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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 2010 (29.12.2010)

PCT

(10) International Publication Number
WO 2010/149169 A2

(51) International Patent Classification:
A61K 9/20 (2006.01)

(21) International Application Number:
PCT/DK2010/050159

(22) International Filing Date:
23 June 2010 (23.06.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

PA 2009 00782	24 June 2009 (24.06.2009)	DK
61/219,817	24 June 2009 (24.06.2009)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

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

WO 2010/149169 A2

(54) **Title**: CONTROLLED RELEASE FORMULATIONS

(57) **Abstract**: The present invention relates to the field of controlled release formulations, and in particular to formulations useful for once daily administration. More particular, the present invention relates to compositions, which are formulated for continued administration to an individual in need thereof within the range of 20 to 28 hours interval between individual administrations.

Controlled release formulations

All patent and non-patent references cited in the application are hereby incorporated by reference in their entirety.

Field of invention

The present invention relates to the field of controlled release formulations, and in particular to formulations useful for once daily administration.

Background of invention

Many active drug substances must be administered relatively frequently in order to be functional over a longer time period. Therefore controlled release formulations allowing less frequent administration, but still having clinical efficacy over the entire time interval between administrations, are desirable.

This is for example the case for analgesics for treating pain. The pain relieving effect should be effective for the entire interval between individual administrations of the analgesic.

The present invention provides a method for preparing controlled release formulations, which may be adjusted to a specific administration scheme.

WO2003/024430 describes Morphine polymer release systems with varying geometry. The document desribes that the polymer release systems may be adapted for oral administration 1-6 times daily. However, the document is silent in regard of which geometry of the systems is useful for which administration frequency.

WO2004/084868 describes a number of morphine controlled release systems with varying geometry. The document describes that the controlled release systems may be adapted for administration 1 to 6 times a day. Similar to WO2003/024430, the

document is silent in regard of which geometry of the systems is useful for which administration frequency.

WO2008/086804 describes a number of different polyglycol-based pharmaceutical compositions. The examples disclose in vitro dissolutions tests of pharmaceutical compositions of varying length. No correlation between length of the pharmaceutical compositions and dissolution time can be established based on the presented data.

Summary of invention

There is thus a need for controlled release formulations, which are suitable for continued administration with in the range of 20 to 28 hours interval between administrations and which remain clinically effective throughout the interval between administrations.

Interestingly, the present invention discloses that the geometry of certain controlled release formulations is important for the obtained release profile and that in particular pharmaceutical compositions of a certain length are useful for continued administration with in the range of 20 to 28 hours interval between administrations. The invention also discloses that shorter pharmaceutical compositions are useful for continued administration with a shorter interval between administrations.

Thus, one aspect of the present invention is to provide pharmaceutical compositions comprising

a) a matrix composition comprising
   i) an active drug substance which may be any of the active drug substances described herein below in the section "Active drug substance"; and
   ii) at least one polyglycol, which may be any of the polyglycols described herein below in the section "Polyglycol"

said matrix composition having a cylindrical shape optionally with tapered end(s) (said cylindrical shape may be any of the shapes described herein below in the section

"Geometry"), the length of said matrix being in the range of 8 to 10 mm, said matrix being surrounded by

b) a coating having one or two openings exposing at least one surface of said matrix, said coating being substantially impermeable to an aqueous medium, wherein the coating may be any of the coatings described herein below in the section "Coating";

and wherein said composition is formulated for continued administration to an individual in need thereof with in the range of 20 to 28 hours (preferably 24 hours) interval between individual administrations.

The term "substantially impermeable" as used herein is meant that the coating is impermeable to aqueous medium for at least 24 hours, more preferred for at least 48 hours.

Said continued administration may be any of the administration methods described herein below in the section "Administration" and said individual in need thereof may be any of the individuals described herein below in the section "Individual in need of treatment".

In addition, these pharmaceutical compositions have any of the pharmacological profiles described herein below in the section "Pharmacological profile".

In addition the present invention relates to use of above mentioned pharmaceutical composition for preparation of a medicament for treatment of a clinical condition (such as pain) in an individual in need thereof.

Description of Drawings

Figure 1 shows the mean hydrocodone plasma concentration (pmol/L) versus time (h) curve after single dose administration by dose group (0-42h). More particular, the figure shows:
Treatment A: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 6.0 mm.
Treatment B: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 7.5 mm.

Treatment C: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 9.0 mm.
Treatment D: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation B, 9.0 mm.
Treatment E (Reference): 1 x NORCO® 10/325 IR tablet (containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen).

Figure 2 shows the mean hydromorphone plasma concentration (pmol/L) versus time (h) curve after single dose administration by dose group (0-42h). More particular, the figure shows:
Treatment A: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 6.0 mm.
Treatment B: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 7.5 mm.
Treatment C: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 9.0 mm.
Treatment D: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation B, 9.0 mm.
Treatment E (Reference): 1 x NORCO® 10/325 IR tablet (containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen).

Figure 3 shows the mean norhydrocodone plasma concentration (pmol/L) versus time (h) curve after single dose administration by dose group (0-42h). More particular, the figure shows:
Treatment A: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 6.0 mm.
Treatment B: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 7.5 mm.
Treatment C: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 9.0 mm.
Treatment D: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation B, 9.0 mm.
Treatment E (Reference): 1 x NORCO® 10/325 IR tablet (containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen).

Figure 4 shows an estimated steady state hydrocodone curve, plasma concentration (pmol/L) versus time (h). More particular, the figure shows:
Treatment A: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 6.0 mm.
Treatment B: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 7.5 mm.
Treatment C: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 9.0 mm.
Treatment D: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation B, 9.0 mm.
Treatment E (Reference): 1 x NORCO® 10/325 IR tablet (containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen).

Figure 5 shows the mean oxycodone plasma concentration (ng/mL) versus time (h) curve after single dose administration by dose group (0-48h). More particular, the figure shows:
Treatment A (test 1, 6.0 mm): 1 x 40 mg Egalet® oxycodone, 6.0 mm
Treatment B (test 2, 7.5 mm): 1 x 40 mg Egalet® oxycodone, 7.5 mm
Treatment C (test 3, 9.0 mm): 1 x 40 mg Egalet® oxycodone, 9.0 mm
Treatment D (reference): 1 x 40 mg OxyContin® (containing oxycodone)

Figure 6 shows the mean oxymorphone plasma concentration (ng/mL) versus time (h) curve after single dose administration by dose group (0-48h). More particular, the figure shows:
Treatment A (test 1, 6.0 mm): 1 x 40 mg Egalet® oxycodone, 6.0 mm
Treatment B (test 2, 7.5 mm): 1 x 40 mg Egalet® oxycodone, 7.5 mm
Treatment C (test 3, 9.0 mm): 1 x 40 mg Egalet® oxycodone, 9.0 mm
Treatment D (reference): 1 x 40 mg OxyContin® (containing oxycodone)

Figure 7 shows the mean noroxycodone plasma concentration (ng/mL) versus time (h) curve after single dose administration by dose group (0-48h). More particular, the figure shows:
Treatment A (test 1, 6.0 mm): 1 x 40 mg Egalet® oxycodone, 6.0 mm
Treatment B (test 2, 7.5 mm): 1 x 40 mg Egalet® oxycodone, 7.5 mm
Treatment C (test 3, 9.0 mm): 1 x 40 mg Egalet® oxycodone, 9.0 mm
Treatment D (reference): 1 x 40 mg OxyContin® (containing oxycodone)

Figure 8 shows an estimated steady state oxycodone curve, plasma concentration (ng/mL) versus time (h). More particular, the figure shows:
Treatment A (test 1, 6.0 mm): 1 x 40 mg Egalet® oxycodone, 6.0 mm
Treatment B (test 2, 7.5 mm): 1 x 40 mg Egalet® oxycodone, 7.5 mm
Treatment C (test 3, 9.0 mm): 1 x 40 mg Egalet® oxycodone, 9.0 mm
Treatment D (reference): 1 x 40 mg OxyContin® (containing oxycodone)

Figure 9 shows the relationship between release times (% drug release versus time (minutes)) in vitro for a pharmaceutical composition according to the present invention containing oxycodone 40 mg versus tablet length 6.0, 7.5 and 9.0 mm.

Figure 10 shows in vitro dissolution results (drug release (%) versus time (minutes)) of pharmaceutical composition A (30 mg morphine), B1 (30, 60, 100 and 200 mg morphine) and B2 (100 mg morphine) according to the present invention.

Figure 11 shows examples of geometries of pharmaceutical compositions according to the present invention. The active drug substance is dispersed in a matrix partly covered by a coating, preferably a non-impermeable coating. I: 3-D view of round tablet and a tablet with one tapered end. II: 3-D view of one type of oval tablet and matrix with different shapes. III: 3-D view of second type of oval tablet with round matrix. IV: 3-D view of third type of oval tablet with an oval matrix. Relative sizes of tablets are not shown.

Figure 12 shows the relationship between release times (% drug release versus time (minutes)) in vitro for a pharmaceutical composition according to the present invention containing hydrocodone versus tablet length 6 mm (medium load), 7.5 mm (medium load), 9 mm (medium load) and 9 mm (high load).

Figure 13 shows the mean steady state morphine plasma concentration (nmol/l) versus time curve (0-24h) for 30 mg Egalet® morphine tablet of Formulation A.

Figure 14 shows the mean morphine plasma concentration (nmol/l) versus time curve by dose group (0-48h). More particular, the figure shows:

Treatment A: 1 x 30 mg Egalet® Morphine controlled-release dosage unit of Formulation B (length 7.5 mm),

Treatment B: 1 x 60 mg Egalet® Morphine controlled-release dosage unit of Formulation B (length 7.5 mm),

Treatment C: 1 x 100 mg Egalet® Morphine controlled-release dosage unit of Formulation B (length 7.5 mm),

Treatment D: 1 x 200 mg Egalet® Morphine controlled-release dosage unit of Formulation B (length 7.5 mm),

Treatment E: 2 x 30 mg Egalet® Morphine controlled-release dosage units of Formulation A (length 9 mm).

Detailed description of the invention

Definitions

The term “cylindrical shape” as used herein refers to any geometrical shape having the same cross section area throughout the length of the geometrical shape. The cross section of a cylinder within the meaning of the present invention may have any two dimensional shape, for example the cross section may be circular, oval, rectangular, triangular, angular or star shaped. The pharmaceutical compositions according to the invention preferably have a cylindrical shape, wherein the end(s) may be tapered.

The term “Cross section of the matrix” is used to describe the cross section of the matrix in the cylindrical part of the matrix. Thus, in embodiments of the invention, wherein the ends of the matrix are tapered, the term “cross section of the matrix” does not refer to the cross section of the tapered ends.

The term “cross section area” refers to the area of the cross section. Depending on the position and shape of the openings of the coating a specific area of the matrix is exposed to the surroundings. In a preferred embodiment of the invention at least one opening, preferably two openings of the coating are essentially the same size and shape as the cross section area (optionally 2x the cross section area if there are two such openings), preferably at least one opening, preferably two openings of the coating are the same size and shape as the cross section area (optionally 2x the cross section area if there are two such openings).

The term “mean residence time” or MRT describes the average time for all the drug molecules to reside in the body. MRT may be considered also as the mean transit time or mean sojourn time.

MRT is calculated as $AUMC_{0\text{-}inf}/AUC_{0\text{-}inf}$ where $AUMC_{0\text{-}inf}$ is the area under the first moment curve from time zero to infinity. $AUMC_{0\text{-}inf} = AUMC_{0\text{-}t} + t * C_t/K_{el} + C_t/(K_{el})$.

The term “steady state” refers to the state when the plasma concentration level following one dosing is the same within the standard deviation as the plasma concentration level following the following dosing. Thus, for pharmaceutical

compositions for once daily administration then at steady state $AUC_{(0\text{-}24h)d}=AUC_{(0\text{-}24h)d+1}$ +/- the standard deviation, and $C_{max(0\text{-}24h)d}=C_{max(0\text{-}24h)d+1}$ +/- the standard deviation where d is day.

The term "Trough" is defined as the average plasma concentration in a steady state individual just prior to the following dose. Thus, for pharmaceutical compositions prepared for continued administration with in the range of 20 to 28 hours (for example 24 hours) interval between individual administrations then trough is the average plasma concentration in a steady state individual 20 to 28 hours (for example 24 hours) after dosing and just prior to the following dose. A steady state simulation may be calculated based on measurement of active drug substance or metabolites in serum after a single dose administration and based on such a simulation a theoretical trough may be determined. Trough is preferably determined as an average of trough in at least 5 different individuals.

The term "C_{min}" is defined by the average lowest plasma concentration observed over a dosing interval. Thus, for pharmaceutical compositions prepared for continued administration with in the range of 20 to 28 hours interval between individual administrations, then C_{min} is defined by the average lowest plasma concentration observed over a 20 to 28 hour dosing-interval. C_{min} is preferably determined as an average of C_{min} in at least 5 different individuals.

The term "steady state C_{24}" is defined as the average plasma concentration of an active drug substance in a steady state individual observed 24 hours after last administration of said active drug substance. A steady state simulation may be calculated based on measurement of active drug substance or metabolites in serum after a single dose administration and based on such a simulation a theoretical C_{24} may be determined. "Steady state C_{24}" is preferably determined as an average of "steady state C_{24}" in at least 5 different individuals.The term "steady state C_{max}" is the average highest plasma concentration at steady state observed over the dosing interval. Thus, for pharmaceutical compositions for continued administration with in the range of 20 to 28 hours interval (for example a 24 hours interval) between individual administrations C_{max} is defined by the highest plasma concentration at steady state observed over a 20 to 28 hours interval (for example a 24 hour dosing-interval). C_{max} may also be referred to as "peak". A steady state simulation may be calculated based on measurement of

active drug substance or metabolites in serum after a single dose administration and based on such a simulation a theoretical steady state C_{max} may be determined. "Steady state C_{max}" is preferably determined as an average of "steady state C_{max}" in at least 5 different individuals.

The term "steady state individual" refers to an individual to whom the pharmaceutical compositions according to the present invention have been administered for a sufficient number of times in order to have arrived at steady state. Thus, for pharmaceutical compositions prepared for administration once daily, then a steady state individual is an individual to whom the pharmaceutical compositions according to the present invention has been administered once daily for a sufficient number of days in order to have arrived at steady state. Steady state is reached when the plasma concentration level after one dosing is the same within the standard deviation as the plasma concentration level after the following dosing, meaning for once daily dosing that $AUC_{(0-24h)d}=AUC_{(0-24h)d+1}$, and $C_{max(0-24h)d}=C_{max(0-24h)d+1}$ where d is day. Preferably, a steady state individual, is an individual to whom the pharmaceutical compositions according to the present invention has been administered once daily for at least 3 days, preferably for at least 4 days, for example for at least 7 days.

The term "T_{max}" refers to the average time lapsing between administration of a pharmaceutical composition and arrival at C_{max}. T_{max} is preferably determined as an average of T_{max} in at least 5 different individuals.

AUC_{0-xh} is defined by the average area under the curve of a plasma concentration profile of an active drug substance from 0-xh after administration of said active drug substance. Thus, AUC_{0-12h} is the average area under the curve of a plasma concentration profile of an active drug substance from 0-12h after administration of said active drug substance. AUC_{0-24h} is the average area under the curve of a plasma concentration profile of an active drug substance from 0-24h after administration of said active drug substance. AUC_{0-48h} is the average area under the curve of a plasma concentration profile of an active drug substance from 0-48h after administration of said active drug substance. AUC_{0-xh} is obtained from sum of steady state AUCs (I.e. $\Sigma(AUC_{0-1h}, AUC_{1-2h}\ldots\ldots AUC_{t-x})$) between measurements from each sample point. The AUCs are calculated by the linear trapezoidal method. If the last blood sample is taken less than xh, e.g. less than 24h after drug administration, the xh value, such as the 24h

value will be extrapolated using the terminal elimination rate constant as described below. Single missing values will remain missing, i.e. corresponding to interpolation between the neighbouring points when calculating AUC. Similarly AUCx-y indicates the area under the curve of a plasma concentration profile of an active drug substance from x to y after administration of said active drug substance calculated in a similar manner.

The term “Protraction index” as used herein illustrates the flatness of the steady state plasma concentration profile and is defined as the average concentration in the 24 hour dosing interval divided by the maximum concentration, i.e. (($AUC_{0\text{-}24h}$ / 24 h) / C_{max}). In the theoretical case where the profile is completely flat the average concentration will be identical to the maximum concentration and the Protraction index will be equal to 1. Hence, due to the fact that the average concentration cannot take a value higher than the maximum concentration, the Protraction index can never be higher than 1. In cases where the profile is substantially flat, the difference between the maximum concentration and the average concentration is small and the Protraction index will take a value close to 1. In other cases where the maximum concentration for instance is 5 times higher than the average concentration the Protraction index wil take the value 0.2.

Polyglycol

The pharmaceutical compositions according to the invention comprise a matrix composition comprising at least one polyglycol.

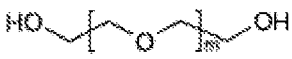
The matrix composition may comprise more than one different kind of polyglycol, such as 2, for example 3, such as 4, for example 5, such as more than 5 different polyglycols. Preferably, the matrix composition comprises in the range of 1 to 4, even more preferably in the range of 1 to 3, yet more preferably 2 different polyglycols.

The polyglycol may e.g. be in the form of a homopolymer and/or a copolymer. If the matrix composition comprises more than one polyglycol they may all be different homopolymer, or different copolymers or a mixture of homopolymers and copolymers. In one preferred embodiment of the invention, the matrix composition comprises at

least one polyglycol, which is a homopolymer and at least one polyglycol, which is a copolymer. In another preferred embodiment of the invention, the matrix composition comprises at least one polyglycol, which is a homopolymer.

In a preferred embodiment the polyglycols are substantially water soluble, thermoplastic, crystalline, semi-crystalline or amorphous or a mixture of substantially water soluble, crystalline, semi-crystalline or amorphous polymers. In particular it is preferred that the polyglycol is at least thermoplastic. Suitable polyglycols for use in a matrix composition according to the invention are polyethylene glycols, as well as derivatives of polyethylene glycol such as mono or dimethoxypolyethylene glycols (mPEGs), polyethylene oxides and/or block copolymers of ethylene oxide and propylene oxide.

Polyethylene glycols (PEGs) are linear polydisperse polymers composed of repeating units of ethylene glycol. Their chemical formula is $HOCH_2[CH_2OCH_2]_mCH_2OH$ where *m* represents the average number of repeating units. Alternatively, the general formula $H[OCH_2CH_2]_nOH$ may be used to represent polyethylene glycol, where *n* is as number *m* in the previous formula + *1*. See the structural presentations of polyethylene glycol below, *n* is the average number of oxyethylene groups, *n* equals *m* + *1*.



In a preferred embodiment, the matrix composition comprises at least one polyglycol which is a polyethylene oxide.

Polyethylene oxides (PEOs) are linear polydisperse nonionic polymers composed of repeating units of ethylene oxide. Their chemical formula is $HO[CH_2CH_2O]_nH$ where *n* represents the average number of oxyethylene groups. See the structural presentation of polyethylene oxide below, *n* is the average number of oxyethylene groups. Depending on preparation method high molecular weigh PEO may have one terminal methyl group.

In general PEG refers to polymer chains with molecular weights below 20,000, while PEO refers to higher molecular weights polymers. However, because of the similarities between PEO and PEG, the terms are often used interchangeably for the same compound.

Polyethylene glycols and/or polyethylene oxides, which are suitable for use in the matrix composition are those having an average molecular weight of at least 20,000 daltons, such as an average molecular weight of in the range of 20,000 to 700,000 daltons, for example in the range of 20,000 to 600,000 daltons, such as in the range of 35,000 to 500,000 daltons, for example in the range of 35,000 to 400,000 daltons, such as in the range of 35,000 to 350,000 daltons, for example in the range of 50,000 to 350,000 daltons, such as in the range of 100.000 to 300.000 daltons, for example in the range of 150.000 to 350.000, such as in the range of 200.000 to 300.000, such as approximately 35,000 daltons, for example approximately 50,000 daltons, such as approximately 75,000 daltons, for example approximately 100,000 daltons, such as approximately 150,000 daltons, for example approximately 200,000 daltons, such as approximately 250,000 daltons, for example approximately 300,000 daltons, such as approximately 400,000 daltons, such as 150,000 daltons, for example 200,000 daltons, such as 250,000 daltons, for example 300,000 daltons, such as 400,000 daltons. In the present context “approximately” preferably means +/- 30%.

In one embodiment of the invention the matrix comprises only one polyethylene oxide, preferably a PEO with an average molecular weight of in the range of 50,000 to 500,000 daltons, for example in the range of 100,000 to 400,000 daltons, such as in the range of 200,000 to 300,000 daltons, preferably in the range of 150.000 to 250.000, for example approximately 200,000, such as 200.000. This is in particular the case for pharmaceutical compositions according to the invention, wherein the matrix has a length of in the range of 7.5 to 15 mm, preferably a length of in the range of 8 to 15 mm, such as a length in the range of 8 to 11 mm, wherein said pharmaceutical composition is formulated for continued administration with in the range of 20 to 28 hours interval between individual administrations.

In another embodiment of the invention the matrix comprises only one polyethylene oxide, preferably a PEO with an average molecular weight of in the range of 100,000 to 500,000 daltons, for example in the range of 200,000 to 400,000 daltons, such as in

the range of 250,000 to 350,000 daltons, for example approximately 300,000, such as 300.000. This is in particular the case for pharmaceutical compositions according to the invention, wherein the matrix has a length of in the range of 7.5 to 15 mm, preferably a length of in the range of 7.5 to 10 mm, such as a length in the range of 7.5 to 8 mm, wherein said pharmaceutical composition is formulated for continued administration with in the range of 20 to 28 hours interval between individual administrations.

