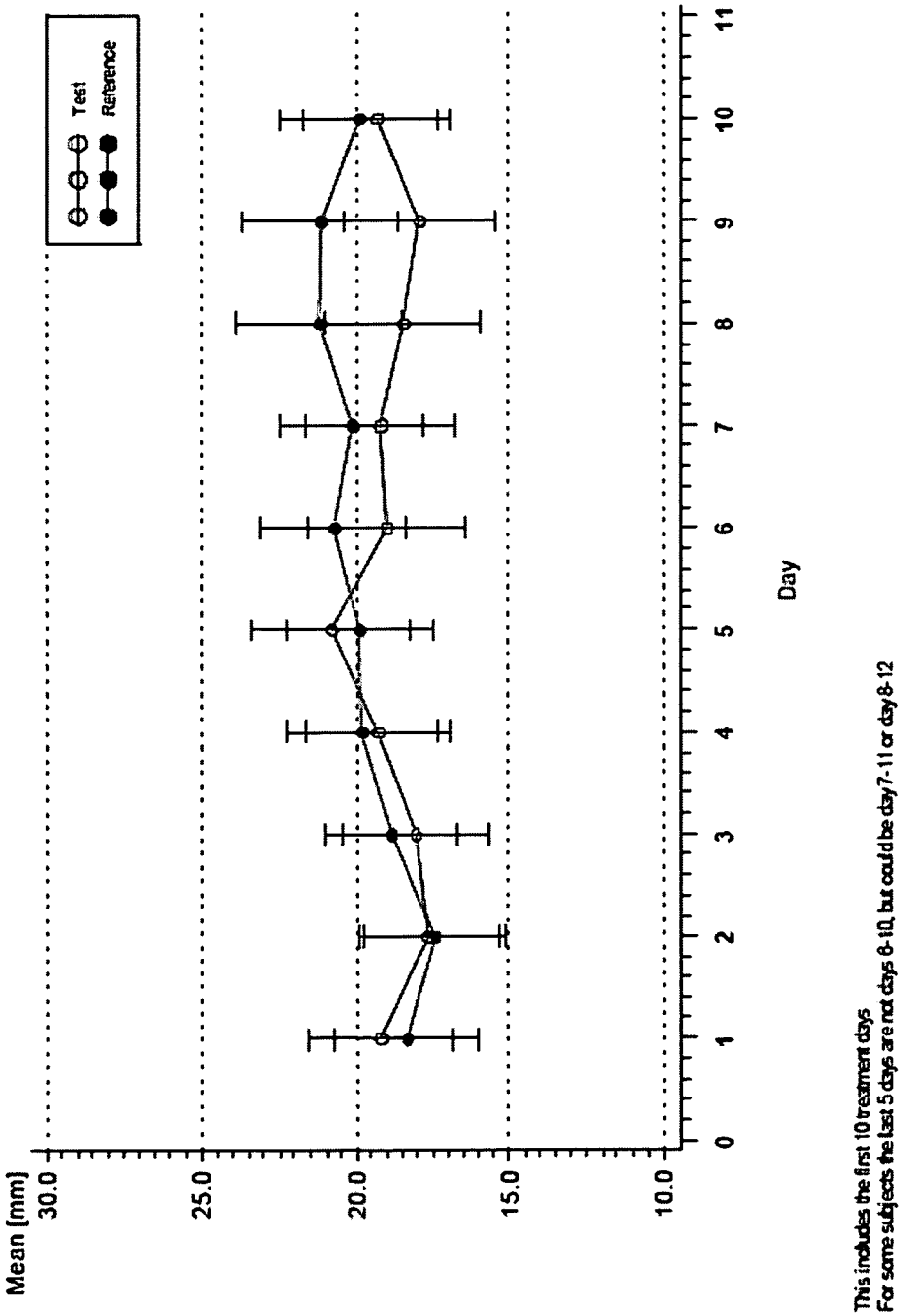



**Figure 3** Dissolution profiles for tablets containing 10 mg oxycodone at pH 2 and 4.5

**Figure 4**

| Subject | $C_{24}$ at 96.0 hours | $C_{max}$ between 72.0 hours and 96.0 hours | Ratio $C_{24}/C_{max}$ |
|---|---|---|---|
| 1 | 1.97 | 5.05 | 0.39 |
| 2 | 2.12 | 5.05 | 0.42 |
| 3 | 2.84 | 6.16 | 0.46 |
| 4 | 2.97 | 7.26 | 0.41 |
| 5 | 2.28 | 5.41 | 0.42 |
| 6 | 0.57 | 5.20 | 0.11 |
| 7 | 2.71 | 9.41 | 0.29 |
| 8 | 2.99 | 8.01 | 0.37 |
| 9 | 2.34 | 6.70 | 0.35 |
| 10 | 2.38 | 4.95 | 0.48 |
| 11 | 3.69 | 6.91 | 0.53 |
| 12 | 2.92 | 6.93 | 0.42 |
| 13 | 2.08 | 4.62 | 0.45 |
| 14 | 3.55 | 8.46 | 0.42 |
| 15 | 1.96 | 5.51 | 0.36 |
| 16 | 2.28 | 6.35 | 0.36 |
| 17 | 3.92 | 11.54 | 0.34 |
| 18 | 5.35 | 10.96 | 0.49 |
| 19 | 2.05 | 5.44 | 0.38 |
| 20 | 2.32 | 4.95 | 0.47 |
| 21 | 3.65 | 9.22 | 0.40 |
| 22 | 1.78 | 4.43 | 0.40 |
| 23 | 1.28 | 4.93 | 0.26 |
| 24 | 2.51 | 6.03 | 0.42 |
| 25 | 2.66 | 7.19 | 0.37 |
| 26 | 2.96 | 7.11 | 0.42 |
| 27 | 3.61 | 9.12 | 0.40 |
| 28 | 3.19 | 7.09 | 0.45 |
| 29 | 2.65 | 5.93 | 0.45 |
| 30 | 2.00 | 5.10 | 0.39 |
| 31 | 6.02 | 11.20 | 0.54 |
| 32 | 2.48 | 5.82 | 0.43 |
| 33 | 1.96 | 6.42 | 0.31 |
| 34 | 4.69 | 13.73 | 0.34 |
| 35 | 2.00 | 6.42 | 0.31 |
| 36 | 2.94 | 8.65 | 0.34 |
| arithmetic mean | 2.77 | 7.04 | 0.39 |

Figure 5


Test
Reference
Mean (mm)
30.0
25.0
20.0
15.0
10.0
0
1
2
3
4
5
6
7
8
9
10
11
Day
This includes the first 10 treatment days
For some subjects the last 5 days are not days 6-10, but could be day7-11 or day8-12

## 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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- WO 02087512 A **[0003]**
- WO 03101384 A2 **[0004]**
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- WO 02087512 A2 **[0006]**
- US 20050074493 A1 **[0007]**


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SZTNH-100024295

1. Multipartikuláris, szabályozott hatóanyag-leadású orális adagolási forma krónikus fájdalom kezelésében történő alkalmazására oxikodon napi egyszeri adagolásával, amely tartalmaz

nagyszámú szubsztrátumot, amely oxikodont vagy ennek gyógyszerészetileg alkalmazható sóját vagy szolvátját tartalmazza,

minden szubsztrátum tartalmaz egy hatóanyag-leadást szabályzó anyagot az oxikodon vagy ennek sója vagy szolvátja felszabadulásának szabályozására,