In a specific embodiment at least one polyglycol is a polyethylene oxide or a polyethylene glycol that has a molecular weight of approximately 20,000 daltons, approximately 35,000 daltons, approximately 50,000 daltons, approximately 100,000 daltons, approximately 200,000 daltons, approximately 300,000 daltons and approximately 400,000 daltons. In the present context “approximately” preferably means +/- 30%. PEG is commercially available with average molecular weights up to 35 000. PEO is commercially available with average molecular weights up to 8,000,000. In specific embodiment, the polymer is a PEO having an average molecular weight of at least 100,000, such as in the range of 100,000 to 8,000,000, for example in the range of 100,000 to 7,000,000, such as in the range of 100,000 to 5,000,000, for example in the range of 100,000 to 4,000,000, such as in the range of 100,000 to 2,000,000, for example in the range of 100,000 to 1,000,000, such as in the range of 100,000 to 900,000. When PEO is employed with a molecular weight in the lower end, the PEO typically has a molecular weight as mentioned in the preceding paragraph. Commercially available PEOs with a molecular weight in the higher end have typically the following molecular weights: approximately 900,000, approximately 1,000,000, approximately 2,000,000, approximately 4,000,000, approximately 5,000,000, approximately 7,000,000, approximately 8,000,000.

The matrix composition according to the invention may also comprise at least one polyglycol which is a copolymer.

In preferred embodiments of the invention the matrix composition comprise at least one polyglycol which is a poloxamer. Poloxamers are copolymers or block copolymers and are a range of non-ionic surfactants of polyethylene glycol (PEG) and polypropylene glycol (PPG).

The poloxamer may be Diol EO/PO block copolymers, which for example in chemical

abstracts are described under the scientific name -hydroxy-hydroxypoly(oxyethylene)poly(oxypropylene)-poly(oxyethylene)-block copolymer in combination with the CAS register number. In specific embodiments a suitable poloxamer for use in a composition of the invention has a HLB value of at least about 18 such as, e.g., at least approximately 20, preferably at least 24. The average molecular weight of a suitable poloxamer is typically at least about 2,000.

Typical block copolymers of ethylene oxide and propylene oxide to be comprised in the matrix composition according to the invention have a molecular weight of at least 2,000 daltons, typically in the range of 3,000 to 30,000 daltons, such as in the range of 4,000 to 15,000 daltons.

Preferred poloxamers have the formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$, and preferably a is an integer from 10 to 150, such as from 30 to 140, for example from 50 to 100, such as from 65 to 90, for example from 70 to 90 and preferably b is an integer from 10 to 80, such as from 15 to 80, for example from 20 to 60, such as from 25 to 55.

In one preferred embodiment the matrix comprises one or more copolymers, preferably one or more copolymers selected from the group consisting of poloxamers, such as poloxamer 188 and/or poloxamer 407. This is in particular the case for pharmaceutical compositions according to the invention, wherein the matrix has a length of in the range of 7.5 to 15 mm, preferably a length of in the range of 8 to 10 mm, wherein said pharmaceutical composition is formulated for continued administration with in the range of 20 to 28 hours interval between individual administrations.

In a specific embodiment of the invention the matrix comprises at least two different copolymers selected from the group consisting of poloxamers, such as poloxamer 188 and poloxamer 407. This is in particular the case for pharmaceutical compositions according to the invention, wherein the matrix has a length of in the range of 8 to 15 mm, preferably a length of in the range of 8 to 10 mm, wherein said pharmaceutical composition is formulated for continued administration with in the range of 20 to 28 hours interval between individual administrations.

In another specific embodiment of the invention the matrix comprises one one kind of poloxamer preferably poloxamer 188. This is in particular the case for pharmaceutical

compositions according to the invention, wherein the matrix has a length of in the range of 7.5 to 15 mm, preferably a length of in the range of 7.5 to 10 mm, wherein said pharmaceutical composition is formulated for continued administration with in the range of 20 to 28 hours interval between individual administrations.

The matrix composition may comprise mixtures of PEO with different average molecular weights for example in order to obtain a PEO with a desirable average molecular weght. The same applies to PEG.

Thus, in a specifically preferred embodiment of the invention, the matrix comprises two different PEO with different average molecular weights, preferably one with an average molecular weight in the range of 150,000 to 250,000, preferably approximately 200,000, such as 200,000 and another with an average molecular weight in the range of 250,000 to 350,000, preferably approximately 300,000, such as 300,000. and another with an average molecular weight in the range of 200,000 to 300,000, preferably approximately 200,000 and 300,000, such as 200,000 and 300,000. This is in particular the case for pharmaceutical compositions according to the invention, wherein the matrix has a length of in the range of 7.5 to 15 mm, preferably a length of in the range of 8 to 10 mm, wherein said pharmacetuci composition is formulated for continued administration with in the range of 20 to 28 hours interval between individual administrations.

It should be noted that in this context Vitamin E polyethylene glycol succinate (TPGS) is not considered a polyglycol.

The polyglycol should preferably have a melting point higher than the body temperature of the human in which the composition is to be used. Thus, the polyglycol(s) employed in the matrix composition will suitably have a melting point of in the range of 38-120°C such as in the range of 38 to 100°C, for example in the range of 40 to 80°C.

In a very preferred embodiment of the invention the matrix composition comprises at least one polyethylene oxide and at least one copolymer.

In addition to a polymer of a polyglycol type, the matrix composition may comprise an additional polymer, for example at least one polymer selected from the group

consisting of: modified or unmodified water soluble natural polymers such as glucomannan, galactan, glucan, polygalacturonic acid, polyxylane, polygalactomannans, rhanogalacturonan, polyxyloglycan, arabinogalactan, and starch, cellulose, chitosan, alginate, fibrin, collagen, gelatin, hyaluronic acid, amylopectin, pectin including low methylated or methoxylated pectins, dextran and fatty acids and alcohols; synthetic polymers such as polyvinylpyrrolidone (PVP), PVA, PVB, Eudragit L methyl ester, Eudragit L, Eudragit RL, Eudragit RS, Eudragit E, Eudragit S, PHPV, PHA, PCL, PLGA and PLA; and hydrogels made from the polymers or combined polymers mentioned above and or from polymers originated from: HEMA, HEEMA, MEMA, MEEMA, EDGMA, NVP, VAc, AA, acrylamide, MAA, HPMA, PEGA, PEGMA, PEGDMA, PEGDA, and PEGDMA.

One or more polymers are typically present in a matrix composition of the invention in a concentration amount of from 5 to 99.9% w/w, such as from 5 to 95% w/w, such as from 5 to 80% w/w, such as from 10 to 80% w/w, such as from 20 to 80% w/w, for example from 30 to 80% w/w, such as from 40 to 80% w/w, for example from 45 to 75% w/w.

The total concentration of the polyglycols (notably the sum of homo- and copolymers of the polyglycol type) in the matrix composition is preferably from 5 to 99% w/w such as from 15 to 95% w/w, for example from 30 to 90% w/w, such as from 30 to 85% w/w, for example from 30 to 80% w/w, such as from 40 to 80% w/w, for example from 45 to 75% w/w, such as from 40 to 50% w/w, for example from 45 to 50% w/w, such as from 60 to 85% w/w, for example from 60 to 80% w/w, for example from 70 to 75% w/w, such as from 71 to 75% w/w.

The concentration of the polyglycol homopolymer in the matrix composition is preferably from 5 to 80% w/w and in those cases where the homopolymer is the only thermoplastic polymer present in the matrix composition, then the concentration is preferably from 20 to 80 w/w, such as from 40 to about 80% w/w, such as for example from 70 to 80% w/w, such as from 70 to 75% w/w, for example from about 71 to about 75% w/w.

In preferred embodiments of the invention, then the concentration of the homopolymers in the matrix composition is in the range of 5 to 90% w/w, such as in the range of 20 to

85% w/w, for example in the range of 20 to 75% w/w, such as in the range of 20 to 70% w/w for example in the range of 20 to 40% w/w, such as in the range of 30 to 85% w/w, for example in the range of about 30 to 75% w/w, such as in the range of 30 to 60% w/w, for example in the range of 30 to 40% w/w, such as in the range of 30 to 35% w/w, such as in the range of 31 to about 33% w/w, such as in the range of 50 to 85% w/w, from 60 to 80% w/w, for example in the range of 70 to 80% w/w, for example in the range of 70 to 75% w/w, such as in the range of 71 to about 73% w/w.

The concentration of the polyglycol copolymer in the matrix composition, if present in combination with a polyglycol homopolymer, is preferably in the range of 0 to 60% w/w, such as for example 0 to 30% w/w. If the copolymer is the sole thermoplastic polymer in the matrix composition the concentration may be from about 5 to about 99.5% w/w such as those ranges described above and described for the homopolymer.

In preferred embodiments, the concentration of polyglycols which are co-polymers in the matrix composition is in the range of 0 to 30% w/w, such as in the range of 1 to 20 % w/w, for example in the range of 2 to 10% w/w, such as in the range of 2 to 5% w/w, such as in the range of 5 to 30% w/w, for example in the range of 5 to 20% w/w, for example in the range of 5 to 15% w/w, such as less than 15% w/w, for example less than 10% w/w, such as less than 5% w/w, such as less than 1% w/w, for example 0% w/w.

Active drug substance

An active drug substance in a composition for use according to the invention is a therapeutically, prophylactically and/or diagnostically active drug substance (herein also abbreviated "active drug substance").

Examples of specific active drug substances suitable for use in a composition of the invention are:

Antiinflammatory and antirheumatic active substances,for example such as; Butylpyrazolidines, Phenylbutazone, Mofebutazone, Oxyphenbutazone, Clofezone, Kebuzone, Acetic acid derivatives and related substances, Indometacin, Sulindac,

Tolmetin, Zomepirac, Diclofenac, Alclofenac, Bumadizone, Etodolac, Lonazolac, Fentiazac, Acemetacin, Difenpiramide, Oxametacin, Proglumetacin, Ketorolac, Aceclofenac, Bufexamac, Oxicams, Piroxicam, Tenoxicam, Droxicam, Lornoxicam, Meloxicam, Methotrexate, Propionic acid derivatives, Ibuprofen, Naproxen, Ketoprofen, Fenoprofen, Fenbufen, Benoxaprofen, Suprofen, Pirprofen, Flurbiprofen, Indoprofen, Tiaprofenic acid, Oxaprozin, Ibuproxam, Dexibuprofen, Flunoxaprofen, Alminoprofen, Dexketoprofen, Fenamates, Mefenamic acid, Tolfenamic acid, Flufenamic acid, Meclofenamic acid, Coxibs, Celecoxib, Rofecoxib, Valdecoxib, Parecoxib, Etoricoxib, Lumiracoxib, Nabumetone, Niflumic acid, Azapropazone, Glucosamine, Benzydamine, Glucosaminoglycan polysulfate, Proquazone, Orgotein, Nimesulide, Feprazone, Diacerein, Morniflumate, Tenidap, Oxaceprol, Chondroitin sulfate, Feprazone, Dipyrocetyl, Acetylsalicylic acid, Quinolines, Oxycinchophen, Gold preparations, Sodium aurothiomalate, Sodium aurotiosulfate, Auranofin, Aurothioglucose, Aurotioprol, Penicillamine and Bucillamine.

Analgesics for example such as; Opioids, Natural opium alkaloids, Morphine, Opium, Hydromorphone, Nicomorphine, Oxycodone, Dihydrocodeine, Diamorphine, Papaveretum, Codeine, Phenylpiperidine derivatives, Ketobemidone, Pethidine, Fentanyl, Diphenylpropylamine derivatives, Dextromoramide, Piritramide, Dextropropoxyphene, Bezitramide, Methadone, Benzomorphan derivatives, Pentazocine, Phenazocine, Oripavine derivatives, Buprenorphine, Morphinan derivatives, Butorphanol, Nalbuphine, Tilidine, Tramadol, Dezocine, Salicylic acid and derivatives, Acetylsalicylic acid, Aloxiprin, Choline salicylate, Sodium salicylate, Salicylamide, Salsalate, Ethenzamide, Morpholine salicylate, Dipyrocetyl, Benorilate, Diflunisal, Potassium salicylate, Guacetisal, Carbasalate calcium, Imidazole salicylate, Pyrazolones, Phenazone, Metamizole sodium, Aminophenazone, Propyphenazone, Nifenazone, Anilides, Paracetamol, Phenacetin, Bucetin, Propacetamol, Other analgesics and antipyretics, Rimazolium, Glafenine, Floctafenine, Viminol, Nefopam, Flupirtine, Ziconotide.

Anesthetics for example such as; Ethers, Diethyl ether, Vinyl ether, Halogenated hydrocarbons, Halothane, Chloroform, Methoxyflurane, Enflurane, Trichloroethylene, Isoflurane, Desflurane, Sevoflurane, Barbiturates, Methohexital, Hexobarbital, Thiopental, Narcobarbital, Opioid anesthetics, Fentanyl, Alfentanil, Sufentanil, Phenoperidine, Anileridine, Remifentanil, Other general anesthetics, Droperidol,

Ketamine, Propanidid, Alfaxalone, Etomidate, Propofol, Hydroxybutyric acid, Nitrous oxide, Esketamine, Xenon, Esters of aminobenzoic acid, Metabutethamine, Procaine, Tetracaine, Chloroprocaine, Benzocaine, Amides, Bupivacaine, Lidocaine, Mepivacaine, Prilocaine, Butanilicaine, Cinchocaine, Etidocaine, Articaine, Ropivacaine, Levobupivacaine, Esters of benzoic acid, Cocaine, Other local anesthetics, Ethyl chloride, Dyclonine, Phenol, Capsaicin.

Antimigraine active substances for example such as; Ergot alkaloids, Dihydroergotamine, Ergotamine, Methysergide, Lisuride, Corticosteroid derivatives, Flumedroxone, Selective serotonin (5HT1) agonists, Sumatriptan, Naratriptan, Zolmitriptan, Rizatriptan, Almotriptan, Eletriptan, Frovatriptan, Other antimigraine preparations, Pizotifen, Clonidine, Iprazochrome, Dimetotiazine, Oxetorone.

Antiepileptic active substances for example such as; Barbiturates and derivatives, Methylphenobarbital, Phenobarbital, Primidone, Barbexaclone, Metharbital, Hydantoin derivatives, Ethotoin, Phenytoin, Amino(diphenylhydantoin) valeric acid, Mephenytoin, Fosphenytoin, Oxazolidine derivatives, Paramethadione, Trimethadione, Ethadione, Succinimide derivatives, Ethosuximide, Phensuximide, Mesuximide, Benzodiazepine derivatives, Clonazepam, Carboxamide derivatives, Carbamazepine, Oxcarbazepine, Rufinamide, Fatty acid derivatives, Valproic acid, Valpromide, Aminobutyric acid, Vigabatrin, Progabide, Tiagabine, Other antiepileptics, Sultiame, Phenacemide, Lamotrigine, Felbamate, Topiramate, Gabapentin, Pheneturide, Levetiracetam, Zonisamide, Pregabalin, Stiripentol, Lacosamide, Beclamide.

Anticholinergic active substances for example such as; Tertiary amines, Trihexyphenidyl, Biperiden, Metixene, Procyclidine, Profenamine, Dexetimide, Phenglutarimide, Mazaticol, Bornaprine, Tropatepine, Ethers chemically close to antihistamines, Etanautine, Orphenadrine (chloride), Ethers of tropine or tropine derivatives, Benzatropine, Etybenzatropine.

Dopaminergic ative substances for example such as; Dopa and dopa derivatives, Levodopa, Melevodopa, Etilevodopa, Adamantane derivatives, Amantadine, Dopamine agonists, Bromocriptine, Pergolide, Dihydroergocryptine mesylate, Ropinirole, Pramipexole, Cabergoline, Apomorphine, Piribedil, Rotigotine, Monoamine, oxidase B

inhibitors, Selegiline, Rasagiline, Other dopaminergic agents, Tolcapone, Entacapone, Budipine.

Antipsychotic active substances for example such as; Phenothiazines with aliphatic side-chain, Chlorpromazine, Levomepromazine, Promazine, Acepromazine, Triflupromazine, Cyamemazine, Chlorproethazine, Phenothiazines with piperazine structure, Dixyrazine, Fluphenazine, Perphenazine, Prochlorperazine, Thiopropazate, Trifluoperazine, Acetophenazine, Thioproperazine, Butaperazine, Perazine, Phenothiazines with piperidine structure, Periciazine, Thioridazine, Mesoridazine, Pipotiazine, Butyrophenone derivatives, Haloperidol, Trifluperidol, Melperone, Moperone, Pipamperone, Bromperidol, Benperidol, Droperidol, Fluanisone, Indole derivatives, Oxypertine, Molindone, Sertindole, Ziprasidone, Thioxanthene derivatives, Flupentixol, Clopenthixol, Chlorprothixene, Tiotixene, Zuclopenthixol, Diphenylbutylpiperidine derivatives, Fluspirilene, Pimozide, Penfluridol, Diazepines, oxazepines and thiazepines, Loxapine, Clozapine, Olanzapine, Quetiapine, Neuroleptics, in tardive dyskinesia, Tetrabenazine, Benzamides, Sulpiride, Sultopride, Tiapride, Remoxipride, Amisulpride, Veralipride, Levosulpiride, Lithium, Other antipsychotics, Prothipendyl, Risperidone, Clotiapine, Mosapramine, Zotepine, Aripiprazole, Paliperidone.

Anxiolytic active substances for example such as; Benzodiazepine derivatives, Diazepam, Chlordiazepoxide, Medazepam, Oxazepam, Potassium clorazepate, Lorazepam, Adinazolam, Bromazepam, Clobazam, Ketazolam, Prazepam, Alprazolam, Halazepam, Pinazepam, Camazepam, Nordazepam, Fludiazepam, Ethyl loflazepate, Etizolam, Clotiazepam, Cloxazolam, Tofisopam, Diphenylmethane derivatives, Hydroxyzine, Captodiame, Carbamates, Meprobamate, Emylcamate, Mebutamate, Dibenzo-bicyclo-octadiene derivatives, Benzoctamine, Azaspirodecanedione derivatives, Buspirone, Other anxiolytics, Mephenoxalone, Gedocarnil, Etifoxine.

Hypnotic and sedative active substances for example such as; Barbiturates, Pentobarbital, Amobarbital, Butobarbital, Barbital, Aprobarbital, Secobarbital, Talbutal, Vinylbital, Vinbarbital, Cyclobarbital, Heptabarbital, Reposal, Methohexital, Hexobarbital, Thiopental, Etallobarbital, Allobarbital, Proxibarbal, Aldehydes and derivatives, Chloral hydrate, Chloralodol, Acetylglycinamide chloral hydrate, Dichloralphenazone, Paraldehyde, Benzodiazepineemepronium derivatives,

Flurazepam, Nitrazepam, Flunitrazepam, Estazolam, Triazolam, Lormetazepam, Temazepam, Midazolam, Brotizolam, Quazepam, Loprazolam, Doxefazepam, Cinolazepam, Piperidinedione derivatives, Glutethimide, Methyprylon, Pyrithyldione, Benzodiazepine related drugs, Zopiclone, Zolpidem, Zaleplon, Ramelteon, Other hypnotics and sedatives, Methaqualone, Clomethiazole, Bromisoval, Carbromal, Scopolamine, Propiomazine, Triclofos, Ethchlorvynol, Valerian, Hexapropymate, Bromides, Apronal, Valnoctamide, Methylpentynol, Niaprazine, Melatonin, Dexmedetomidine, Dipiperonylaminoethanol.

Antidepressant active substances for example such as; Non-selective monoamine reuptake inhibitors, Desipramine, Imipramine, Imipramine oxide, Clomipramine, Opipramol, Trimipramine, Lofepramine, Dibenzepin, Amitriptyline, Nortriptyline, Protriptyline, Doxepin, Iprindole, Melitracen, Butriptyline, Dosulepin, Amoxapine, Dimetacrine, Amineptine, Maprotiline, Quinupramine, Selective serotonin reuptake inhibitors, Zimeldine, Fluoxetine, Citalopram, Paroxetine, Sertraline, Alaproclate, Fluvoxamine, Etoperidone, Escitalopram, Monoamine oxidase inhibitors, non-selective, Isocarboxazid, Nialamide, Phenelzine, Tranylcypromine, Iproniazide, Iproclozide, Monoamine oxidase A inhibitors, Moclobemide, Toloxatone, Other antidepressants, Oxitriptan, Tryptophan, Mianserin, Nomifensine, Trazodone, Nefazodone, Minaprine, Bifemelane, Viloxazine, Oxaflozane, Mirtazapine, Medifoxamine, Tianeptine, Pivagabine, Venlafaxine, Milnacipran, Reboxetine, Gepirone, Duloxetine, Agomelatine, Desvenlafaxine, Centrally acting sympathomimetics, Amfetamine, Dexamfetamine, Lisdexamfetamine, Metamfetamine, Methylphenidate, Dexmethylphenidate,Pemoline, Fencamfamin, Modafinil, Fenozolone, Atomoxetine, Fenetylline, Xanthine derivatives, Caffeine, Propentofylline, Other psychostimulants and nootropics, Meclofenoxate, Pyritinol, Piracetam, Deanol, Fipexide, Citicoline, Oxiracetam, Pirisudanol, Linopirdine, Nizofenone, Aniracetam, Acetylcarnitine, Idebenone, Prolintane, Pipradrol, Pramiracetam, Adrafinil, Vinpocetine.

Anti-dementia active subtances for example such as; Anticholinesterases, Tacrine, Donepezil, Rivastigmine, Galantamine, Other anti-dementia drugs, Memantine, Ginkgo biloba.

Other nervous system active substances for example such as; Parasympathomimetics, Anticholinesterases, Neostigmine, Pyridostigmine, Distigmine, Ambenonium, Choline

esters, Carbachol, Bethanechol, Other parasympathomimetics, Pilocarpine, Choline alfoscerate.

Active substances used in addictive disorders for example such as; Nicotine, Bupropion, Varenicline, Disulfiram, Calcium carbimide, Acamprosate, Naltrexone, , Buprenorphine, Methadone, Levacetylmethadol, Lofexidine, Betahistine, Cinnarizine, Flunarizine, Acetylleucine, Gangliosides and ganglioside derivatives, Tirilazad, Riluzole, Xaliproden, Hydroxybutyric acid, Amifampridine.

Opium alkaloids and derivatives for example such as, Ethylmorphine, Hydrocodone, Codeine, Opium alkaloids with morphine, Normethadone, Noscapine, Pholcodine, Dextromethorphan, Thebacon, Dimemorfan, Acetyldihydrocodeine, Benzonatate, Benproperine, Clobutinol, Isoaminile, Pentoxyverine, Oxolamine, Oxeladin, Clofedanol, Pipazetate, Bibenzonium bromide, Butamirate, Fedrilate, Zipeprol, Dibunate, Droxypropine, Prenoxdiazine, Dropropizine, Cloperastine, Meprotixol, Piperidione, Tipepidine, Morclofone, Nepinalone, Levodropropizine, Dimethoxanate.

The active drug substance may for example be an active drug substance with abuse potential or safety risk suitable. Such active drug substance may for example be selected from the group consisting of:

1-(1-Phenylcyclohexyl)pyrrolidine, 1-(2-Phenylethyl)-4-phenyl-4-acetoxypiperidine, 1-[1-(2-Thienyl)- cyclohexyljpiperidine, 1-[1-(2-Thienyl)cyclohexyl]pyrrolidine, 1-Methyl-4-phenyl-4-propionoxy-piperidine, 1-Phenylcyclohexylamine, 1-Piperidinocyclohexanecarbonitrile, 2,5-Dimethoxy-4-ethylamphetamine, 2,5-Dimethoxyamphetamine, 2C-B-(4-bromo-2,5-dimethoxypenethylamine), 2C-D (2,5-dimethoxy-4-methylphenethylamine), 2C-I (4-iodo-2,5-dimethoxy-phenethylamine), 2C-T-2 (2,5-dimethoxy-4-ethylthiophenethylamine), 2C-T-4 (2,5-dimethoxy-4-isopropyl thiophenethylamine), 2C-T-7 (2,5-dimethoxy-4-(n)-propylthiopenethylamine), 3,4-Methylene-dioxymethamphetamine, 3,4,5-Trimethoxyamphetamine, 3,4-Methylenedioxyamphetamine, 3,4-Methylenedioxy-N-ethylamphetamine, 3-Methylfentanyl, 3-Methylthiofentanyl, 4-Brorno-2,5-dimethoxyamphetamine, 4-Bromo-2,5-dimethoxyphenethylamine, 4-Methoxyamphetamine, 4-Methyl-2,5-dimethoxyamphetamine, 4-Methylaminorex (cis isomer), 5-MeO-DIPT (5-Methoxy-N,N-diisopropyltryptamine), 5-MeO-DMT (5-Methoxy-N,N-dimethyltryptamine), 5-Methoxy-

3,4-methylenedioxyamphetamine, Acetorphin, Acetorphine, Acetyl-alpha-methylfentanyl, Acetyl-alpha-methylfentanyl, Acetyldihydrocodeine, Acetylmethadol, Acetylmethadol, Alfentanil, Allobarbital, Allylprodin, Allylprodine, Alphacetylmethadol except levo-alphacetylmethadol, Alpha-ethyltryptamine, Alphameprodine, Alphamethadol, Alphamethadol, Alpha-Methylfentanyl, Alpha-Methylthiofentanyl, Alphaprodine, Alprazolam, Amfepramon, Amfetaminil, Amineptin, Aminorex, Amobarbital, Amphetamine, Dextroamphetamine, Amylnitrit (all isomers of the amyl group), Anabolic steroids, Anileridine, Aprobarbital, Barbital, Barbituric acid derivative, BDB (3,4- methylenedioxyphenyl)-2-butanamine), Benzethidin, Benzethidine, Benzoylecgonine, Benzphetamine, Benzphetamine, Benzylmethylketon, Benzylmorphine, Betacetylmethadol, Beta-Hydroxy-3-methylfentanyl, Beta-Hydroxyfentanyl, Betameprodine, Betameprodine, Betamethadol, Betaprodine, Bezitramide, Bezitramide, Boldenone, Brolamfetamin, Bromazepam, Brotizolam, Bufotenine, Buprenorphine, Butabarbital, Butalbital, Butobarbital, Butorphanol, BZP (A 2)(1- benzylpiperazin), Camazepam, Cannabis, Carfentanil, Catha edulis, Cathine, Cathinone, Chloral betaine, Chloral hydrate, Chlordiazepoxide, Chlorhexadol, Chlorotestosterone (same as clostebol), Chlorphentermine, Clobazam, Clonazepam, Clonitazene, Clonitazene, Clorazepate, Clortermine, Clostebol, Clotiazepam, Cloxazolam, Coca Leaves, Cocaine, Codeine, Codeine & isoquinoline alkaloid, Codeine methylbromide, Codeine-N-oxide, Codoxim, Cyclobarbital (Hexemal NFN), Cyprenorphine, Dehydrochlormethyltestosterone, Delorazepam, Desomorphine, Dexamfetamine, Dexfenfluramine, Dexmethylphenidate, Dextromoramide, Dextropropoxyphene, Diacetylmorphine, Diampromide, Diazepam, Dichloralphenazone, Diethylpropion, Diethylthiambutene, Diethyltryptamine, Difenoxin, Dihydrocodeine, Dihydroetorphine, Dihydromorphine, Dihydrotestosterone, Dimenoxadol, Dimepheptanol, Dimethylthiambutene, Dimethyltryptamine, Dioxaphetyl butyrate, Diphenoxylate, Dipipanone, Diprenorphine, Dronabinol, Drostanolone, Drotebanol, Ecgonine, Estazolam, Ethchlorvynol, Ethinamate, Ethyl loflazepate, Ethylestrenol, Ethylmethylthiambutene, Ethylmorphine, Ethylmorphine, Eticyclidin, Etilamfetamine, Etonitazene, Etorphine, Etoxeridine, Etryptamine, Fencamfamin, Fenethylline, Fenetylline, Fenfluramine, Fenproporex, Fentanyl, Fludiazepam, Flunitrazepam, Fluoxymesterone, Flurazepam, Formebolone, Fungi and Spores of the sepcies Psilocype Semilanceata, Furethidine, Gammahydroxybutanic acid, Glutethimide, Halazepam, Haloxazolam, Heroine, Hydrocodone, Hydrocodone & isoquinoline alkaloid, Hydromorphinol, Hydromorphone, Hydroxypethidine, Ibogaine,

Isobutylnitrit, Isomethadone, Ketamine, Ketazolam, Ketobemidone, Levamfetamine, Levo- alphacetylmethadol, Levo-methamphetamine, Levomethorphan, Levomoramide, Levophenacylmorphan, Levorphanol, Lisdexamfetamin, Loprazolam, Lorazepam, Lormetazepam, Lysergic acid, Lysergic acid amide, Lysergic acid diethylamide, Marijuana, Mazindol, MBDN (N-methyl-1-(3,4-methylenedioxyphenyl)-2- butanamine), mCPP (1-(3- chlorphenyl)piperazine), Mebutamate, Mecloqualone, Medazepam, Mefenorex, MeOPP (1-(4-methoxyphenyl)piperazine), Meperidine, Meperidine intermediate, Meprobamate, Mescaline, Mesocarb, Mesterolone, Metamfetamine, Metazocine, Methadone, Methadone intermediate, Methamphetamine, Methandienone, Methandranone, Methandriol, Methandrostenolone, Methaqualone, Methcathinone, Methenolone, Methohexital, Methyldesorphine, Methyldihydromorphine, Methylphenidate, Methylphenobarbital (mephobarbital), Methyltestosterone, Methyprylone, Metopone, Mibolerone, Midazolam, Modafinil, Moramide-intermediate, Morpheridine, Morphine, Morphine methylbromide, Morphine methylsulfonate, Morphine-N-oxide, Myrophine, N,N-Dimethylamphetamine, Nabilone, Nalorphine, Nandrolone, N-Ethyl-1-phenylcyclohexylamine, N-Ethyl-3-piperidyl benzilate, N-Ethylamphetamine, N-Hydroxy-3,4-methylenedioxyamphetamine, Nicocodeine, Nicocodine, Nicodicodine, Nicomorphine, Nimetazepam, Nitrazepam, N-Methyl-3-piperidyl benzilate, Noracymethadol, Norcodeine, Nordiazepam, Norethandrolone, Norlevorphanol, Normethadone, Normorphine, Norpipanone, Norpipanone, Opium, Oxandrolone, Oxazepam, Oxazolam, Oxycodone, Oxymesterone, Oxymetholone, Oxymorphone, Para-Fluorofentanyl, Parahexyl, Paraldehyde, Pemoline, Pentazocine, Pentobarbital, Petrichloral, Peyote, Phenadoxone, Phenampromide, Phenazocine, Phencyclidine, Phendimetrazine, Phenmetrazine, Phenobarbital, Phenomorphan, Phenoperidine, Phentermine, Phenylacetone, Pholcodine, Piminodine, Pinazepam, Pipradrole, Piritramide, PMMA (paramethyxymethyl amphetamine), Prazepam, Proheptazine, Properidine, Propiram, Psilocybine, Psilocyn, Pyrovalerone, Quazepam, Racemethorphane, Racemoramide, Racemorphane, Remifentanil, Salvia divinorum, Salvinorin A, Secobarbital, Secobarbital, Sibutramine, SPA, Stanolone, Stanozolol, Sufentanil, Sulfondiethylmethane, Sulfonethylmethane, Sulfonmethane, Talbutal, Temazepam, Tenamfetamin, Testolactone, Testosterone, Tetrahydrocannabinols, Tetrazepam, TFMPP (1-(3-triflourmethylphenyl)piperazine), Thebacon, Thebaine, Thiamylal, Thiofentanyl, Thiopental, Tiletamine & Zolazepam in Combination, Tilidine, Trenbolone, Triazolam, Trimeperidine, Vinbarbital, Zaleplon, Zipeprol, Zolpidem and Zopiclon.

Other suitable examples of a useful active drug substance include for example such as alfentanil, allylprodine, alphaprodine, aniloridine, benzylmorphine, bezitramide, buprenorphine, butophanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diapromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimephetanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, dextropropoxyphene, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, morphine 6- glucuronide, morphine 3-glucuronide, myrophine, nalbuphine, narccine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxycodeine, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, thebaine, levo- alphacetylmethadol (LAAM), remifentanil, carfentanyl, ohmefentanyl, MPPP, prodine, PEPAP, levomethorphan, etorphine, lefetamine, loperamide, diphenoxylate or pethidine.

Other suitable examples also include Anabolic steroids, cannabis, cocaine and diazepam.

In one embodiment, the active substance is selected from the group consisting of the therapeutic classes including non-steroids anti-inflammatory and antirheumatic active substances.

In preferred embodiments, the active substance is selected from the group consisting of the therapeutic classes including analgesics, opioids, antipyretics, anesthetics, antimigraine agents, antiepileptics, anti-parkinson agents, dopaminergic agents, antipsychotics, anxiolytics, sedatives, antidepressants, psychostimulants agents, dopamine, noradrenaline, nicotinic, alfa-andrenergic, serotonin, H_3 antagonist used for ADHD and nootropics agents used in addictive disorders.

In preferred embodiments, the active substance is selected from the group consisting of the therapeutic classes including anesthetics, centrally-acting analgesics, sedative-

hypnotics, anxiolytics; appetite suppressants, decongestants, antitussives, antihistamines, antiemetics, antidiarrheals, and drugs used to treat narcolepsy and attention deficit hyperactivity disorder.

In preferred embodiments, the active drug substance is associated with abuse syndromes and the active drug substance may thus for example be selected from the group consisting of opioids, CNS depressants, CNS stimulants, cannabinoids, nicotine-like compounds, glutamate antagonists and N-methyl-D-aspartate (NMDA) antagonists.

Preferably, the active drug substance is an analgesic. Examples of preferred analgesics according to the present invention includes for example Opioids, Natural opium alkaloids, Morphine, Opium, Hydromorphone, Nicomorphine, Oxycodone, Dihydrocodeine, Diamorphine, Papaveretum, Codeine, Phenylpiperidine derivatives, Ketobemidone, Pethidine, Fentanyl, Diphenylpropylamine derivatives, Dextromoramide, Piritramide, Dextropropoxyphene, Bezitramide, Methadone, Benzomorphan derivatives, Pentazocine, Phenazocine, Oripavine derivatives, Buprenorphine, Morphinan derivatives, Butorphanol, Nalbuphine, Tilidine, Tramadol, Dezocine, Salicylic acid and derivatives, Acetylsalicylic acid, Aloxiprin, Choline salicylate, Sodium salicylate, Salicylamide, Salsalate, Ethenzamide, Morpholine salicylate, Dipyrocetyl, Benorilate, Diflunisal, Potassium salicylate, Guacetisal, Carbasalate calcium, Imidazole salicylate, Pyrazolones, Phenazone, Metamizole sodium, Aminophenazone, Propyphenazone, Nifenazone, Anilides, Paracetamol, Phenacetin, Bucetin, Propacetamol, Other analgesics and antipyretics, Rimazolium, Glafenine, Floctafenine, Viminol, Nefopam, Flupirtine, Ziconotide.

Very preferred active drug substances, which are analgesics to be included in the pharmaceutical compositions according to the present invention is opioids. Said opioids may be selected from the group consisting of naturally occurring opioids, synthetic opioids and semisynthetic opioids.

In another preferred embodiment the active drug substance is selected from the group consisting of Amfetamine, Dexamfetamine, Lisdexamfetamine, Metamfetamine, Methylphenidate, Dexmethylphenidate and combinations thereof.

In preferred embodiments of the invention the pharmaceutical compositions contain an opioid selected from the group consisting of buprenorphine, codeine, dextromoramide, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, morphine, pentazocine, oxycodeine, oxycodone, oxymorphone, norhydrocodone, noroxycodone, morphine-6-glucuronode, tramadol and dihydromorphine.

Furthermore, the opioid such as morphine, hydrocodone, hydromorphone or oxycodone may be in any of its crystalline, polymorphous, amorphous forms or combinations thereof.

In a very preferred embodiment of the invention the active drug substance is selected from the group consisting of morphine, oxycodone, hydrocodone, hydromorphone, norhydrocodone, oxymorphone, noroxycodone, morphine-6-glucuronode and pharmaceutically acceptable salts of any of the aforementioned, such as from the group consisting of oxycodone hydrochloride, hydrocodone bitartrate, hydromorphone hydrochloride and morphine sulphate pentahydrate.

All of the above mentioned active drug substances may also be in the form of pharmaceutically acceptable salts, uncharged or charged molecules, molecular complexes, solvates or anhydrates thereof, and, if relevant, isomers, enantiomers, racemic mixtures, and mixtures thereof.

In particular, the pharmaceutical compositions according to the invention may comprise pharmaceutically acceptable salts of any of the above mentioned active drug substances.

The term "pharmaceutically acceptable salts" of an active drug substance includes alkali metal salts such as, e.g., sodium or potassium salts, alkaline earth metal salts such as, e.g., calcium and magnesium salts, and salts with organic or inorganic acid like e.g. hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, maleic acid, succinic acid, tartaric acid, methansulphonic acid, toluenesulphonic acid etc.

The term "pharmaceutically acceptable salts" of an opioid includes alkali metal salts such as, e.g., sodium or potassium salts, alkaline earth metal salts such as, e. g.,

calcium and magnesium salts, and salts with organic or inorganic acids like e. g. hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, maleic acid, succinic acid, tartaric acid, methansulphonic acid, toluenesulphonic acid etc or tartrate acid. Preferred salts may be selected from the group consisting of sulphate salts, hydrochloride salts and bitartrate salts.

The term "solvates" includes hydrates or solvates wherein other solvates than water are involved such as, e.g., organic solvents like chloroform and the like.

Furthermore, the active drug substance may be in any of its crystalline, polymorphous, semi-crystalline, amorphous or polyamorphous forms and mixtures thereof.

The concentration of the active drug substance in a composition for use according to the invention depends on the specific active drug substance, the disease to be treated, the condition of the patient, the age and gender of the patient etc. The above-mentioned active drug substances are well-known active drug substances and a person skilled in the art will be able to find information as to the dosage of each active drug substance and, accordingly, he will know how to determine the amount of each active drug substance in a composition. The active drug substance is typically present in a matrix composition of the invention in a concentration amount of from 0.01- 99 %w/w such as, e.g., from about 0.01 to about 90% w/w, from about 0.01 to about 80% w/w, from about 0.01 to about 70% w/w, from about 0.01 to about 50% w/w, from about 0.01 to about 45% w/w or from about 0.01 to about 40% w/w.

When the active drug substance is an opioid, such as morphine, oxycodone, hydromorphone or hydrocodone or salts thereof, then said opioid is typically present in the matrix compositions in a concentration of in the range of 1 to 70% w/w, for example in the range of 1 to 60% w/w, such as in the range of 1 to 50% w/w, such as in the range of 1 to 45% w/w, for example in the range of 1 to 40% w/w, such as in the range of 1 to 30% w/w, for example in the range of 1 to 20% w/w, such as in the range of 1 to 17% w/w.

When the active drug substance is an opioid, such as morphine or salts thereof, then said opioid is typically present in the matrix compositions in a concentration of in the range of 1 to 70% w/w, for example in the range of 1 to 60% w/w, such as in the range

of 1 to 55% w/w, for example in the range of 1 to 50% w/w, such as in the range of 1 to 40% w/w, for example in the range of 1 to 35% w/w, such as in the range of 1 to 30% w/w, for example in the range of 1 to 20% w/w, such as in the range of 1 to 17% w/w, or the opoid, such as morphine, may be present in the matrix in the range of 5 to 60% w/w, for example in the range of 20 to 60% w/w, such as in the range of 30 to 60 % w/w, for example in the range of 30 to 55% w/w, such as in the range of 35 to 55% w/w.

In one preferred embodiment of the invention, the matrix composition comprises in the range of 1 to 17% w/w, such as 10 to 17% w/w, for example 15 to 17% w/w, such as 16% w/w of the opioid, such as morphine or salts thereof. In other embodiments of the invention, the matrix composition comprises more than 17% w/w, such as in the range of 20 to 60% w/w of the opioid, such as morphine or salts thereof.

In another preferred embodiment, the matrix composition comprises in the range of 1 to 70% w/w, for example in the range of 1 to 60% w/w, such as in the range of 1 to 50% w/w, for example in the range of 1 to 45 % w/w, such as in the range of 1 to 40% w/w, such as in the range of 1 to 30% w/w, for example in the range of 5 to 20% w/w, such as in the range of 10 to 20% w/w, for example in the range of 12 to 15% w/w of said opioid, such as hydrocodone bitartrate.

In another preferred embodiment, the matrix composition comprises a high load of said opioid, wherein a high load preferably is at least 15% w/w, preferably in the range of 15 to 70% w/w, for example in the range of 15 to 60% w/w, such as in the range of 15 to 50% w/w, for example in the range of 15 to 45% w/w, such as in the range of 15 to 40% w/w, such as in the range of 15 to 30% w/w, for example in the range of 20 to 30% w/w, such as in the range of 24 to 28% w/w of said opioid, such as hydrocodone bitartrate.

In yet another preferred embodiment the matrix composition comprises in the range of 1 to 70% w/w, for example in the range of 1 to 60% w/w, such as in the range of 1 to 50% w/w, for example in the range of 1 to 45% w/w, such as in the range of 1 to 40% w/w, such as in the range of 1 to 30% w/w, for example at least 15% w/w, preferably in the range of 15 to 70% w/w, for example in the range of 15 to 60% w/w, such as in the range of 15 to 50% w/w, such as in the range of 15 to 45% w/w, for example in the

range of 15 to 40% w/w, such as in the range of 15 to 30% w/w, for example in the range of 20 to 30% w/w, such as in the range of 24 to 28% w/w of said opioid, such as oxycodone hydrochloride.

In certain embodiments of the invention it is preferred that the matrix compositions comprise a low load of the active drug substance, such as an opioid. A low load is generally less than 50%, less than 45% w/w, preferably less than 40% of said active drug substance.

A pharmaceutical composition according to the invention containing an active drug substance as described herein above is typically for oral administration. In one preferred embodiment of the invention, the matrix composition provides for administration only once daily, which in particular is the case for pharmaceutical compostion with a length of in the range of 7.5 to 15 mm, preferably 8 to 15 mm, more preferably 8 to 10 mm. The matrix composition may also provide for administration twice daily, which in particular is the case for pharmaceutical compositions shorter than 8 mm, such as with a length on in the range of 4 to 8 mm, preferably in the range of 5.5 to 8 mm or in the range of 5.8 to 8 mm.

Certain active drug substances may be subject to entero-hepatic recirculation. Thus, for example morphine, hydromorphone and other opioids are metabolised mainly in the liver to both active and inactive compounds that are excreted in urine and bile. Morphine and hydromorphone are excreted partly in the bile as water-soluble glucuronides. In the gut, these glucuronides are metabolised by the normal gut flora to the parent opioid compound and reabsorbed (entero-hepatic recirculation), which may prolong the residence of morphine and hydromorphone and theirs metabolites in the systemic cicurlation.

Pharmaceutical compositions comprising active drug substances subject to entero-hepatic recirculation may in general be shorter than other pharmaceutical compositions. Thus, pharmaceutical compositions comprising active drug substances subject to entero-hepatic recirculation (for example morphine, hydromorphone or pharmaceutically acceptable salts thereof) may preferably have a length of in the range of 7.5 to 15 mm, such as 7.5 to in the range of 7.5 to 10 mm, more preferably in the range of 7.5 to 8 mm long, even when the pharmaceutical composition is prepared for

continued administration with an interval of in the range of 22 to 28 hours, such as 24 hours between individual admoinsitrations.

Neither Hydrocodone nor Oxycodone are metabolized by glucuronidation in the liver, but are primarily demethylated via CYP pathways. It is therefore highly surprising in particular for these compounds that the pharmaceutical compositions disclosed herein are useful for continued administration with in the range of 20 to 28 hours (such as 24 hours) interval between individual administrations.

Pharmaceutical compositions comprising active drug substances which are essentially not subject to entero-hepatic recirculation should in general be longer than other pharmaceutical compositions. Thus, pharmaceutical compositions comprising active drug substances which are not subject to entero-hepatic recirculation (for example oxycodone or hydrocodone or pharmaceutically acceptable salts thereof) may preferably have a length of in the range of 8 to 15 mm, such as in the range of 8 to 12 mm, more preferably in the range of 8 to 10 mm long, when the pharmaceutical composition is prepared for continued administration with an interval of in the range of 22 to 28 hours, such as 24 hours between individual administrations.

A composition according to the invention may comprise one active drug substance or more than one different active drug substances. Typically, the amount of the active substance corresponds to a daily or part of a daily therapeutic dose.

A composition according to the invention is suitable for use for both water soluble as well as slightly soluble or insoluble active substances.

Pharmaceutically acceptable excipients

The matrix composition may also contain other excipients as well, e.g. in order to improve the technical properties of the matrix composition so that it may be easier to produce or in order to improve the properties of the composition such as release rate of the active drug substance, stability of the active drug substance or of the composition itself.