ahol minden szubsztrátum tartalmaz egy oxikodont tartalmazó magot és egy hatóanyag-leadást szabályozó réteget, amely tartalmazza a hatóanyag-leadást szabályzó anyagot, a szubsztrátumból az oxikodon vagy ennek sója vagy szolvátja felszabadulásának szabályozására,

ahol állandósult (steady state) állapotban az orális adagolási forma 0,30 és 0,56 közötti átlagos $C_{24}/C_{max}$ értéket eredményez orális adagolás után,

ahol a mag tartalmaz egy réteget, amely inert magon oxikodon bevonatot tartalmaz, és/vagy ahol a hatóanyag-leadást szabályozó anyag egy hidrofób polimer,

ahol a nagyszámú szubsztrátum legalább egy, gyógyszerészetileg alkalmazható segédanyagból álló külső fázisban van elhelyezve.

2. Az 1. igénypont szerinti szabályozott hatóanyag-leadású orális adagolási forma, ahol a külső fázis gyógyszerészetileg alkalmazható segédanyagként karboximetilcellulózt tartalmaz, adott esetben só formájában.

3. Az 1. vagy 2. igénypont szerinti szabályozott hatóanyag-leadású orális adagolási forma, amely tabletta.

4. Az előző igénypontok bármelyike szerinti szabályozott hatóanyag-leadású orális adagolási forma, amely két vagy több egységre történő felosztódást lehetővé tevő eszközöket tartalmaz, ahol minden ilyen egység biztosítja az oxikodon szabályozott felszabadulását.

5. Az előző igénypontok bármelyike szerinti szabályozott hatóanyag-leadású orális adagolási forma, ahol az oxikodon só oxikodon-hidroklorid.

6. Az előző igénypontok bármelyike szerinti szabályozott hatóanyag-leadású orális adagolási forma, amely biztosítja az oxikodon in vitro felszabadulását, az USP Paddle módszerrel 900 ml vizes pufferben 100 fordulat/perc és pH 2 értéken mérve 2 óra után 1 és 20 tömeg% közötti, 4 óra után 10 és 35 tömeg% közötti és/vagy 8 óra után 40 és 70 tömeg% közötti mértékben.

7. Az előző igénypontok bármelyike szerinti szabályozott hatóanyag-leadású orális adagolási forma, amelyre jellemző, hogy a 37°C mellett 20 tömeg% etanolt tartalmazó oldatban mért in vitro felszabadulási sebesség és a 37°C mellett etanol mentes vizes oldatban mért in vitro felszabadulási sebesség eltérése nem több mint 20%, ha a mérést az USP Paddle módszerrel 900 ml vizes pufferben 100 fordulat/perc értéken végezzük.

8. Az előző igénypontok bármelyike szerinti szabályozott hatóanyag-leadású orális adagolási forma, ahol az adagolási forma 10 mg, 20 mg, 40 mg vagy 8 mg oxikodon-hidrokloridot tartalmaz.