A suitable pharmaceutically acceptable excipient for use in a matrix composition of the invention may be selected from the group consisting of fillers, diluents, disintegrants, glidants, pH-adjusting agents, viscosity adjusting agents, solubility increasing or decreasing agents, osmotically active agents and solvents.

Suitable excipients include conventional tablet or capsule excipients. These excipients may be, for example, diluents such as dicalcium phosphate, calcium sulfate, lactose or sucrose or other disaccharides, cellulose, cellulose derivatives, kaolin, mannitol, dry starch, glucose or other monosaccharides, dextrin or other polysaccharides, sorbitol, inositol or mixtures thereof; binders such as alginic acid, calcium alginate, sodium alginate, starch, gelatin, saccharides (including glucose, sucrose, dextrose and lactose), molasses, panwar gum, ghatti gum, mucilage of isapol husk, carboxymethylcellulose, methylcellulose, veegum, larch arabolactan, polyethylene glycols, ethylcellulose, water, alcohols, waxes, polyvinylpyrrolidone such as PVP K90 or mixtures thereof; lubricants such as talc, silicium dioxide, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, sodium benzoate, sodium chloride, leucine, carbowax 4000, magnesium lauryl sulfate, Sodium laurilsulfate, Stearyl alcohol, Polysorbate 20, Polysorbate 60, Polysorbate 80, Macrogol stearate, Macrogol lauryl ether, Stearoyl macrogolglycerides, Sorbitan stearate, Sorbitan laurate, Macrogol glycerol hydroxystearat, colloidal silicon dioxide and mixtures thereof, disintegrants such as starches, clays, cellulose derivatives including crosscarmellose, gums, aligns, various combinations of hydrogencarbonates with weak acids (e.g. sodium hydrogencarbonate/tartaric acid or citric acid) crosprovidone, sodium starch glycolate, agar, cation exchange resins, citrus pulp, veegum, glycollate, natural sponge, bentonite, sucralfate, calcium hydroxyl-apatite or mixtures thereof.

The composition such as the matrix composition may comprise one or more agents selected from the group consisting of gelling agents. Examples are polymers selected from the group consisting of modified or unmodified water soluble natural polymers such as glucomannan, galactan, glucan, polygalacturonic acid, polyxylane, polygalactomannans, polyxyloglycan, arabinogalactan, starch, cellulose, chitosan, alginate, fibrin, collagen, gelatin, amylopectin, pectin including low methylated or methoxylated pectins, dextran; synthetic polymers such as PVA and PVB; and hydrogels made from the polymers or combined polymers mentioned above and or from polymers originated from: HEMA, HEEMA, MEMA, MEEMA, EDGMA, NVP, VAc,

AA, acrylamide, MAA, HPMA, PEGA, PEGMA, PEGDMA, PEGDA, and/or PEGDMA, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, hydroxyethyl ncellulose, ethylcellulose, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose Acetate Succinate or other cellulose derivates, carboxymethylcellulose sodium, carboxymethylcellulose calcium, carrageenans, guar gum, gellan gum, xanthan gum, tragacanth and Arabic gum.

Furthermore, the composition may comprise one or more agents selected from the group consisting of sweetening agents, flavouring agents and colouring agents, in order to provide an elegant and palatable preparation. Examples are maltol, citric acid, water soluble FD&C dyes and mixtures thereof with corresponding lakes and direct compression sugars such as Di-Pac from Amstar. In addition, coloured dye migration inhibitors such as tragacanth, acacia or attapulgite talc may be added. Specific examples include Calcium carbonate, 1,3,5-trihydroxybenzene, Chromium-cobalt-aluminium oxide, ferric ferrocyanide, Ferric oxide, Iron ammonium citrate, Iron (III) oxide hydrated, Iron oxides, Carmine red, Magnesium carbonate and Titanium dioxide.

Plasticizers may be incorporated in the composition. A suitable plasticizer may be selected from the group consisting of mono- and di-acetylated monoglycerides, diacetylated monoglycerides, acetylated hydrogenated cottonseed glyceride, glyceryl cocoate, Polyethylene glycols or polyethylene oxides (e.g. with a molecular weight of about 1 ,000-500,000 daltons), dipropylene glycol salicylate glycerin, fatty acids and esters, phthalate esters, phosphate esters, amides, diocyl phthalate, phthalyl glycolate, mineral oils, hydrogenated vegetable oils, vegetable oils, acetylated hydrogenated soybean oil glycerides, Castor oil, acetyl tributyl citrate, acetyl triethyl citrate, methyl abietate, nitrobenzene, carbon disulfide, [beta]-naphtyl salicylate, sorbitol, sorbitol glyceryl tricitrate, fatty alcohols, cetostearyl alcohol, cetyl alcohol, stearyl alcohol, oleyl alcohol, myristyl alcohol, sucrose octaacetate, alfa<~>-tocopheryl polyethylene glycol succinate (TPGS), tocopheryl derivative, diacetylated monoglycerides, diethylene glycol monostearate, ethylene glycol monostearate, glyceryl monooleate, glyceryl monostearate, propylene glycol monostearate, macrogol esters, macrogol stearate 400, macrogol stearate 2000, polyoxyethylene 50 stearate, macrogol ethers, cetomacrogol 1000, lauromacrogols, nonoxinols, octocinols, tyloxapol, poloxamers, polyvinyl alcohols, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80, polysorbate 85, sorbitan monolaurate, sorbitan monooleate, sorbitan

monopalmitate, sorbitan monostearate, sorbitan sesquioleate, sorbitan trioleate, sorbitan tristearate and sucrose esters, amyl oleate, butyl oleate, butyl stearate, diethylene glycol monolaurate, glycerol tributyrate, Cumar W-1 , Cumar MH-1 , Cumar V-1 , Flexol B-400, monomeric polyethylene ester, Piccolastic A-5, Piccalastic A-25, Beckolin, Clorafin 40, acetyl tributyl citrate, acetyl triethyl citrate, benzyl benzoate, butoxyethyl stearate, butyl and glycol esters of fatty acids, butyl diglycol carbonate, butyl ricinoleate, butyl phthalyl butyl glycolate, camphor, dibutyl sebacate, dibutyl tartrate, diphenyl oxide, glycerine, HB-40, hydrogenated methyl ester of rosin, methoxyethyl oleate, monoamylphthalate, Nevillac 10, Paracril 26, technical hydroabietyl alcohol, Methylene glycol dipelargonate, solid aliphatic alcohols and mixtures thereof.

Preferred stabilizers (chemical) include TPG preferably in the form of TPGS (Vitamin E Polyehtylene glycol succinate) due to surfactant properties and BHT, BHA, t-butyl hydroquinone, butylhydroxy toluene, calcium ascorbate, gallic acid, hydroquinone, maltol, octyl gallate, sodium bisulfite, sodium metabisulfite.tocopherol and derivates thereof, citric acid, tartaric acid, and ascorbic acid. Thus, in one preferred embodiment, the matrix composition comprises TPGS and/or BHT. Other stabilisers include trivalent phosphorous like e.g phosphite, phenolic antioxidants, hydroxylamines, lactones such as substituted benzofuranones. Hindered phenols, thiosynergists and/or hindered amines, acids (ascorbic acid, erythorbic acid, etidronic acid, hypophosphorous acid, nordihydroguaiaretic acid, propionic acid etc.), phenols, dodecyl gallate, octyl gallate, 1 ,3,5-trihydroxybenzene, organic and inorganic salts (calcium ascorbate, sodium ascorbate, sodium bisulphite, sodium metabisulfite, sodium sulfite, potassium bisulphite, potassium metabisulphite), esters (calcium ascorbate, dilauryl thiodipropionate, dimyristyl thiodipropionate, distearyl thiodipropionate), pyranon (maltol), and vitamin E (tocopherol, D-[alpha]-tocopherol, DL-[alpha]-tocopherol, tocopheryl acetate, d-[alpha]-tocopheryl acetate, dl-[alpha]-tocopheryl acetate. However, other anti- oxidative agents known in the art may be used according to the present invention. Other suitable stabilizer is selected from such as e.g. sorbitol glyceryl tricitrate, sucrose octaacetate.

In one preferred embodiment the matrix comprises one or more stabilizers selected from above mentioned group of stabilizers, preferably butylhydoxytoluene.

In another preferred embodiment the matrix comprises one or more stabilizers selected from above mentioned group of stabilizers, preferably TPGS.

A release modifier may be incorporated in the composition. A suitable release modifier is selected from the group consisting of fatty acids and esters, fatty alcohols, cetyl alcohol, stearyl alcohol, mineral oils, hydrogenated vegetable oils, vegetable oils, acetylated hydrogenated soybean oil glycerides, Castor oil, phosphate esters, amides, phthalate esters, glyceryl cocoate oleyl alcohol, myristyl alcohol, sucrose octaacetate, diacetylated monoglycerides, diethylene glycol monostearate, ethylene glycol monostearate, glyceryl monooleate, glyceryl monostearate, propylene glycol monostearate, macrogol esters, macrogol stearate 400, macrogol stearate 2000, polyoxyethylene 50 stearate, macrogol ethers, cetomacrogol 1000, lauromacrogols, poloxamers, polyvinyl alcohols, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesquioleate, sorbitan trioleate, sorbitan tristearate, ethylcellulose, cellulose acetate, cellulose propionate, cellulose nitrate, cellulose derivative selected from the group consisting of methylcellulose, carboxymethylcellulose and salts thereof, cellulose acetate phthalate, microcrystalline cellulose, ethylhydroxyethylcellulose, ethylmethylcellulose, hydroxyethylcellulose, hydroxyethylmethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose and hydroxymethylpropylcellulose, cellulose acetate, polylactic acid or polyglycolic acid and copolymers thereof, methacrylates, a co-polymer of methacrylate-galactomannan etc., Polyvinyl alcohols, glycerinated gelatine and cocoa butter.

Other suitable release modifiers may be selected from the group consisting of inorganic acids, inorganic bases, inorganic salts, organic acids or bases and pharmaceutically acceptable salts thereof, saccharides, oligosaccharides, polysaccharides, polyethylene glycol derivatives and cellulose and cellulose derivatives.

Alternatively or additionally, a suitable pharmaceutically acceptable excipient is a mono-, di-, oligo, polycarboxylic acid or amino acids such as, e.g. acetic acid, succinic acid, citric acid, tartaric acid, acrylic acid, benzoic acid, malic acid, maleic acid, sorbic acid etc., aspartic acid or glutamic acid etc.

Examples of suitable organic acids include for example acetic acid/ ethanoic acid,

adipic acid, angelic acid, ascorbic acid/vitamin C, carbamic acid, cinnamic acid, citramalic acid, formic acid, fumaric acid, gallic acid, gentisic acid, glutaconic acid, glutaric acid, glyceric acid, glycolic acid, glyoxylic acid, lactic acid, levulinic acid, malonic acid, mandelic acid, oxalic acid, oxamic acid, pimelic acid, or pyruvic acid.

Examples of suitable inorganic acids include for example pyrophosphoric, glycerophosphoric, phosphoric such as ortho and meta phosphoric, boric acid, hydrochloric acid, or sulfuric acid.

Examples of suitable inorganic compounds include for example aluminium.

Examples of organic bases include for example p-nitrophenol, succinimide, benzenesulfonamide, 2- hydroxy-2cyclohexenone, imidazole, pyrrole, diethanolamine, ethyleneamine.tris (hydroxymethyl) aminomethane, hydroxylamine and derivates of amines, sodium citrate, aniline or hydrazine. Examples of inorganic bases include for example aluminium oxide such as, e.g., aluminium oxide trihydrate, alumina, sodium hydroxide, potassium hydroxide, calcium carbonate, ammonium carbonate, ammnonium hydroxide or KOH.

Suitable pharmaceutically acceptable salts of an organic acid is e.g. an alkali metal salt or an alkaline earth metal salt such as, e.g. sodium phosphate, sodium dihydrogenphosphate, disodium hydrogenphosphate etc., potassium phosphate, potassium dihydrogenphosphate, potassium hydrogenphosphate etc., calcium phosphate, dicalcium phosphate etc., sodium sulfate, potassium sulfate, calcium sulfate, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, potassium hydrogencarbonate, calcium carbonate, magnesium carbonate etc., sodium acetate, potassium acetate, calcium acetate, sodium succinate, potassium succinate, calcium succinate, sodium citrate, potassium citrate, calcium citrate, sodium tartrate, potassium tartrate or calcium tartrate.

A suitable inorganic salt for use in a matrix composition of the invention is for example sodium chloride, potassium chloride, calcium chloride or magnesium chloride.

The matrix composition may preferably comprise at least one saccharide, such as glucose, ribose, arabinose, xylose, lyxose, xylol, allose, altrose, inosito, glucose,

sorbitol, mannose, gulose, Glycerol, idose, galactose, talose, mannitol, erythritol, ribitol, xylitol, maltitol, isomalt, lactitol, sucrose, fructose, lactose, dextrin, dextran, amylase or xylan. In a preferred embodiment the matrix composition comprises mannitol.

The matrix composition may also comprise polyethylene glycol derivatives such as e.g. polyethylene glycol di(2-ethyl hexoate), polyethylene glycols (200 - 600 daltons) or polyethylene oxides, e.g. with an average molecular weight of about 800-500,000 daltons, typically about 1 ,000-100,000 daltons, more typically 1,000-50,000 daltons, especially about 1 ,000-10,000 daltons, in particular about 1 ,500-5,000 daltons, or mixtures thereof,.

The matrix composition may also comprise cellulose and/or cellulose derivatives selected from the group consisting of methylcellulose, carboxymethylcellulose and salts thereof, microcrystalline cellulose, ethylhydroxyethylcellulose, ethylcellulose, cellulose acetate, cellulose proprionate, cellulose nitrate, cellulose acetate phthalate, ethylmethylcellulose, hydroxyethylcellulose, hydroxyethylmethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose and hydroxymethylpropylcellulose.

Preparation

The pharmaceutical composition as well as the matrix composition of the invention may be produced by various methods which are either known per se in the pharmaceutical industry or which, for example, are used in the production of polymer-based materials, depending upon the desired embodiment and the materials employed in the composition in question. One advantage of the composition according to the invention is that it may be produced by methods, which are relatively simple and inexpensive.

Suitable preparation methods for compositions according to the invention include extrusion, injection moulding, moulding, tabletting, capsule filling, melt-processing, , spray coating, micro encapsulation and other methods of preparing controlled release compositions. Also a combination of one or more of the aforementioned may be employed.

The controlled release composition may be prepared by several different methods. Many systems for controlled release are marketed and it is currently an aim for the industry to reduce the risk of dose dumping, drug abuse or alcohol induced dose dumping in each of the systems.

In other words, in addition to a less frequent administration, one challenge in controlled release delivery may be expressed by the goal of decreasing the incidence of adverse effects and at the same time increasing the effect of the treatment. This may be obtained by an interaction between the specific pharmacological properties of the active drug substance and the matrix composition.

High concentrations or a fast rise in the concentration of for example opioids is one important factor resulting in side effects including the risk of getting addicted to opioids. The fear of addiction is often a major obstacle for initiation of the otherwise effective pain treatment with e.g. morphine, hydrocodone or oxycodone both in the view of the clinical personnel as well as in the view of the patients themselves.

Compositions for controlled release according to the invention may be prepared in numerous ways giving rise to different release mechanisms. Particularly the composition may be prepared by 1, 2 or multiple component injection mouldings, by conventional tablet compression, by micro encapsulation, by 1, 2 or multiple component extrusions, by moulding, by capsule filling or by melt-processing . In cases where a preparation is needed in order to make the controlled release properties before/after the above mentions preparation steps, the preparation may also comprise separate steps as for example wet granulation, dry granulation, melt granulation, pelletizing, spray coating, electrostatic coating or other forms of controlled release forming preparation methods.

In a particular example the composition is prepared by two component injection moulding of a matrix composition and a coating (which may be any of the coatings described herein below in the section “Coating”) surrounding the matrix and exposing at least one surface of the matrix, preferably the two ends of the matrix composition for erosion governed release.

A composition may also be produced by, for example, moulding, injection moulding, co-

extrusion of the coating with the matrix composition and the active drug substance, extrusion and dip coating, injection moulding and dip coating, or by extrusion or injection moulding and solvent coating by spraying or dipping. Multiple component injection moulding, or a combination of these methods.

Geometry

Interestingly, the present invention discloses that the release mechanisms described above are at least partly depending on the geometry of the composition. For example erosion based release from a matrix depends on the exposed area of the matrix, which in embodiments of the invention wherein the opening(s) in the coating are of the same shape and size as the cross section, will be the cross section area (optionally 2x the cross section area if there are two such openings). According to the present invention the area may be manipulated by employment of a coat that is not subject to erosion and thus covering areas of the matrix that should not be releasing sites.

The geometric form of the composition is very important for the obtainment of the above-mentioned controlled release. Thus, in one embodiment of the invention, the pharmaceutical composition has a geometric shape, which enables a substantially constant surface area to become exposed during erosion of the matrix.

Preferably, the pharmaceutical compositions of the invention are cylindrical compositions optionally with tapered end(s). It follows that the matrix composition also preferably is of a cylindrical shape (optionally with tapered end(s)), which preferably is surrounded by a coating having at least one or two openings exposing at least one surface of said matrix.

The cylindrical shape may be any geometrical shape having the same cross section area throughout the length of the geometrical shape. Thus, the term “cylindrical shape” as used herein preferably refers to any geometrical shape having the same cross section area along an axis, preferably the longitudinal axis. Within the present context, cross sections are perpendicular to the axis of the cylinder. By way of example, if the cylindrical shape is elongated then the cross sections are perpendicular to the longitudinal axis. Preferably, the cylindrical shape is elongated. The cross section of a

cylinder within the meaning of the present invention may have any two dimensional shape, for example the cross section may be circular, oval, parabola, hyperbola, rectangular, triangular, otherwise angular, polygonal, star shaped or an irregular shape. In preferred embodiments of the invention the cross section is oval or circular. The pharmaceutical compositions according to the invention preferably have a cylindrical shape, wherein one or both end(s) may be tapered, for example one or both end(s) may be rounded. Thus, the matrix may taper along the longitudinal axis, i.e. the area of the cross section may decrease along the longitudinal axis towards one or both ends of the matrix.

Accordingly, the cylindrical shape may for example be an elliptic cylinder, a parabolic cylinder, a hyperbolic cylinder or a prism. A prism within the present context is a cylinder whose cross-section is a polygon.

Figure 11 shows examples of specific pharmaceutical compositions. The skilled person will appreciate that the depicted shapes also may be applied to other pharmaceutical compositions. Accordingly, the pharmaceutical compositions consisting of a matrix surrounded by a coating according to the present invention may for example have any of the cylindrical shapes shown in figure 11, wherein, fig. 11I-1 shows the 3 dimensional structure of a round pharmaceutical composistion and fig. 11 I-2 shows a 3 dimensional shape of a matrix, figure 11 II, III and IV shows pharmaceutical compositions with an oval shape, wherein the cross section of the matrix has either an oval shape or a round shape (fig. 11 II-4). The skilled person will appreciate that other shapes are also useful for the pharmaceutical compositions of the invention. E.g. the matrix shown in figure 11 II-2 may also be a cylinder without a tapered end or it may have two tapered ends rather than one.

Figure 11 I-3 shows an example of a pharmaceutical composition according to the invention. The pharmaceutical compositions has a matrix with a cylindrical part the length of which is designated F and the diameter designated C. The matrix further has a tapered end, the length of which is designeated E and the diameter of the part of the end which is shortest is designated A. The entire length of the matrix is designated B. The matrix is surrounded by a coating, which has a thickness of G in one end. The overall diameter of the the pharmaceutical composition is designated D. Fig. 11 I-3 shows an example of a pharmaceutical composition according to the invention and it

will be apparent to the skilled person that modifications may be made, for example pharmaceutical compositions without tapered ends or with two tapered ends or pharmaceutical compositions where the coating is uniformly thick and wherein the cross section of the matrix has either an oval shape or a round shape

The pharmaceutical composition as well as the matrix composition according to the invention may be a cylindrical shape with one tapered end or two tapered ends.

Thus, the shape of the matrix may be defined by a main cylindrical body (herein referred to as “cylinder part of the matrix”) optionally with one or two tapered ends. Figure 11 I-3 e.g. shows a cylinder part of the matrix defined by FxC. The cylinder part of the matrix is in general completely cylindrical. It is preferred that the length of said cylinder part of the matrix (e.g. F in fig. 11 I-3) is in the range of 7.5mm to 15 mm, preferably in the range of 8 to 15 mm, more preferably in the range of 8 to 10 mm, even more preferably in the range of 8.2 to 9.8 mm, yet more preferably in the range of 8.4 to 9.6 mm, even more preferably in the range of 8.5 to 9.5 mm, yet more preferably in the range of 8.7 to 9.3 mm, even more preferably in the range of 8.9 to 9.1 mm, yet more preferably approximately 9 mm, for example 9 mm long, or for example approximately 9.5 mm long, such as 9.5 mm long, e.g. along the longitudinal axis. Aforementioned lengths are in particular relevant for pharmaceutical compositions formulated for continued administration with in the range of 20 to 28 hours, preferably in the range of 22 to 26, more preferably in the range of 23 to 25, for example approximately 24 hours, such as 24 hours interval between individual administrations.

In specific embodiments of the invention the matrix is relatively long, such as longer than 9mm, for example in the range of 9 to 15 mm, such as in the range of 9 to 12 mm, for example approximately 9 mm, such as approximately 10 mm, for example approximately 11mm, such as approximately 12 mm, for example 9 mm, such as 10 mm, for example 11mm, such as 12 mm long. These longer lengths are in particular relevant for pharmaceutical compositions formulated for continued administration with in the range of 20 to 28 hours, preferably in the range of 22 to 26, more preferably in the range of 23 to 25, for example approximately 24 hours, such as 24 hours interval between individual administrations.

In another specific embodiment of the invention the length of said cylinder part of the matrix (e.g. F in fig. 11 I-3) or preferably the entire length of the matrix (e.g. B in figure 11 I-3) is in the range of 7.5mm to 15 mm, preferably in the range of 7.5 to 10 mm, more preferably in the range of 7.5 to 8 mm long, e.g. along the longitudinal axis. Aforementioned lengths are in particular relevant for pharmaceutical compositions formulated for continued administration with in the range of 20 to 28 hours, preferably in the range of 22 to 26, more preferably in the range of 23 to 25, for example approximately 24 hours, such as 24 hours interval between individual administrations, when the active drug substance is an active drug substance subject to entero-hepatic recirculation.

As defined above, the cross section area along an axis, preferably the longitudinal axis of said cylinder part of the matrix is constant. In one embodiment of the invention it is preferred that the cross section are of the cylinder part of the matrix is at least 1 mm^2, preferably in the range of 1 to 150 mm^2, more preferably in the range of 1 to 100 mm^2, more preferably in the range of 1 to 75 mm^2, more preferably in the range of 1 to 60 mm^2, more preferably in the range of 2 to 60 mm^2.

In another embodiment of the invention it is preferred that the cross section area of the cylinder part of the matrix is at least 20 mm^2, preferably at least 22 mm^2, more preferably at least 24 mm^2, even more preferably at least 26 mm^2, such as at least 28 mm^2, preferably in the range of 20 to 100 mm^2, more preferably in the range of 20 to 75 mm^2, more preferably in the range of 20 to 60 mm^2, more preferably in the range of 20 to 40 mm^2, more preferably in the range of 22 to 100 mm^2, more preferably in the range of 22 to 75 mm^2, more preferably in the range of 20 to 60 mm^2, more preferably in the range of 22 to 40 mm^2, more preferably in the range of 24 to 100 mm^2, more preferably in the range of 24 to 75 mm^2, more preferably in the range of 24 to 60 mm^2, more preferably in the range of 24 to 40 mm^2, more preferably in the range of 26 to 100 mm^2, more preferably in the range of 26 to 75 mm^2, more preferably in the range of 26 to 60 mm^2, more preferably in the range of 26 to 40 mm^2, more preferably in the range of 28 to 100 mm^2, more preferably in the range of 28 to 75 mm^2, more preferably in the range of 28 to 60 mm^2, more preferably in the range of 28 to 40 mm^2. For example in figure 11 I-3 the diameter of the cross section is indicated as C.

This embodiment is in particular useful for compositions comprising a low load of active drug substance, e.g. less than 50%, preferably less than 40% of the active drug substance. Aforementioned cross-section areas are in particular relevant for pharmaceutical compositions formulated for continued administration with in the range of 20 to 28 hours, preferably in the range of 22 to 26, more preferably in the range of 23 to 25, for example approximately 24 hours, such as 24 hours interval between individual administrations.

Thus, it is very preferred that said cylinder part of the matrix has any of the aforementioned lengths and any of the aforementioned cross sections. Thus, preferably, the cylinder part of the matrix has a length of the range of 7.5 to 15 mm, preferably 8 to 10 mm and a cross section area of at least 20 mm^2, for example the cylinder part of the matrix has a length of the range of 7.5 to 15 mm, preferably 8 to 10 mm and a cross section area of in the range of 20 to 100 mm^2, such as a length of the range of 8,5 to 9,5 mm and a cross section area of in the range of 20 to 100 mm^2, for example a length of the range of 8.9 to 9.1 mm and a cross section area of in the range of 20 to 100 mm^2, such as a length of 9 mm and a cross section area of in the range of 20 to 100 mm^2. In another embodiment it is preferred that the the cylinder part of the matrix has a length of the range of 7.5 to 15 mm, preferably 8 to 10 mm and a cross section area of at least 1 mm^2, for example the cylinder part of the matrix has a length of the range of 7.5 to 15 mm, preferably 8 to 10 mm and a cross section area of in the range of 1 to 150 mm^2, more preferably in the range of 1 to 100 mm^2, more preferably in the range of 1 to 75 mm^2, more preferably in the range of 1 to 60 mm^2, more preferably in the range of 2 to 60 mm^2.

As described above, the pharmaceutical composition may comprise a main cylindrical body (also referred to as “cylinder part of the matrix”) optionally with one or two tapered ends. For example figure 11 I-3 shows one tapered end the length of which is E, the shortest diameter A and the longest diameter C. The length of the tapered end (e.g. E in fig. 11 I-3) may be 0 (i.e. no tapered end) or it may be as long as 40% of the total length, preferably up to 33% of the total length. In embodiments of the invention wherein the pharmaceutical composition comprises one or two tapered ends it is preferred that the total length of the matrix including both the cylindrical part of the matrix as well as the tapered end(s) (for example B in figure 11 I-3) is in the range of 7.5 to 15 mm, preferably in the range of 8 to 15 mm, more preferably in the range of 8

to 10 mm, even more preferably in the range of 8.2 to 9.8 mm, yet more preferably in the range of 8.4 to 9.6 mm, even more preferably in the range of 8.5 to 9.5 mm, yet more preferably in the range of 8.7 to 9.3 mm, even more preferably in the range of 8.9 to 9.1 mm, yet more preferably approximately 9 mm, for example 9 mm long, or for example approximately 9.5 mm long, such as 9.5 mm long e.g. aling the longitudinal axis.

Preferably, the matrix composition is being surrounded by a coating having at least one, preferably one or two openings exposing at least one surface of said matrix, preferably one or two surfaces of said matrix. Preferably, said one or two openings are positioned at one or both end(s) of said cylindrical matrix, thereby exposing one end of the cylindrical shape, more preferably the coating has two openings each exposing an end of the cylindrical shape.

It is thus preferred that the matrix is surrounded by a coating, and it is preferred that said coating lines matrix. Accordingly, the inner lining of the coating will have essentially the same shape (or generally exactly the same shape) as the matrix except that the coating contains one or two openings. It is comprised within the invention that the thickness of the coating is uniform and thus the coating will have essentially a similar shape as the matrix except that the coating contains one or two openings and that the coating in the absence of the matrix is hollow. Obviously, the outer diameter of the coating will be larger than the outer diameter of the matrix. The difference in diameter will be dependent on the thickness of the coating. The thickness of the coating may for example be as shown in figure 11 I-3 indicated as G.

It is however also contained within the the present invention that the coating is not uniformly thick all over and thus, while the inner lining of the coating will have essentially the same shape (or generally exactly the same shape) as the matrix, the outer lining of the coating may have a different shape. Preferably, the outer lining of the coating is cylindrical and may preferably take any of the cylindrical shapes described herein above in relation to the matrix.

It is also contained within the invention that the coating (sometimes also referred to as “shell”) is cylindrical, preferably that both the inner lining and the outer lining of the coating is cylindrical. However, optionally the coating may furthermore be rounded at

the first end and/or the second end. The coating may also taper along the longitudinal axis at one or both ends.

As mentioned above, the coating is preferably cylindrical optionally with tapered ends and it is preferred that the length of said coating (e.g. B in figure 11 I-3) is in the range of 7.5mm to 15 mm, preferably in the range of 8 to 15 mm, more preferably in the range of 8 to 10 mm, even more preferably in the range of 8.2 to 9.8 mm, yet more preferably in the range of 8.4 to 9.6 mm, even more preferably in the range of 8.5 to 9.5 mm, yet more preferably in the range of 8.7 to 9.3 mm, even more preferably in the range of 8.9 to 9.1 mm, yet more preferably approximately 9 mm, for example 9 mm measured along the longitudinal axis of said cylinder. Aforementioned lengths of said coating are in particular relevant for pharmaceutical compositions formulated for continued administration with in the range of 20 to 28 hours, preferably in the range of 22 to 26, more preferably in the range of 23 to 25, for example approximately 24 hours, such as 24 hours interval between individual administrations.

It is frequently preferred that the coating is the same length as the matrix, thus by way of example if the matrix is 9 mm, then it is preferred that the coating is preferably also 9 mm. In some embodiments of the invention, and in particular in embodiments of the invention, wherein the matrix contains one or two tapered ends, then the coating may be shorter than the matrix. In these embodiments it is preferred that the coating has the same length as the cylinder part of the matrix and thus covers the cylinder part of the matrix leaving the tapered ends exposed.

Pharmaceutical compositions formulated for more frequent administration than continued administration with in the range of 20 to 28 hours interval between administrations are in general shorter. Thus, the invention in one aspect relates to pharmaceutical compositions comprising

a) a matrix composition comprising

i) an active drug substance (which may be any of the active drug substances described herein above in the section “Active drug substance”, preferably an opiod); and

ii) at least one polyglycol (which may be any of the polyglycols described herein above in the section "Polyglycol")

said matrix composition having a cylindrical shape optionally with tapered end(s), the length of said matrix being in the range of 4 to 8 mm, preferably in the range of 5.5 to 8 mm, such as in the range of 6 to 7.5 mm, for example 6mm or 7.5 mm, said matrix being surrounded by

b) a coating having one or two openings exposing at least one surface of said matrix, said coating being substantially impermeable to an aqueous medium.

The cross section of these compositions are preferably at least 1 mm^2, more preferably in the range of 1 to 150 mm^2, more preferably in the range of 1 to 100 mm^2, more preferably in the range of 1 to 75 mm^2, more preferably in the range of 20 to 75 mm^2. This pharmaceutical composition is in general formulated for continued administration with in the range of 5 to 20 hours, preferably with in the range of 7 to 20 hours, more preferably with in the range of 10 to 20 hours, for example with in the range of 10 to 18 hours, such as with in the range of 10 to 16 hours, for example with in the range of 10 to 14 hours, such as with in the range of 11 to 13 hours, for example with 12 hours interval between individual administrations.

Thus, the pharmaceutical compositions according to the invention may be a cylindrical shape with the two ends exposing the eroding matrix composition. Such a shape will give rise to zero order release because the releasing area is constant. In a specific example, the compositions employed are coated in such a manner that the surface has a substantially constant or controlled surface area during release or erosion. In the present context controlled surface area relates to a predetermined surface area typically predicted from the shape of the coat of the unit dosage system. It may have a simple uniform cylindrical shape or the cylindrical form can have one or more tapered ends in order to decrease (or increase) the initial release period.

As yet another example the release mechanism of dissolving/solubilization also depend on the releasing area and the release rate may be controlled by what area of the matrix is covered by said coating. In general the majority of the matrix is covered by a coating having one or two openings, preferably the sides of the cylindrical shape (i.e. of the

cylindrical matrix) is partly covered by said coating, preferably at least 70%, more preferably at least 80%, even more preferably at least 90%, yet more preferably at least 95%, even more preferably all of the sides of the cylindrical shape (i.e. of the cylindrical matrix) are covered by said coating. One or both ends of the matrix, including optionally tapered ends may be partly covered by said coating, or they may be uncovered by any coating. Thus, one or both ends may be exposed to the surroundings.

In a preferred embodiment of the invention the pharmaceutical composition is prepared for oral intake, preferably for oral intake by swallowing. Accordingly, the size of the pharmaceutical composition should be in a range that allows oral intake by swallowing.

Preferably, the coating or shell has outer dimensions making the shell suitable for oral administration. The shell may preferably have a length (extension along the first axis, e.g. B in figure 11 I-3) in the range from about 7.5mm to 15 mm, preferably from 8 mm to 10 mm (see above). The shell may have a height (extension along the second axis, e.g. the diameter, e.g. D in figure 11 I-3) in the range from 2 mm to 20 mm, preferably in the range from 2 mm to 15 mm, such as in the range of 2 to 10, for example in the range of 4 to 10, such as approximately 4.5 mm, for example approximately 5.6 mm, such as approximately 8.3 mm. The shell may have a width (extension along the third axis, e.g. diameter, e.g. D in figure 11 I-3) in the range from 2 mm to 20 mm, preferably in the range from 2 mm to 15 mm, more preferably in the range of 2 to 10 mm, such as in the range of 4 to 10 mm, preferably in the range of 3 to 5 mm, such as approximately 3.4 mm, for example approximately 4.3 mm, such as approximately 4.4 mm, for example approximately 4.5 mm, such as approximately 4.7 mm. In this context approximately preferably means +/- 10%. The outer surface of the shell may have a double curved surface to facilitate oral administration of a pharmaceutical composition comprised in the shell.

The opening may have any suitable shape, such as e.g. circular, oval, rectangular, triangular, angular, polygonal or star shaped. Preferably, the opening has a shape similar to the cross section of the matrix, more preferably, the opening has the same shape as the cross section of the matrix. It is even more preferred that the pharmaceutical compositions comprise a matrix surrounded by a coating having two openings, wherein each opening is positioned at each end of said matrix and each

opening have essentially the same shape as the cross section of said matrix. For example, in figure 11 I-3, one opening has a diameter of A and the other a diameter of C. It is also possible that two openings have a diameter of C. An opening may have any suitable size, such as an area in the range from about 1 mm^2 to about 150 mm^2, preferably, in the range from about 1 mm^2 to about 100 mm^2, preferably, in the range from about 1 mm^2 to about 75 mm^2, such as from about 2 mm^2 to about 65 mm^2. In one preferred embodiment, the opening has the same area as the cross section area of the cylindrical part of the matrix. Thus by way of example, if the cross section area is in the range of 1 to 75 mm^2, then the area of one opening is preferably also in the range of 1 to 75 mm^2 and accordingly, the area of two openings in total is then preferably 2 to 150 mm^2. Similarly, if the cross section area is at least 20 mm^2, then the area of one opening is preferably also at least 20 mm^2 and accordingly, the area of two openings in total is then preferably at least 40 mm^2.

Coating

The pharmaceutical compositions according to the invention comprises (or even consists of) a matrix surround by a coating with one or two openings.

The coating may also be referred to as “shell” herein and these terms are used interchangably. The shape of the shell or coating is described herein above in the section “Geometry”. The composition of the shell or coating is described herein below.

For the present purpose, it is important to ensure that the shell or coating is impermeable to an aqueous medium, such as water. This ensures that the matrix only is in contact with surrounding aquous media via the openings in the coatings. In addition it is preferred that the coating also is substantially insoluble in an aqueous medium, preferably the coating is insoluble in an aqueous medium.

In a specific example the coating is substantially insoluble, non-erodable and impermeable to water leaving only the exposed areas of the matrix for release. Within the present context, the coating is considered substantially insoluble in an aqueous medium if the coating dissolves so much slower in a aqueous medium than

the matrix composition so that the coating remains intact until the matrix has eroded and/or released the active drug substance.

Preferably, the coating is considered substantially insoluble in water, when it has a solubility in water of at least 100, for example at least 1000, wherein solubility is determined as parts of water needed to dissolve 1 part of solute at ambient temperature. Preferably, the coating is considered insoluble in water, when it has a solubility in water of at least 10.000, wherein solubility is determined as parts of water needed to dissolve 1 part of solute at ambient temperature.

In an embodiment of the invention, the coating is one, which biodegrades, disintegrates crumbles or dissolves after erosion of the matrix and/or during the release of the active drug substance. A coating applied for an erosion matrix will remain intact as long as it is supported by the matrix containing the active drug substance, but it lacks the ability to remain intact after erosion of the matrix, because it then biodegrades, disintegrates or crumbles, so that it will not remain in e.g. a human for any significant amount of time after the complete erosion of the matrix and the release of the active drug substance.

In a one embodiment of the invention, the shell (coating) may biodegrade, disintegrate, crumble or dissolve after erosion of the matrix composition and/or during the release of the active drug substance in the matrix composition.

The coating or shell in general comprises or even consist of one or more polymers. It is preferred that at least some, however more preferably all of these polymers are thermoplastic polymers.

Thus, in one embodiment of the invention all the polymers comprised in the shell (coating) are thermoplastic polymers. By thermoplastic polymers is meant that the polymer(s) is/are an elastic and flexible liquid when heated and freezes to a solid state when cooled (e.g. cooled to 20°C or to ambient temperature).

The shell (coating) may be made of a material comprising one or more of the polymers described herein in this section, e.g. a material comprising one or more starch based polymers, one or more cellulose based polymers, one or more synthetic polymers, one

or more biodegradable polymers or a combination thereof, such as mixtures of starch and synthetic polymers or mixtures of starch and biodegradable polymers.

The shell (coating) may preferably be made of a material comprising one or more polymers selected from the group consisting of Ethyl cellulose grade 20 and 100, polylactic acid (PLA), Cornpack 200, polycaprolactone, PEO 7000000 and polyhydroxybuturate.

Starch based polymers

The shell (coating) may comprise one or more starch based polymers. The starch based polymer may be starch as such or a polymer having a high starch content, preferably more than 70%, such as more than 80%, for example more than 90%. Starch is a linear polysaccaride made up of repeating glucose groups with glyco-sidic linkages in the 1-4 carbon positions with chain lengths of 500 to 2,000 glucose units. There are two major polymer molecules in starch—amylose and amylopectin.

The starch based polymers to be used according to the present invention may preferably be thermoplastic starch biodegradable plastics (TPS). TPS have a starch (amylose) content greater than 70% and are in general based on gelatinised vegetable starch. Said vegetable starch may for example be selected from the group consisting of potato starch, rice starch, maize starch, tapioca starch, wheat starch, dextrin, carrageenan and chitosan. Said vegetable starch may also as such be suitable polymers used in the shell (coating) composition. The group of starch based polymer in general do not have a specified melting point, but changes phase within a temperature range of 90 °C to 260 °C typically depending upon the chain length of the starch based polymer, water content, and their branching and added side-groups as does the degree of crystallinity of the starch. Long chained-starches are usually completely amorphous, while shorter length starches may be semi-crystalline (20-80% crystalline). Long polymer chains are preferable because it contributes to the hardness, while not being too brittle.

Starch-based polymers are in general fully biodegradable as they are product of plant materials. The degradation rate varies and can be further induced by addition of other biodegradable polymers as listed herein.

One example of a preferred starch based polymer, which may be comprised in the shell or coating according to the present invention is maize starch. Maize starch is a linear polysaccaride made up of repeating glucose groups with glyco-sidic linkages in the 1-4 carbon positions with chain lengths of 500 to 2,000 glucose units. There are two major polymer molecules in starch—amylose and amylopectin. A preferred maize starch is cornpack. Cornpack is the maize starch used in some examples described herein below.

Starch is widely used in food and pharmaceutical industry as binder and dilluent. It is edible and essentially nontoxic. Starch is in general cheap and obtains a good hardness when moulded. Starch may in general also be reheated several times without losing its thermodynamic properties. Accordingly, it is preferred that the coating comprises at least one starch based polymer, and more preferably a starch, because starch may be a great advantage when applying injection moulding or co-extrusion as a production process.

Starch based polymers are in general decomposable, and usually have a fast disintegration rate, especially in mixture with biodegradable polymers. These polymers are in generally recognized as stabile and inert in solid dosage forms.

Cellulose based polymers

The coating or the shell may also comprise one or more cellulose based polymers. In certain embodiments of the invention the coating may even consist of one or more cellulose based polymers (such as ethyl cellulose) and platizicers (such as any of the plastizicers described in this section below) and UV stabilisers (such as any of the UV stabilisers described in this section below).

Cellulose based polymers are useful in the shell (coating) composition because cellulose based polymers e.g. ethylcellulose (particularly grade 100-300) frequently have increased hardness and high ductility.

It is therefore preferred that the coating comprises a cellulose based polymer, preferably a cellulose based polymer, which is substantially insoluble in an aqueous

medium, more preferably a cellulose based polymer, which is insoluble in an aqueous medium. The cellulose based polymer is preferably cellulose, wherein one or more of the free -OH groups have been substituted with an R-group to form a –O-R group. R may in this context for example be linear or branched lower alkyl, linear or branched lower alkyl-OH, linear or branched lower alkyl-COOH, -CO-(linear or branched lower alkyl), nitrate, aromatic rings or combinations of the aforementioned. Lower alkyl is preferably a C_{1-10} alkyl, more preferably C_{1-6} alkyl.

Accordingly, the cellulose based polymer may for example be one or more selected from the group consisting of ethylcellulose, cellulose acetate, cellulose propionate, cellulose nitrate, methylcellulose, carboxymethylcellulose and salts thereof, cellulose acetate phthalate, ethylhydroxyethylcellulose, ethylmethylcellulose, hydroxyethylcellulose, hydroxyethylmethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose and hydroxymethylpropylcellulose and cellulose acetate.

The coating may also comprise one or more cellulose based polymers selected from the group consisting of cellulose acetate, cellulose propionate, silicified microcrystalline cellulose, cellulose nitrate, methylcellulose, carboxymethylcellulose and salts thereof, cellulose acetate phthalate, microcrystalline cellulose, ethylhydroxyethylcellulose, ethylmethylcellulose, hydroxyethylcellulose, hydroxyethylmethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose phthalate, hydroxymethylcellulose and hydroxymethylpropylcellulose, cellulose acetate, ceratonia(high molecular-weight 310 000.

Cellulose based polymers are in general fully biodegradable as they preferably are products of plant materials. The degradation rate is in general slower than for starch based polymers. This degradation rate can be induced by addition of other biodegradable polymers as listed herein. These other polymers may be polymers which can be attacked by microorganism which degrades the shell (coating) composition into smaller pieces giving rise to a bigger surface and thereby faster degradation.

It is very preferred that the coating comprises ethyl cellulose $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_nC_{12}H_{23}O_5$ where *n* can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of β-

anhydroglucose units joined together by acetal linkages Ethyl cellulose comes in different grades which varies in molecular weight and number of ethoxy groups. Grades from 20 – 300 are preferred and these are also commercially available. Grades with high molecular weights are also preferred because they are optimal to give a hard shell (coating). The shell (coating) may comprise one or more ethyl celluloses with different grades, for example one ethyl cellulose with a grade of in the range of 20 to 300, preferably in the range of 20 to 100, more preferably in the range of 20 to 40, such as 20 and another ethyl cellulose with a grade of in the range of 20 to 300, preferably in the range of 50 to 200, more preferably in the range of 80 to 120, such as 100. Ethyl cellulose generally has a glass transition temperature within 129-133°C. These polymers are widely used in food and pharmaceutical industry as coater, stabilizer, matrix former and taste masking and are regarded as non toxic substances.

Cellulose based polymers are in general derived from plant material and may subsequently be modified. Many cellulose based polymers are cheap and give a good hardness when moulded. As derivatives of plants, cellulose based polymers are in general easily decomposable when disposed. These polymers are stabile and inert in solid dosage.

Synthetic polymers

The coating according to the invention may also comprise one or more synthetic polymers. Suitable synthetic polymers for use in the shell (coating) composition may for example be one or more selected from the group consisting of polyamide, polyethylene, polyethylene terephthalate, polypropylene, polyurethane, polyvinyl acetate, polyvinyl alcohol, polyvinyl butural, polyvinyl chloride,), Eudragit L methyl ester, Eudragit RL, Eudragit RS, Eudragit S and Eudragit E. silicone rubber, latex, teflon, copolymers such as ethylene vinyl acetate (EVA), styrene-butadienestyrene (SBS) and styrene-isoprene-styrene (SIS), Polyethylene glycols, polyvinylpyrrolidone, polyethylene oxide (ranging in molecular weights 100,000 to 8,000,000), carboxymethylene (Carbomer) and sugars thereof (e.g. allylsucrose,) and co-polymers of ethylene and propylene oxide (PoloXamer).

Biodegradable polymers

Biodegradation is the process by which microorganisms (microbes such as bacteria, fungi or algae) convert materials into biomass, carbon dioxide and water. Biomass is a general term used to refer to the cells of the microorganisms that are using the material as a carbon source to grow on.

The coating may also comprise one or more biodegradable polymers. Said biodegradable polymer(s) may be one or more selected from the group consisting of starch based polymers as described herein above in this section and cellulose based polymers as described herein above in this section. However the biodegradable polymer may also one or more selected from the group consisting of polyhydroxybutyrate(PHB), polyhydroxyvalerate(PHV), polyhydroxyvalerate-co-hydroxyvalerate(PHV/VH), Polyhydroxyalkanoates(PHA), poly-3-hydroxy-5-phenylvalerate (PHPV), aliphatic polyesters, polycaprolactone(PCL), polylactic acid(PLA), polyglycolic acid(PGA), copolymers or block copolymers of polycaprolactone(PCL), polylactic acid(PLA) and/or polyglycolic acid(PGA), poly-propylene carbonate (PPC), polyester amide (PEA), polybutylene succinate adipate (PBSA), polybutylene adipate co-terephtalate (PBAT) and polybutylene succinate-adipate (PESA).

Copolymers or block copolymers of polycaprolactone (PCL), polylactic acid (PLA) and/or polyglycolic acid (PGA) may for example be selected from the group consisting of poly(lactic-*co*-glycolic acid)(PLGA), polylactic acid and epsilon-caprolactone copolymer(PLA/CL) and polylactic acid/glycolic acid polymers)(PLA/GA), which are all commercially available.

In a preferred embodiment the coating comprises one or more biodegradable polymers selected from the group consisting of polylactic acid (PLA), polycaprolactone (PCL) and polyhydroxybutyrate (PHB), preferably the coating comprises both polylactic acid (PLA), polycaprolactone (PCL) and polyhydroxybutyrate (PHB).

The use of polycaprolactone and other polymers in this group has been increased over the last decade, while the demand for environmental friendly plastics has grown. These polymers are regarded as nontoxic and are already used in parenteral pharmaceutical formulations. The advantages of these polymers are their ability to make a more flexible shell (coating) when moulded in mixture with starch derived polymers. The

somewhat rigid structure of pure thermoplastic starch is improved. Furthermore the polymers are decomposable and disintegrate by microorganisms.

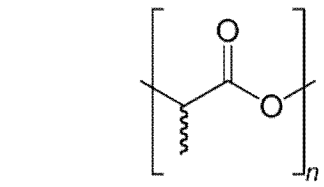
Polylactic acid

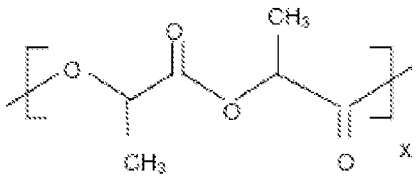
Polylactic acid or polylactide (PLA) is a biodegradable, thermoplastic, aliphatic polyester derived from renewable resources, such as corn starch. PLA belongs to the chemical family of polyesters, such as e.g. ε-caprolactone, PLA-caprolactone in different *ratios 15% PLA to 100% (25, 35, 50, 75, 85%)*, polyglycolides, polyglycolic acids (PGA), poly (lactide-co-glycolide) in different *ratios 15 to 100% PLA (25, 35, 50, 75, 85%)*, poly (lactide-co-glycolide)-OH in different *ratios 15% PLA to 100% (25, 35, 50, 75, 85%)*. Each of the before mentioned polymers exist in L or D- form (making them optically active) and in equal amounts (1:1) of L- and D-forms results in an amorphous mixture, while the L- or D-form all possess a certain degree of crystallinity. The degree of crystallinity is highly related to the mechanical properties (incl. processability), physico-chemical properties related to particularly stability of the polymer. A high degree of crystallinity provides hardness, and possibly, more brittleness. This may affect processability as well as highly crystalline materials have a high melting temperature, hence process temperature, while amorphous esters have a lower melting temperature and thus a lower process temperature.

Moreover, an increased degree of crystallinity implies that the material is more thermodynamically stable, which leads to a longer shelf-life. A lower degree of crystallinity or amorphous materials are usually softer with a lower process temperature. The back-draw of amorphous materials or materials with a lower degree of crystallinity is that their physic-chemical stability is lower as it is in a thermodynamically unstable state.

Regarding PLA, it is necessary to find the optimal degree of crystallinity. Each degree of crystalliinity has different mechanical properties, thus its adhesion to the matrix will vary depending on the degree of crystallinity of the given material (PLA).

The skeletal structure of PLA is shown below.





Due to the chiral nature of lactic acid, several distinct forms of polylactide exist: poly-L-lactide (PLA in its L-form) referred to as PLLA is the product resulting from polymerization of L,L-lactide (also known as L-lactide) and poly-D-lactide (PLA in its D-form) referred to as PDLA is the product resulting from polymerization of L,L-lactide (also known as L-lactide). Furthermore, PLLA and PDLA may be mixed with various ratios of the two stereo forms. As the L-form has stronger mechanical properties than the D-form and the L-form has been used in pharmaceutical products, it is attempted to optimize the blend by adding the D-form to the L-form i.e. in amounts of 5, 10, 20, 30, 40% w/w up to a ratio of 1:1, consequently making the material completely amorphous, however it may also form a highly regular stereo complex with increased crystallinity, since addition of PDLA increases the molecular energy of the mixture by forming a concentration gradient. Depending on the extent/magnitude of the temperature gradient, it may induce slow nucleation and hence crystallization. On the other hand, it may as well induce a nucleation with an incontrollable nucleation rate, which leads to an amorphous state.

PLA in its L-form has a crystallinity of around 35-45%, a glass transition temperature between 35-80 °C and a melting temperature between 173-178 °C.

Due to the structure of PLA, PLA may be exposed to hydrolysis during its path through the gastro-intenstinal tract, however PLA is impermeable and insoluble in aqueous media and in relation to applying PLA as shell (coating) material, it has been demonstrated that the shell (coating) at least macroscopically is intact within the first 48 hours of exposure. Furthermore, the possible degradation product of PLA is merely lactic acid.

Polyglycols

It is also comprised within the present invention that the coating may comprise any of the above-mentioned polyglycols in a form, which erodes at a substantially slower rate than the matrix composition. The coating may thus be one which is eroded in an aqueous medium at a substantially slower rate than the matrix composition comprising the active drug substance, whereby a substantially controlled area of the matrix composition comprising the active drug substance is exposed during erosion and/or release of the matrix composition, and whereby the coating is substantially eroded upon erosion and/or release of the matrix composition comprising the active drug substance. Such a coating will preferably be designed so that its longitudinal erosion rate is substantially the same as the longitudinal erosion and/or release rate of the matrix, whereby the matrix and the coating will erode longitudinally towards the centre of the composition at substantially the same rate. Thus, when the matrix composition has been completely eroded and/or released by the aqueous medium, the coating will also be substantially completely eroded. A matrix composition having such a coating has the obvious advantage of being completely biodegraded upon release of the active drug substance.

A preferred polyglycol to be comprised within the coating is high molecular weight PEO, preferably PEO with an average molecular weight which is significantly higher that the average molecular weight of any of the PEOs contained in the matrix composition. Thus, for any given pharmaceutical composition it is preferred that any PEO contained in the shell (coating) has a significantly higher average molecular weight than any PEO contained in the matrix. Accordingly, it is preferred that the coating comprises one or more PEO with an average molecular weight of at least 900,000, more preferably at least 2,000,000, yet more preferably at least 4,000,000, even more preferably at least 6,000,000, such as approximately 7,000,000, for example 7,000,000.

Mixtures of polymers

As noted herein above the coating may comprise one or more different polymers, and in particular one or more different polymers selected from the group consisting of starch based polymers, cellulose based polymers, synthetic polymers and

biodegradable polymers, in particular from the group consisting of any of the starch based polymers, cellulose based polymers, synthetic polymers and biodegradable polymers described herein above in this section.

In one embodiment of the invention it is preferred that the coating comprises polymers selected from or even that all polymers of the coating are selected from the group consisting of starch based polymer and biodegradable polymers, preferably from the group consisting of any of the starch based polymers and biodegradable polymers described herein above in this section. In particular, biodegradeable polymers such as polycaprolactone, polyhydroxybuturate, polyhydroxyvalerate, polylactic acid, polyhydroxyalkanoates and/or polypropylenecarbonate can be blended with various starches (such as any of the starches described herein above in this section) in different ratios. Suitable mixtures for use in the shell (coating) composition are e.g. polycaprolactone and sago and/or cassava starch, polycaprolactone or polyhydroxybuturate and pre-dried, thermoplastic starch, polycaprolactone and gelatinized starch or thermoplastic starch. Other suitable mixtures are starch-based blends with biodegradable thermoplastic components like polyester amide, polyhydroxybuturate-co-valerate or polybutylene succinate-adipate. Polymers starches can be cross-linked with Maleic anhydride (MA) and dicumyl peroxide (DCP) giving harder items when moulded.

In another embodiment of the invention it is preferred that the coating comprises polymers selected from or even that all polymers of the coating are selected from the group consisting of starch based polymer and synthetic polymers, preferably from the group consisting of any of the starch based polymers and synthetic polymers described herein above in this section. In particular, suitable mixtures for use in the shell (coating) composition are e.g. native granular starch, modified starch, plasticized starch blended or grafted with many synthetic polymers such as polyethylene, polystyrene, Purified Terephthalic acid (PTA), optionally in mixture with aliphatic polyesters or polyvinyl alcohols in different ratios. Polybutylene succinate (PBS), polybutylene succinate adipate in blend with various starches in different ratios are also suitable such as e.g. Polybutylene succinate in mixture with thermoplastic starch, alkylene oxide modified starches in combination with hydrolyzed polyvinyl alcohol.

In yet another embodiment of the invention it is preferred that the coating comprises polymers selected from or even that all polymers of the coating are selected from the group consisting of cellulose based polymers and biodegradable polymers, preferably from the group consisting of any of the cellulose based polymers and biodegradable polymers described herein above in this section. Thus, the coating may for example comprise a mixture of PLA and ethylcellulose. In one embodiment the coating even consists of PLA, ethyl cellulose, one or more plasticizers (such as any of the plasticizers described herein below) and one or more UV stabilisers (such as any of the UV stabilisers described herein below).

UV stabiliser

Radiation from sunlight can accelerate the degradation of plastics, such as the shell (coating) according to the invention. The packaging material to protect the pharmaceutical compositions (e.g. tablets) from direct sunlight may not be enough protection. Especially for a shell (coating) with high concentration of biodegradable polymers, it can be relevant to add UV-stabilizers to the compositions, due to many unsaturated functional groups (eg. carbonyl groups). UV-stabilizers could e.g. be titanium dioxide, metal complexes with sulfurcontaining groups, hindered amine light stabilisers (HALS), benzophenones, benzotriazoles.Titanium dioxide is already widely used in pharmaceutical preparations as pigment and is considered non toxic.

Plasticizer

In addition to above mentioned polymers, the coating may comprise one or more additional components. Thus, the coating may comprise at least one selected from the group consisting of

i) polymers which are soluble or dispersible in water,
ii) plasticizers, and
iii) fillers

in a preferred embodiment the polymers, which are soluble or dispersible in water, are cellulose derivatives, which are soluble or dispersible in water. Thus, the shell (coating) material may comprise one or more plasticizers, preferably, any of the plasticizers described herein above in the section “pharmaceutically acceptable excipients” and/or

any of the plasticizers described below. Preferably, the shell (coating) material comprises one or more of the following plasticizers: Cetostearyl alcohol, castor oil, dibutyl sebacate, polyethylene oxides and/or PoloXamer; however other plasticizers may be contemplated to provide desired material properties.

Other suitable plasticizers may be selected from the group consisting of mono- and di-acetylated monoglycerides, diacetylated monoglycerides, acetylated hydrogenated cottonseed glyceride, glyceryl cocoate, Polyethylene glycols or polyethylene oxides (e.g. with a molecular weight of about 1,000-500,000 daltons), dipropylene glycol salicylate glycerin, fatty acids and esters, phthalate esters, phosphate esters, amides, diocyl phthalate, phthalyl glycolate, mineral oils, hydrogenated vegetable oils, vegetable oils, acetylated hydrogenated soybean oil glycerides, Castor oil, acetyl tributyl citrate, acetyl triethyl citrate, methyl abietate, nitrobenzene, carbon disulfide, β-naphtyl salicylate, sorbitol, sorbitol glyceryl tricitrate, fatty alcohols, cetostearyl alcohol, cetyl alcohol, stearyl alcohol, oleyl alcohol, myristyl alcohol, sucrose octaacetate, alfa-tocopheryl polyethylene glycol succinate (TPGS), tocopheryl derivative, diacetylated monoglycerides, diethylene glycol monostearate, ethylene glycol monostearate, glyceryl monooleate, glyceryl monostearate, propylene glycol monostearate, macrogol esters, macrogol stearate 400, macrogol stearate 2000, polyoxyethylene 50 stearate, macrogol ethers, cetomacrogol 1000, lauromacrogols, nonoxinols, octocinols, tyloxapol, poloxamers, polyvinyl alcohols, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80, polysorbate 85, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesquioleate, sorbitan trioleate, sorbitan tristearate and sucrose esters, amyl oleate, butyl oleate, butyl stearate, diethylene glycol monolaurate, glycerol tributyrate, Flexol B-400, monomeric polyethylene ester, Piccolastic A-5, Piccalastic A-25, Clorafin 40, acetyl tributyl citrate, acetyl triethyl citrate, benzyl benzoate, butoxyethyl stearate, butyl and glycol esters of fatty acids, butyl diglycol carbonate, butyl ricinoleate, butyl phthalyl butyl glycolate, camphor, dibutyl sebacate, dibutyl tartrate, diphenyl oxide, glycerine, HB-40, hydrogenated methyl ester of rosin, methoxyethyl oleate, monoamylphthalate, Nevillac 10, Paracril 26, technical hydroabietyl alcohol, triethylene glycol dipelargonate, solid aliphatic alcohols and mixtures thereof.

In a preferred embodiment, the shell (coating) is made of a material, wherein the concentration of plasticizer is from 0 to 30% w/w.

Accordingly it is preferred that the coating comprises or even consists of one or more plasticizer(s) and one or more polymer(s).

Furthermore, the coating may comprise sweetening agents, flavouring agents and/or colouring agents, which may be any of the sweetening agents, flavouring agents and/or colouring agents described herein above in the section “pharmaceutically acceptable excipients”.

The shell (coating) may be made of a material comprising one polymer, and wherein the concentration of the polymer is from 5 to 100% w/w.

The shell (coating) may be made of a material comprising a mixture of polymers, and wherein the total concentration of polymers is from 70 to 100% w/w.

Preferably, the coating comprises at least 50% w/w, more preferably at least 60% w/w, yet more preferably at least 70% w/w, even more preferably at least 80% w/w in total of polymers substantially insoluble in water as described herein above.

Thus, in preferred embodiments, wherein the coating comprises cellulose derivatives (such as ethyl cellulose), then the coating preferably comprises at least 50% w/w, more preferably at least 60% w/w, yet more preferably at least 70% w/w, even more preferably at least 80% w/w, such as at least 85% w/w, for example 87% w/w cellulose derivative (such as ethyl cellulose).

In a preferred embodiment the coating comprises at the most 19% w/w, more preferably at the most 15% w/w, such as at the most 12% w/w, for example 12% w/w plasticizer (such as cetostearyl alcohol).

Thus, in preferred embodiments, wherein the coating comprises biodegradable polymers (such as polylactic acid), then the coating preferably comprises at least 50% w/w, more preferably at least 60% w/w, yet more preferably at least 70% w/w, even more preferably at least 80% w/w, such as at least 85% w/w, for example 86% w/w biodegradable polymers (such as polylactic acid).

In a preferred embodiment the coating comprises at the most 20% w/w, more preferably at the most 17% w/w, such as at the most 15% w/w, for example 14% w/w plasticizer (polyethylene oxides 200,000 daltons).

Outer coat

In some cases the pharmaceutical composition of the present invention may also comprise an outer coat that fully covers the composition, i.e. the matrix and the coating. Said outer coat may be selected from the group consisting of task masking coats, coats with aqueous moisture barriers and/or oxidative barriers to improve the stability of the composition, and cosmetic coats e.g. a coat containing colouring agents, sweetening agents and/or flavouring agents in order to provide an elegant and palatable tablet and/or to easy distinguishable dose strengths. Especially, it is preferred to coat compositions having different strength with outer coats of different colours so that the different dose strengths are easily distinguished. Preferably, the outer coat is easily soluble in aqueous media in order to provide that the matrix becomes in contact with the surrounding aqueous media via the openings in the coating immediately after administration.

Pharmaceutical compositions

Pharmaceutical compositions according to the present invention preferably comprises an active drug selected from the group consisting of morphine, oxycodone, hydrocodone, hydromorphone, norhydrocordone, oxymorphone, noroxycodone, morphine-6-glucuronode and pharmaceutically acceptable salt thereof, such as morphine sulphate, morphine sulphate pentahydrate, oxycodone hydrochloride, hydrocodone bitartrate and hydromorphone hydrochloride at least one polyglycol selected from the group consisting of polyethyleneglycol and polyethylene oxide and any mixtures thereof, a coat material selected from the group consisting of ethyl cellulose, polylactic acid, polycaprolactone, polyhydroxy butyrate and polyethylene oxide and any mixtures thereof, a plasticizer selected from the group consisting of poloxamer, polyethylene oxide, cetostearyl alcohol, castor oil and dibutyl sebacate and any mixtures thereof, and a filler, which is titanium dioxide.

Pharmaceutical compositions according to the present invention preferably comprises an active drug selected from the group consisting of morphine, oxycodone, hydrocodone, hydromorphone, norhydrocordone, oxymorphone, noroxycodone, morphine-6-glucuronode and pharmaceutically acceptable salt thereof, such as morphine sulphate, morphine sulphate pentahydrate, oxycodone hydrochloride, hydrocodone bitartrate and hydromorphone hydrochloride, at least one polyglycol selected from the group consisting of polyethyleneglycol and polyethylene oxide and any mixtures thereof, at least one plasticizer which is poloxamer, at least one stabilizer selected from the group consisting of mannitol, butylated hydroxytoluene and Vitamin E Polyethylene Glycol Succinate, Eudragit L, Eudragit RL, Eudragit RS, Eudragit E, Eudragit S, and at least one gelling agent selected from the group consisting of carrageenan and hydroxypropylmethylcellulose, a coat material selected from the group consisting of ethyl cellulose, polylactic acid, polycaprolactone and polyethylene oxide and any mixtures thereof, a plasticizer selected from the group consisting of polyethylene oxide and cetostearyl alcohol and any mixtures thereof and a filler, which is titanium dioxide.

In cases where the pharmaceutical composition also comprises an outer coat, the pharmaceutical compoisition according to the present invention comprises an active drug selected from the group consisting of morphine, oxycodone, hydrocodone, hydromorphone, norhydrocordone, oxymorphone, noroxycodone, morphine-6-glucuronode and pharmaceutically acceptable salt thereof, such as morphine sulphate, morphine sulphate pentahydrate, oxycodone hydrochloride, hydrocodone bitartrate and hydromorphone hydrochloride, at least one polyglycol selected from the group consisting of polyethyleneglycol and polyethylene oxide and any mixtures thereof, a coat material selected from the group consisting of ethyl cellulose, polylactic acid, polycaprolactone, polyhydroxy butyrate and polyethylene oxide, and any mixtures thereof, a plasticizer selected from the group consisting of poloxamer, polyethylene oxide, cetostearyl alcohol, castor oil and dibutyl sebacate and any mixtures thereof, a filler, which is titanium dioxide, and an outer coat selected from the group consisting of task masking coats, coats with aqueous moisture barriers and/or oxidative barriers, cosmetic coats, and any mixtures thereof.

In a very preferred embodiment the pharmaceutical composition comprises morphine sulphate as the active drug, a mixture of polyethylene oxide 200,000 and polyethylene oxide 300,000 as polyglycol, poloxamer as plasticizer, mannitol as stabilizer, a mixture of carrageenan and hydroxypropylmethylcellulose as gelling agent, butylated hydroxytoluene as antioxidant and a mixture of polylactic acid and polyethylene oxide as the coating.

In a very preferred embodiment the pharmaceutical composition comprises morphine sulphate as the active drug, a mixture of polyethylene oxide 200,000 and polyethylene oxide 300,000 as polyglycol, poloxamer as plasticizer, mannitol as stabilizer, butylated hydroxytoluene as antioxidant and a mixture of polylactic acid and polyethylene oxide as the coating.

In another very preferred embodiment the pharmaceutical composition comprises morphine sulphate as the active drug, polyethylene oxide 300,000 as polyglycol, poloxamer as plasticizer, a mixture of mannitol and butylated hydroxytoluene as stabilizer and a mixture of ethylcellulose, cetostearyl alcohol and titanium dioxide as the coating.

In another very preferred embodiment the pharmaceutical composition comprises morphine sulphate as the active drug, polyethylene oxide 200,000 as polyglycol, a mixture of mannitol and Vitamin E Polyethylene Glycol Succinate as stabilizer and a mixture of ethylcellulose, cetostearyl alcohol and titanium dioxide as the coating.

In a very preferred embodiment the pharmaceutical composition comprises oxycodone hydrochloride as the active drug, a mixture of polyethylene oxide 200,000 and polyethylene oxide 300,000 as polyglycol, poloxamer as plasticizer, Eudragit as stabilizer, hydroxypropylmethylcellulose as gelling agent, butylated hydroxytoluene as antioxidant and a mixture of polylactic acid and polyethylene oxide as the coating.

In a very preferred embodiment the pharmaceutical composition comprises oxycodone hydrochloride as the active drug, a mixture of polyethylene oxide 200,000 and polyethylene oxide 300,000 as polyglycol, poloxamer as plasticizer, Eudragit as stabilizer, butylated hydroxytoluene as antioxidant and a mixture of polylactic acid and polyethylene oxide as the coating.

In another very preferred embodiment the pharmaceutical composition comprises oxycodone hydrochloride as the active drug, a mixture of polyethylene oxide 200,000 and polyethylene oxide 300,000 as polyglycol, poloxamer as plasticizer, Eudragit as stabilizer, butylated hydroxytoluene as antioxidant and a mixture of ethylcellulose, cetostearyl alcohol and titanium dioxide as the coating.

In a very preferred embodiment the pharmaceutical composition comprises hydrocodone bitartrate as the active drug, a mixture of polyethylene oxide 200,000 and polyethylene oxide 300,000 as polyglycol, poloxamer as plasticizer, hydroxypropylmethylcellulose as gelling agent, butylated hydroxytoluene as antioxidant and a mixture of polylactic acid and polyethylene oxide as the coating.

In a very preferred embodiment the pharmaceutical composition comprises hydrocodone bitartrate as the active drug, a mixture of polyethylene oxide 200,000 and polyethylene oxide 300,000 as polyglycol, poloxamer as plasticizer, butylated hydroxytoluene as antioxidant and a mixture of polylactic acid and polyethylene oxide as the coating.

In another very preferred embodiment the pharmaceutical composition comprises hydrocodone bitartrate as the active drug, a mixture of polyethylene oxide 200,000 and polyethylene oxide 300,000 as polyglycol, poloxamer as plasticizer, butylated hydroxytoluene as stabilizer and a mixture of ethylcellulose, cetostearyl alcohol and titanium dioxide as the coating.

In a very preferred embodiment the pharmaceutical composition comprises hydromorphone hydrochloride as the active drug, a mixture of polyethylene oxide 200,000 and polyethylene oxide 300,000 as polyglycol, poloxamer as plasticizer, hydroxypropylmethylcellulose as gelling agent, butylated hydroxytoluene as antioxidant and a mixture of polylactic acid and polyethylene oxide as the coating.

In a very preferred embodiment the pharmaceutical composition comprises hydromorphone hydrochloride as the active drug, a mixture of polyethylene oxide 200,000 and polyethylene oxide 300,000 as polyglycol, poloxamer as plasticizer,

butylated hydroxytoluene as antioxidant and a mixture of polylactic acid and polyethylene oxide as the coating.

In another very preferred embodiment the pharmaceutical composition comprises hydromorphone hydrochloride as the active drug, a mixture of polyethylene oxide 200,000 and polyethylene oxide 300,000 as polyglycol, poloxamer as plasticizer, butylated hydroxytoluene as antioxidant and a mixture of ethylcellulose, cetostearyl alcohol and titanium dioxide as the coating.

Administration

The pharmaceutical composition according to the invention is preferably designed for oral administration. More preferably, oral intake is by swallowing one or more intact units of the pharmaceutical composition.

Due to the possibility of controlling the release profile of the active drug substance, the pharmaceutical compostion may be adapted for oral administration 1-6 times a day, normally 1-4 times daily such as 1-3 times, 1-2 times or 1 times daily, for example oral administration only once or twice daily.

In one embodiment the pharmaceutical composition is prepared in dosage units, such that a dosage of the active drug substance is comprised within one unit, wherein dosages are preferably are for administration with an interval of in the range of 20 to 28 hours, preferably 24 hours. The pharmaceutical composition may in a preferred embodiment be in the form of tablets and thus even more preferably each tablet comprises one dosage of the active drug substance, wherein dosages preferably are for administration with an interval of in the range of 20 to 28 hours, preferably 24 hours.

Furthermore, the pharmaceutical composition according to the invention is preferably prepared for continued administration, wherein dosages are preferably administered with an interval of in the range of 20 to 28 hours, preferably 24 hours. Interestingly, the pharmaceutical compositions according to the invention are effective for at least 24 hours after intake. In particular, in embodiments of the invention, wherein the pharmaceutical composition are for treatment of pain, then the pharmaceutical compositions relieve or ameliorate pain for at least 24 hours after intake.

The pharmaceutical composition according to the invention is preferably prepared for continued administration, and accordingly, the composition is prepared for repeated administration with an interval of in the range of 20 to 28 hours, preferably 24 hours between administrations. More preferably, the continued administration is administration over several days with an interval of in the range of 20 to 28 hours, preferably 24 hours between administrations, preferably at least 3 days, more preferably at least 4 days, even more preferably at least 5 days, yet more preferably at least 6 days, even more preferably at least 7 days, for example at least 9 days, such as at least 11 days, for example for at least 14 days, such as for at least 30 days. Continued administration is preferably at least administration for a sufficient number of days to arrive at steady state in the individual to whom the pharmaceutical composition of the invention is being administered.

The pharmaceutical composition of the invention is prepared for administration of a given dosage. The dosage will be dependent on the individual to whom the pharmaceutical composition of the invention is being administered and the active drug substance.

In general, the dosage for each administration, wherein dosages preferably are prepared for administration with an interval of in the range of 20 to 28 hours, preferably 24 hours, is in the range of 1 to 1000 mg, such as in the range of 10 to 1000 mg, for example in the range of 30 to 1000 mg, such as in the range of 1 to 750 mg, for example in the range of 1 to 500 mg, such as in the range of 1 to 250 mg, preferably in the range of 10 to 500 mg, more preferably in the range of 10 to 240 mg of said active drug substance.

In particular, when the active drug substance is an opioid, and more particular when the active drug substance is morphine or a pharmaceutically acceptable salt thereof, then the daily dosage is in the range of 1 to 1000 mg, such as in the range of 10 to 1000 mg, for example in the range of 15 to 1000 mg, such as in the range of 1 to 750 mg, for example in the range of 1 to 500 mg, such as in the range of 1 to 250 mg, preferably in the range of 10 to 500 mg, more preferably in the range of 15 to 240 mg, for example in the range of 15 to 200 mg, such as in the range of 30 to 200 mg, for example 15, 20, 30,45, 60, 75, 90, 100, 120, 140, 160, 180 or 200 mg..

In particular, when the active drug substance is an opioid, and more particular when the active drug substance is oxycodone or a pharmaceutically acceptable salt thereof, then the daily dosage is in the range of 1 to 1000 mg, such as in the range of 10 to 1000 mg, for example in the range of 30 to 1000 mg, such as in the range of 10 to 500 mg, for example in the range of 10 to 250 mg, such as in the range of 10 to 200 mg, for example in the range of 10 to 50, preferably in the range of 10 to 500 mg, more preferably in the range of 10 to 160 mg, even more preferred in the range of 10 to 100 mg, such as in the range of 10 to 80 mg, for example in the range of 20 to 80 mg, such as in the range of 40 to 80 mg, preferably in the range of 30 to 50 mg, such as for example 10, 15, 20, 30, 40 50, 60, 70, 80, 90, 100 or 160 mg.

In particular, when the active drug substance is an opioid, and more particular when the active drug substance is hydrocodone or a pharmaceutically acceptable salt thereof, then the daily dosage is in the range of 1 to 1000 mg, such as in the range of 10 to 1000 mg, for example in the range of 15 to 1000 mg, such as in the range of 1 to 750 mg, for example in the range of 1 to 500 mg, such as in the range of 1 to 250 mg, for example in the range of 1 to 100 mg, such as in the range of 1 to 30 mg, preferably in the range of 10 to 500 mg, more preferably in the range of 10 to 200 mg, such as in the range of 10 to 160 mg, for example in the range of 10 to 30 mg, more preferably in the range of 20 to 160 mg, such as in the range of 20 to 80 mg, for example 10, 20 30, 40, 50, 60, 70, 80, 100, 120, 140, 160 mg.

In particular, when the active drug substance is an opioid, and more particular when the active drug substance is hydromorphone or a pharmaceutically acceptable salt thereof, then the daily dosage is in the range of 1 to 1000 mg, such as in the range of 1 to 500 mg, for example in the range of 1 to 250 mg, such as in the range of 1 to 100 mg, preferably in the range of 2 to 250 mg, more preferably in the range of 2 to 100 mg, for example in the range of 4 to 100 mg, such as in the range of 4 to 80 mg, preferably in the range of 4 to 64 mg, for example, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 40, 48, 56, 64, 72 or 80 mg.

Above-mentioned dosages are in particular relevant when the individual in need of treatment is a human being, such as an adult human being.

Individuals in need of treatment

The pharmaceutical composition of the invention is prepared for administration to an individual in need thereof. Said individual is preferably a mammal, more preferably a human being.

Preferably, the pharmaceutical composition is for continuous treatment of pain and accordingly, the individual in need of treatment is an individual suffering from pain, preferably an individual suffering from pain for a prolonged period of time requiring continuous treatment, wherein continuous treatment is as described in this section above.

In embodiments of the invention, wherein the active drug substance is an opioid, such as oxycodone, hydrocodon, morphine or pharmaceutically acceptable salts thereof, then the pharmaceutical compositions are suitable for treatment of moderate to severe pain such as severe pain.

Examples of individuals, who may benefit from treatment with the pharmaceutical compositions according to the invention includes for example the following:

The individual may be an individual suffering from chronic pain, such as moderate to severe chronic pain.

The individual may be an individual suffering from cancer and the pharmaceutical composition may be useful for continuous treatment of pain or even moderate to severe pain, such as severe pain in an individual suffering from cancer.

The individual may also be an individual who has suffered a moderate to severe injury.

The individual may be an individual suffering from pain associated with surgical conditions, such as a pre-surgical individual (an individual in need of surgery) or a post surgical individual (an individual who has undergone surgery).

The individual may also be an individual suffering from or having suffered from a myocardial infarction, sickle cell crises, kidney stone or severe back pain.

The individual may also be an individual suffering from degenerative pain, herniated disc pain, fibromyalgia, neuropatic pain and/or nociceptive pain.

The individual may also be an individual suffering from arthritis, such as arthritis osteo, arthritis rheumatoid, arthritis psoriatica and/or arthritis urica.

Pharmacokinetics

It is an important feature of the pharmaceutical compositions according to the present invention that they are useful for continued administration with 20 to 28 hours interval between individual administrations and accordingly it is preferred that the pharmaceutical compositions of the invention have the pharmacokinetic profiles described in this section. Accordingly, upon administration the pharmaceuticel compositions according to the invention preferably give rise to a ratio between trough (or C_{24} in embodiments wherein the the pharmaceutical composition is for continued administration with an interval of 24 hours between individual administrations) and C_{max}, which is sufficiently high. It is also preferred that the pharmaceutical compositions of the invention upon administration to an individual does not reach the maximal concentration of the active drug substance too soon and also that 50% of C_{max} is not reached too soon after the C_{max} or even that 50% of C_{max} is never reached because the trough/C_{max} ratio is >0.5. It is furthermore preferred that the pharmaceutical compositions when administered frequently enough to reach steady state, the trough is sufficiently high to ensure continuous efficacy over the entire administration period.

An individual is in steady state with regard to a particular active drug substance when the plasma concentration level after one dosing is the same within the standard deviation as the plasma concentration level after the following dosing. Thus, for pharmaceutical compositions for continued administration with 24 hours interval between individual administrations then at steady state $AUC_{(0\text{-}24h)d}=AUC_{(0\text{-}24h)d+1}$+/- the standard deviation, and $C_{max(0\text{-}24h)d}=C_{max(0\text{-}24h)d+1}$ +/- the standard deviation, where d is day. AUC refers to the “area under the curve” and is a measurement for the plasma concentration over the entire dosing interval.

In order to determine steady state parameters the pharmaceutical compositions are preferably administered for a sufficient amount of time to reach steady state. However theoretical steady state parameters may be determined by a simulation based on information on serum concentration of an active drug substance or its metabolites after a single administration. Such a similation may for example be prepared as described in Example 1 or Example 2 herein below.

Thus, in one preferred embodiment of the invention then upon administration of the pharmaceutical compositions with a length of the range of 7.5 to 15 mm, preferably 8 to 10 mm said compostions comprising an active drug substance (preferably an analgesic, such as an opioid, for example morphine, oxycodone or hydrocodone) according to the invention, then average steady state trough (such as the theorectical steady state trough) in respect of the active drug substance is preferably at least 30%, more preferably at least 35%, even more preferably at least 40%, such as in the range of 30% to 80%, for example in the range of 35 to 80%, such as in the range of 40 to 80% of average steady state C_{max} in respect of the active drug substance. Aforementioned % is in particularly preferred when the active drug substance is an opioid, preferably hydrocodone.

In another preferred embodiment of the invention then upon administration of the pharmaceutical compositions with a length of the range of 7.5 to 15 mm, preferably 8 to 10 mm said compostions comprising an active drug substance (preferably an analgesic, such as an opioid, for example morphine, oxycodone or hydrocodone) according to the invention, then average steady state trough (such as the theorectical steady state trough) in respect of the active drug substance is preferably at least 20%, more preferably at least 25%, even more preferably at least 30%, such as in the range of 20 to 80%, for example in the range of 25 to 80%, such as in the range of 30 to 80% of average steady state C_{max} in respect of the active drug substance. Aforementioned % is in particularly preferred when the active drug substance is an opioid, preferably oxycodone.

In yet another embodiment of the invention then upon administration of the pharmaceutical compositions with a length of the range of 7.5 to 15 mm, preferably 7.5 to 10 mm said compostions comprising an active drug substance (preferably an analgesic, such as an opioid, for example morphine, oxycodone or hydrocodone)

according to the invention then steady state C_{24} in respect of the active drug substance is preferably at least 20%, more preferably at least 25%, even more preferably at least 30%, such as at least 40%, for example at least 50% of steady state C_{max} in respect of the active drug substance. Aforementioned % is in particularly preferred when the active drug substance is an opioid, preferably morphine.

Said average steady state trough is preferably based on measurements in at least 5 different individuals, preferably 5 different human beings. Similarly, said said average steady state trough is preferably based on measurements in at least 5 different individuals, preferably 5 different human beings.

In respect of the pharmaceutical compositions formulated for continued administration with 24 hours interval between administrations, then trough will in general be similar too, or even identical to steady state C_{24}.

Upon administration of the pharmaceutical compositions according to the invention (in particular such compositions which have a length of 7.5 to 15 mm, preferably 8 to 10 mm), C_{min} is preferably not reached too early after C_{max}, thus preferably C_{min} is reached no earlier than half way through a given dosing interval in a steady state individual. Thus, for the pharmaceutical compositions of the invention comprising an active drug substance (preferably an analgesic, such as an opioid, for example morphine, oxycodone or hydrocodone), which are prepared for continued administration with in the range of 20 to 28 hours, preferably 24 hours interval between administrations, then C_{min} is preferably reached no earlier than 10 hours after, preferably no earlier than 12 hours, more preferably no earlier than 14 hours, even more preferably at least 16 hours, yet more preferably at least 18 hours after last administration to an individual, such as a human being. Preferably, the time when C_{min} is reached is determined as an average based on measurements in at least 5 different individuals, such as 5 human beings.

The plasma concentration usually reaches 50% of steady state C_{max} twice after each administration. Once at the time when plasma concentration is rising soon after administration (referred to 1st point) and once when plasma concentration is decreasing after the peak concentration has been reached (referred to as 2nd point).

For continued administration with in the range of 20 to 28 hours, preferably 24 hours interval between administrations of the pharmaceutical compositions of the invention comprising an active drug substance (preferably an analgesic, such as an opioid, for example morphine, oxycodone or hydrocodone), then preferably the 2nd point where the plasma concentration reaches 50% of steady state C_{max} should not be reached too fast or even not at all. Interestingly, the pharmaceutical compositions according to invention, in particular such compositions which have a length of in the range of 7.5 to 15 mm, preferably in the range of 8 to 15mm solves this problem. Additionally, fast onset may be an advantage and this would be supported by a profile with a short time to the 1st point where the plasma concentration reaches 50% of steady state C_{max}. Theoretically, if the profile becomes really protacted/blunted, the 50% of steady state C_{max} may never be reached and another marker i.e. 75% of steady state C_{max} could be chosen to define the period for the passing the first and second time.

Interestingly, the pharmaceutical compositions according to invention are able to both provide a profile with a very high minimum plasma concentration (C_{min}) with a long time between the first and second time of passing a fraction of C_{max} (i.e. 50 or 75%) and as compared to other controlled release formulations. Thus, the 2nd point where a concentration of 50% of steady state C_{max} is reached is preferably no earlier than 4 hours, more preferably no earlier than 6 hours, even more preferably no earlier than 8 hours, yet more preferably no earlier than 10 hours, such as no earlier than 12 hours, for example no earlier than 14 hours, such as no earlier than 15 hours after last administration of the pharmaceutical compositions according to the invention to a steady state individual. For example the 2nd point where a concentration of 50% of steady state C_{max} is reached is preferably in the range of 4 to 48 hours, more preferably in the range of 6 to 48 hours, even more preferably in the range of 8 to 48 hours, yet more preferably in the range of 10 to 48 hours, for example in the range of 12 to 48 hours, such as in the range of 14 to 48 hours, for example in the range of 4 to 34 hours, such as in the range of 6 to 34 hours, for example in the range of 8 to 34 hours after last administration of the pharmaceutical compositions accrding to the invention to a steady state individual. In some embodiments of the invention the 2nd point where the plasma concentration reaches 50% of steady state C_{max} is not reached withint the interval between administrations and according to the pharmaceutical compositioned is administrated continuedly, then the 2nd point where the plasma concentration reaches 50% of steady state C_{max} is not reached. Preferably, the time to 50% of C_{max} is

determined based on measurements in least 5 different individuals, such as human beings.

For continued administration with in the range of 20 to 28 hours, preferably 24 hours interval between administrations of the pharmaceutical compositions of the invention comprising an active drug substance (preferably an analgesic, such as an opioid, for example morphine, oxycodone or hydrocodone), then preferably the 1st point where the plasma concentration reaches 50% of steady state C_{max} should not be reached too fast. Interestingly, the pharmaceutical compositions according to invention, in particular such compositions which have a length of in the range of 7.5 to 15 mm, preferably 8 to 10 mm solve this problem. Thus, the 1st point where a concentration of 50% of steady state C_{max} is reached is preferably no earlier than 30 min., more preferably no earlier than 45 min., such as in the range of 45 to 150 min, for example in the range of 45 to 120 min, such as in the range of 45 to 90 min. after last administration of the pharmaceutical compositions according to the invention to a steady state individual. For example the 1st point where a concentration of 50% of steady state C_{max} is reached is preferably in the range of 0.25 to 2 hours, more preferably in the range of 0.5 to 2 hours after last administration of the pharmaceutical compositions according to the invention to a steady state individual. Preferably, the time to 50% of C_{max} is determined based on measurements in least 5 different individuals, such as human beings.

T_{max} of the pharmaceutical compositions according to the invention comprising an active drug substance (preferably an analgesic, such as an opioid, for example morphine, oxycodone or hydrocodone) is preferably in the range of 3 to 10 hours, more preferably in the range of 4 to 7 hours, for example in the range of 4 to 6 hours after last administration to a steady state individual. Preferably, T_{max} is based on an average of measurements in at least 5 different individuals, preferably 5 human beings.

It is also preferred that after administration of the pharmaceutical compositions with a length of in the range of 7.5 to 15 mm, preferably 8 to 10 mm comprising 30 mg of an active drug substance (preferably an analgesic, such as an opioid, for example morphine) according to the invention, then steady state AUC_{0-24h} in respect of the active drug substance is preferably at least 200 nmol*h/L, more preferably at least 300 nmol*h/L, for example at least 350 nmol*h/L, such as in the range of 200 to 1000 nmol*h/L, for example in the range of 300 to 1000 nmol*h/L, such as in the range of 300 to 500 nmol*h/L, for example in the range of 300 to 400 nmol*h/L.

It is also preferred that after administration of the pharmaceutical compositions with a length of in the range of 7.5 to 15 mm, preferably 8 to 10 mm comprising 100 mg of an active drug substance (preferably an analgesic, such as an opioid, for example morphine) according to the invention, then steady state AUC_{0-24h} in respect of the active drug substance is preferably at least 400 nmol*h/L, more preferably at least 600 nmol*h/L, even more preferably at least 800 nmol*h/L, yet more preferably at least 1000 nmol*h/L, for example at least 1200 nmol*h/L, such as at least 1400 nmol*h/L, for example in the range of 1000 to 3000 nmol*h/L, such as in the range of 1000 to 2000 nmol*h/L, for example in the range of 1200 to 2000 nmol*h/L, such as in the range of 1200 to 1600 nmol*h/L, for example in the range of 1400 to 1600 nmol*h/L.

It is also preferred that after administration of the pharmaceutical compositions with a length of in the range of 7.5 to 15 mm, preferably 8 to 10 mm comprising 20 mg of an active drug substance (preferably an analgesic, such as an opioid, for example hydrocodone) according to the invention, then AUC_{0-42h} in respect of the active drug substance is preferably at least 800,000 pmol*h/mL, more preferably at least 900,000 pmol*h/mL, even more preferably at least 940,000 pmol*h/mL, for example in the range of 800,000 to 1200,000 pmol*h/mL, such as in the range of 900,000 to 1200,000 pmol*h/mL, for example in the range of 940,000 to 1100,000 pmol*h/mL.

It is also preferred that after administration of the pharmaceutical compositions with a length of in the range of 7.5 to 15 mm, preferably 8 to 10 mm comprising 40 mg of an active drug substance (preferably an analgesic, such as an opioid, for example oxycodone) according to the invention, then AUC_{0-48h} in respect of the active drug substance is preferably at least 400 nmol*h/L, more preferably at least 450 nmol*h/L, even more preferably at least 500 nmol*h/L, for example in the range of 400 to 1000 nmol*h/L, such as in the range of 450 to 1000 nmol*h/L, for example in the range of 500 to 1000 nmol*h/L, such as in the range of 500 to 600 nmol*h/l.

Preferably, AUC_{0-24h} and AUC_{0-48h} are determined as an average based on meaurements in at least 5 different individuals, for example 5 human beings.

It is furthermore preferred that the MRT (mean residence time) is a sufficiently long. Thus, is it preferred that upon continued administration with in the range of 20 to 28

hours, preferably 24 hours interval between administrations of the pharmaceutical compositions of the invention comprising an active drug substance (preferably an analgesic, such as an opioid, for example morphine, oxycodone or hydrocodone), then preferably the MRT is at least 11 hours, preferably at least 12 hours, more preferably at least 12 hours, even more preferably at least 13 hours, yet more preferably at least 14 hours, even more preferably at least 14 hours, yet more preferably at least 15 hours, for example in the range of 11 to 30 hours, preferably in the range of 12 to 30 hours, more preferably in the range of 12 to 30 hours, even more preferably in the range of 13 to 30 hours, yet more preferably in the range of 14 to 30 hours, even more preferably in the range of 14 to 30 hours, yet more preferably in the range of 15 to 30 hours.

It is of great importance that controlled release formulations of active drug substances, releases the active ingredient in a manner that the desired clinical efficacy is achieved. For treatment of pain, it is important, that the pain is relieved continuously throughout the treatment period.

As mentioned herein above in the section “Active drug substance” the pharmaceutical compositions according to the present invention are in particular useful when the active drug substance is an opioid. The present invention discloses that important factors in creating a desirable plasma concentration curve includes the length and cross section area of the pharmaceutical compositions. Also the matrix composition may be of importance.

For pharmaceutical compositions prepared for continued administration with 5 to 20 hours, preferably with in the range of 7 to 20 hours, such as 6 to 18 hours, more preferably with in the range of 10 to 20 hours, for example with in the range of 10 to 18 hours, such as with in the range of 10 to 16 hours, for example 12 hours interval between individual administrations, then the pharmacokinetic profile may be different.

Thus for such formulations it is preferred that upon administration then average steady state trough (such as the theorectical steady state trough) in respect of the active drug substance is preferably in the range of 5 to 40%, more preferably in the range of 5 to 30%, even more preferably in the range of 10 to 30%, for example in the range of 10 to 20%, such as in the range of 14 to 27%, for example in the of 8 to 20% of average steady state C_{max} in respect of the active drug substance. This is in particular relevant

for pharmaceutical compositions with a length of the range 4 to 8 mm, preferably in the range of 5.5 to 8 mm, such as in the range of 6 to 7.5 mm, said compostions comprising an active drug substance (preferably an analgesic, such as an opioid, for example morphine, oxycodone or hydrocodone) according to the invention.

For such formulations it is furthermore preferred that upon continued administration with in the range of 7 to 20 hours, such as 12 hours between individual administrations then MRT is in the range of 8 to 15, preferably in the range of 10 to 15, such as in the range of 11 to 14.5 hours. This is in particular relevant for pharmaceutical compositions with a length of the range 4 to 8 mm, preferably in the range of 5.5 to 8 mm, such as in the range of 6 to 7.5 mm, said compostions comprising an active drug substance (preferably an analgesic, such as an opioid, for example morphine, oxycodone or hydrocodone) according to the invention.

For continued administration with in the range of 7 to 20 hours, preferably 12 hours interval between administrations of the pharmaceutical compositions of the invention comprising an active drug substance (preferably an analgesic, such as an opioid, for example morphine, oxycodone or hydrocodone), then preferably the 2nd point where the plasma concentration reaches 50% of steady state C_{max} should be reached in the range of 4 to 6 hours. This is in particular relevant for pharmaceutical compositions with a length of the range 4 to 8 mm, preferably in the range of 5.5 to 8 mm, such as in the range of 6 to 7.5 mm.

It is another important feature of the present invention that the Protraction index lies as closely to 1 as possible, because such value of the index denotes that the pharmacological profile is very flat. In such cases the plasma concentration is substantially constant throughout the 24 hour dosing interval, i.e. throughout the period between two consecutive administrations. Hence, the Protraction index is preferably at least 0.2, such as at least 0.25, more preferred at least 0.30, for example at least 0.35, such as at least 0.40, for example at least 0.45, for example at least 0.50, such as at least 0.55, for example at least 0.60, such as at least 0.70, for example at least 0.80.

Drug abuse

Abuse of active drug substances and in particular opioids constitutes a problem. The pharmaceutical compositions according to the present invention have a reduced risk for drug abuse and/or alcohol induced dose dumping.

In order to ensure that the use of a composition mitigates alcohol induced dose dumping, the ratio (R50) between $t_{50\%}$ w/w (40% w/w ethanol in medium 1) and $t_{50\%}$ w/w (medium 1) is 1 or more. $t_{50\%}$ w/w (medium 1) denotes the time it takes to release 50% w/w of the active drug substance from the pharmaceutical composition in an in vitro dissolution test according to USP 30, NF 25, (711), Apparatus 2, paddle employing water optionally buffered to a specific pH as dissolution medium (medium 1), and $t_{50\%}$ w/w (40% w/w ethanol in medium 1) denotes the time it takes to release 50% w/w of the active drug substance from the pharmaceutical composition in an in vitro dissolution test according to USP 30, NF 25, (711), Apparatus 2, paddle employing 40% w/w ethanol in medium 1 as dissolution medium.

In a specific embodiment, the ratio R50 is at the most 5 such as at the most 4, at the most 3 or at the most 2. Notably, the ratio R50 is from 1 to 1.5 such as, e.g., from 1 to 1.4, from 1 to 1.3, from 1 to 1.2, from 1 to 1.1, from 1 to 1.05, about 1, from 1 to 0.95 or from 1 to 0.9.

The same may also apply for ratios determined e.g. when 25%, 30%, 40%, 60%, 70%, 80%, 90% and/or 95% w/w has been released, the conditions being as described above.

The likelihood of a composition being subject to drug abuse may for example be tested by different tests:

1. Crushing test
2. Melting test
3. Extraction/dissolving test
4. Injection test

In the crushing test, the composition is subjected to crushing using a hammer or an

apparatus designed to measure the hardness of an oral dosage form. A suitable apparatus is specified in Ph. Eur. If the composition disintegrates into particles, then it may be possible to dissolve or suspend these particles and use them for abuse purposes. Moreover, if it is possible to disintegrate (crunch) the composition, then it is possible to use the powder for snorting or sniffing and in this way abuse the composition, however, if it is not possible to crush the composition in this test, then there will be no particles to use for such abuse purposes. Thus, preferably, the compositions of the invention can not be crushed into particles.

In the melting test, the composition is subjected to heating e.g. on a spoon or by exposure to microwave induced heating. If the composition is suitable for abuse purposes, the composition should become so liquid that it is possible to inject it without being too hot. However, if this is not the case, the composition is not suitable for abuse purposes. Accordingly, the compositions of the invention preferably do not become so liquid that it is possible to inject them upon heating.

In the extraction test it is tested whether it is possible to extract the active drug substance from the composition by means of normally available organic solvents. If it is possible to dissolve the composition then if may be possible to misuse the drug. On the contrary, if it is not possible, then it is likely that the composition cannot be misused. Thus, preferably, it is not possible to dissolve the pharmaceutical compositions of the invention faster than in a dissolution medium which may be either ethanol or phosphate buffer pH 6.8.

In the Injection test, the composition is dissolved in 2 ml water possibly after extensive heating. The preparation is put into a syringe and the time of passage through a fitted 0.5 mm needle is measured upon a weight applied to the syringe of 3 kg. The time of passage of the pharmaceutical compositions according to the invention is preferably at least 10 sec. more preferably at least 15 sec. yet more preferably at least 20 sec.

The pharmaceutical compositions of the invention are preferably of such nature that it is basically impossible to abuse either by crushing, melting, extraction, dissolving or similar. Furthermore, the pharmaceutical composition exhibits decreased (or essentially the same) release rate in alcohol containing media as compared to a purely aqueous media. The release rate from the pharmaceutical composition will depend on several

parameters such as in an unlimited list: solubility of the polyglycol, active drug substance and the excipients, the wetability of the composition, the diffusion of water into the composition, the enthalpy of melting and enthalpy of solubilization, and the disentanglement rate of the polyglycol during dissolution. Controlled release dosage forms are used to extend the release from the dosage form for an extended period of time. In the present context the term "controlled release" is used to designate a release a desired rate during a predetermined release period.

Examples

The invention is further illustrated in the following non-limiting examples.

Example 1

A single-center, single dose, randomised, open label; exploratory, 5-way cross-over study evaluating the pharmacokinetic profile of various Egalet® Hydrocodone Test Formlations in healthy volunteers under fasting conditions

This study is also referred to as HC-EG-001 herein.

Objectives:

The objectives of this single dose pharmacokinetic study was to investigate the pharmacokinetics of Egalet® hydrocodone, focusing on AUC and obtaining 100% bioavailability relative to an immediate release hydrocodone formulation Norco® 10 mg hydrocodone-325 mg acetaminophen. The study should provide plasma profiles for each of the test formulations and form a basis for the selection of a formulation/geometry suited for twice daily dosing and a formulation candidate suited for once daily dosing.

The secondary objective of this study was to evaluate the safety and tolerability of Egalet® hydrocodone formulations.

Rationale:

Optimisation of the dosage regimen for patients suffering from moderate-to-severe pain by offering a controlled-release formulation for dosing twice a day possibly only once a day

1) Offering a single agent hydrocodone product for which the therapeutic potential has been neglected, having the advantage of being independently titrated, not limited by adverse or toxic actions related to another active analgesic ingredient.
2) Offering a pure hydrocodone product in a high strength
3) Providing a drug preferably classified as abuse resistant, lowering the potential of its abuse.

Design:

The study was a single centre, open-label, single-dose, randomised, 4-way crossover, comparative Phase I study, performed under fasting conditions in accordance with regulatory requirements of bioequivalence limits (80-125% confidence interval) in 28 healthy subjects.

This study is a single-dose study in which the pharmacokinetic profile of four different Egalet® hydrocodone test-formulations was evaluated and compared to a marketed, reference listed drug (NORCO® 10/325). At this time, 2 different chemical formulations (with medium and a high drug load respectively) and 3 different geometries (6.0 mm, 7.5 mm, and 9.0 mm) were developed. For the medium load formulation, all three geometries were available, whereas only the 9 mm was available in the high load formulation.

Hydromorphone contributes to the total analgesic effect and norhydrocodone is an abundant metabolite. Therefore, for the purposes of this study, hydrocodone, hydromorphone and norhydrocodone were measured in plasma samples.

Investigational Products:

Treatment A: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 6.0 mm.
Treatment B: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 7.5 mm.
Treatment C: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation A, 9.0 mm.
Treatment D: 1 x 20 mg Egalet® hydrocodone PR tablet of Formulation B, 9.0 mm.
Treatment E (Reference): 1 x NORCO® 10/325 IR tablet (containing 10 mg hydrocodone bitartrate and 325 mg acetaminophen).

The compositions of the products are shown herein below in Example 3, Tables 16 and

17.

Methodology:

The 28 healthy, adult subjects enrolled in this study were members of the community at large. Subjects were judged eligible for participation in the study when assessed against the inclusion and exclusion criteria.

In each period, drug administration was performed on the morning of Day 1, after subjects had undergone a supervised overnight fast of at least 10 hours. Subjects, seated in upright position, were administered a single oral dose of either Egalet® hydrocodone 20 mg test formulations or NORCO® 10/325 with approximately 240 mL of water.

Subjects were dosed as specified in the protocol, and subsequently fasted for a period of at least 4 hours. Subjects were instructed to swallow the study medication whole. There were washout periods of 6-7 days or more between doses.

Restrictions

During the confinement, subjects were served controlled meals. On Day 1, subjects were served a controlled lunch no less than 4 hours post-dose, an evening meal approximately 9 hours post-dose, and an evening snack approximately 13 hours post-dose.

With the exception of the volume administered at the time of dosing, fluids were not permitted from 1 hour before dosing to 1 hour after dosing, but water was permitted *ad libitum* at all other times.

Subjects abstained from food or drink containing xanthine derivatives or xanthine-related compounds and energy drinks from 48 hours prior to drug administration until after the last sample collection of each period, alcohol-based products from 24 hours prior to admission until after the last sample collection of each period, and food or beverages containing grapefruit or pomelo products, and natural health products from 7 days prior to drug administration until after the last sample collection of each period. Subjects abstained from food containing poppy seeds for 24 hours prior to admission of each period.

Vigorous physical activity was prohibited at all times during the confinement.

Blinding

The study was open-label; since comparative bioavailability studies involve a comparison of pharmacokinetic profiles, which are not subjective measurements, blinding was not deemed necessary for this study. The randomisation code was not available either to the clinic personnel involved in the collection, monitoring, revision, or evaluation of adverse events, to the Bioanalytical Division of Anapharm, or to personnel who could have had an impact on the outcome of the study, until the clinical and analytical phases of the study had been completed.

Sample Collection

In each period, all blood samples were drawn into blood collection tubes (1 x 4 mL) containing EDTA K2; prior to drug administration and 0.333, 0.667, 1.00, 1.33, 1.67, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 15.0, 18.0, 21.0, 24.0, 27.0, 30.0, 36.0, and 42.0 hours post-dose. When deemed appropriate by the clinical staff, and as agreed upon by the subject, a dead-volume intravenous catheter was used for blood collection to avoid multiple skin punctures. Otherwise, blood samples were collected by direct venipuncture.

Safety

The safety assessments were including vital signs, ECGs, biochemistry, hematology, urine analysis, urin drug screen, pregnancy tests and adverse experience recording. They were conducted according to standard medical practices and are generally accepted as reliable, accurate, and relevant. The study data were analysed using standard methods widely accepted by medical and regulatory agencies.

Pharmacokinetic Parameters

The following pharmacokinetic parameters were calculated by standard non-compartmental methods for hydrocodone plasma concentrations:

1) AUC(0-t): area under the concentration-time curve from time zero to the last non-zero concentration: The area under the concentration-time-curve from time 0h until the last concentration sample at time 42h, AUC_{0-t}., were calculated by the linear trapezoidal method, using the actual sampling time points. If the last blood sample was taken less

than 42 hours after drug administration, the 42h values were extrapolated using the terminal elimination rate constant, K_{el} as described below. If the last sample was taken after 42 hours, a 42h value was estimated by interpolation. Intermediate missing values remained missing (equivalent to interpolating between neighbouring points when calculating AUC). Intermediate values below the limit of quantification (LOQ) were assigned a value of LOQ/2, while trailing values below LOQ were assigned a value of zero.

2) $AUC_{(0\text{-}inf)}$: area under the concentration-time curve from time zero to infinity (extrapolated): was determined for profiles that did not return to zero within 42 hours. $AUC_{0\text{-}inf}$, was calculated as the sum of $AUC_{0\text{-}t}$ and Ct Primary bioequivalence analysis of hydrocodone where Ct was the last sample above LOQ.

3) C_{max}: maximum observed concentration: were derived from the samples 0 - 42h after drug administration. Actual sampling time points were used for T_{max}.

4) Residual area: calculated as $100*(1- AUC_{(0\text{-}t)} / AUC_{(0\text{-}inf)})$.

5) T_{max}: time of observed C_{max}: were derived from the samples 0 - 42h after drug administration. Actual sampling time points were used for T_{max}.

6) $T_{½}$ el: elimination half-life was found by $Ln(2)/K_{el}$.

7) K_{el}: elimination rate constant: was the slope of the terminal part of the log-concentration-time-curve and was found using log-linear regression. The final three plasma concentrations above LOQ were included in the calculation as a minimum. However, the log-linear plots of plasma concentration were inspected and a different selection of data points could have been chosen to ensure that the time period represented the terminal elimination phase. Actual time values were used.

8) MRT: Mean residence time; was calculated as

$MRT_{0\text{-}inf} = AUMC_{0\text{-}inf} / AUC_{0\text{-}inf}$, where

$AUMC_{0\text{-}inf} = AUMC_{0\text{-}t} + t*Ct/K_{el} + Ct/(K_{el})2$,

and where $AUMC_{0-t}$ was the area under the first moment curve from time 0 until the last valid measurement at the time point t. Ct was the last valid plasma concentration found at this time point, t.

9) AUC_{0-12} and AUC_{0-24}: were calculated by utilisation of the linear trapezoidal method in the same way as for AUC_{0-t}.

11) Proportion $AUC_{(0-Tmax)}$: was calculated as
Proportion $AUC_{(0-Tmax)} = 100 * AUC_{0-Tmax} / AUC_{0-inf}$

12) Protraction index (AUC_{0-24h} / 24h) / C_{max} was calculated for each individual with regard to the hydrocodone concentration profile

Pharmacokinetic Methods

Numerical data was presented in summary tables by number of subjects, arithmetic mean (geometric mean and CV where applicable), median, standard deviation, minimum and maximum. Categorical data is presented by number and percent of subjects as well as number events (where applicable).

All calculations of endpoints, analyses and presentation of endpoints were carried out in SAS version 9.1 (Statistical Analysis System) or later versions. Analysis datasets were derived from the study data and was adhere to the CDISC ADaM standard (Clinical Data Interchange Standard Consortium Analysis Data Model).

For the hydrocodone AUC_{0-42}, AUC_{0-inf}, and C_{max} primary PK parameters, the ratio between test treatments A, B, C and D compared to treatment E (reference) were, after log transformation, estimated in a mixed linear model as

$$\text{Log (Endpoint)} = \text{Treatment} + \text{Period} + \text{Subject} + \text{random error},$$

Where treatment (A, B, C, D or E) and period were fixed effects and subject was a random effect.

The estimation included all valid PK data from all treatments for each comparison. Treatment sequence was included as a fixed effect in the above model.

The ratios of means (A/E, B/E, C/E and D/E) were calculated with 90% geometric confidence intervals based on least squares means. The treatment difference and corresponding confidence interval were back-transformed, thus yielding ratio estimates. Hence, the CI was evaluated against the range (0.80; 1.25).

Other endpoints were tabulated.

Pharmacokinetic Results

A total of 28 subjects were enrolled in the study. Twenty-eight (28) subjects received at least one dose of the study medication and comprised the safety population. The pharmacokinetic analyses included 22 subjects who completed at least 2 periods, 21 subjects who completed at least 4 periods, and 19 subjects who completed the study.

The mean dose-normalized AUC_{0-t} and AUC_{0-inf} values for all Egalet® test PR formulations were similar to those obtained for the reference IR formulation (NORCO® 10/325) as evidenced by the ratios and 90% confidence intervals contained within the interval limits of 80%-125%. As expected, the mean C_{max} values for all test PR formulations were lower than those observed for the reference IR formulation (NORCO® 10/325). The ratios of the least-squares means (Test/Reference) were 48%, 40%, 30% and 28% for formulations A1, A2, A3 and B1, respectively.

Table 1: Hydrocodone pharmacokinetic parameters (dose-normalised to 10 mg) for each treatment (N = 22)

Treatment	**AUC_{0-42} (pmol·h/mL)**	**AUC_{0-inf} (pmol·h/mL)**	**C_{max} (pmol/mL)**
Formulation A; 6 mm (A)	526858.92	533766.04	38434.97
Formulation A; 7.5 mm (B)	541913.82	554169.22	31949.23
Formulation A; 9 mm (C)	479527.18	499662.11	24018.17
Formulation B; 9 mm (D)	506327.16	528655.35	23021.18
NORCO® 10/325 (E)	534903.70	541562.13	81660.68

Table 2: Hydromorphone pharmacokinetic parameters (dose-normalised to 10 mg) for each treatment (N = 22)

Treatment	**AUC_{0-42} (pmol·h/mL)**	**AUC_{0-inf}* (pmol·h/mL)**	**C_{max} (pmol/mL)**
Formulation A; 6 mm (A)	9070.15	9994.89	465.64
Formulation A; 7.5 mm (B)	8318.16	9255.32	369.78
Formulation A; 9 mm (C)	8405.98	9639.06	313.23
Formulation B; 9 mm (D)	8534.74	10443.43	306.84
NORCO® 10/325 (E)	8590.99	9550.34	989.60

*For this parameter, N = 20 for Treatments C and D.

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Table 3: Norhydrocodone pharmacokinetic parameters (dose-normalised to 10 mg) for each treatment (N = 22)

Treatment	**AUC_{0-42} (pmol·h/mL)**	**AUC_{0-inf} (pmol·h/mL)**	**C_{max} (pmol/mL)**
Formulation A; 6 mm (A)	182950.37	188351.73	10492.78
Formulation A; 7.5 mm (B)	178872.71	188108.45	8431.64
Formulation A; 9 mm (C)	159263.00	173834.25	6938.85
Formulation B; 9 mm (D)	157005.92	173530.75	5988.92
NORCO® 10/325 (E)	191267.71	196338.68	17984.46

Table 4: Summery of hydrocodone pharmacokinetic parameters for each treatment (N=22)

Parameters		Formulation A 6 mm (A) (N = 20) Mean (min-max)	Formulation A 7.5 mm (B) (N = 20) Mean (min-max)	Formulation A 9 mm (C) (N=20) Mean (min-max)	Formulation B 9 mm (D) (N=20) Mean (min-max)	NORCO® 10/325 (E) (N = 21) Mean
AUC_{0-t}	(pmol·h/mL)	1053717.85 (566723-1501558)	1083827.64 (573855-1601524)	959054.36 (513753-1412443)	1012654.33 (511294-1488550)	534903.70(263032-854269)
AUC_{inf}	(pmol·h/mL)	1067532.07 (570971-1525746)	1108338.44 579026-1640043)	999324.21 (518525-1455476)	1057310.70 (518118-1587096)	541562.13 (268171-867127)
Residual area	(%)	1.25 (0.64-2.48)	2.10 (0.81-4.38)	3.73 (0.76-11.89)	4.13 (1.32-9.53)	1.23 (0.59-2.62)
C_{max}	(pmol/mL)	76869.94 (52083-105730)	63898.46 (44804-93280)	48036.34 (31808-88033)	46042.36 (28407-69417)	81660.68 (44714-130655)
T_{max}	(h)	6.25 (4.5-10.0)	5.38 (2.5-15)	5.25 (3.5-10.0)	4.52 (3.00-7.00)	1.08 (0.67-2.00)
T_{max}^{*}	(h)	4.75	4.50	4.75	4.50	1.00
K_{el}	(h^{-1})	0.1204 (0.0839-0.1611)	0.1178 (0.0870-0.1684)	0.1196 (0.0568-0.1794)	0.1174 (0.0733-0.1737)	0.1176 (0.0695-0.1569)
$T_{½ el}$	(h)	5.91 (4.30-8.26)	6.07 (4.11-7.97)	6.11 (3.86-12.20)	6.11 (3.99-9.46)	6.16 (4.42-9.97)
MRT	(h)	11.73 (9.49-13.99)	14.23 (10.63-16.75)	17.09 (10.18-21.61)	18.12 (15.72-20.89)	7.69 (5.73-10.56)

* Median.

The protraction index was determined, and the data below in table 5 are derived from the hydrocodone concentration profile obtained in the individuals, which participated in this study.

Table 5: Protraction index

Formulation A (6 mm)	Formulation A (7.5 mm)	Formulation A (9 mm)	Formulation B (9 mm)	Norco
$(AUC_{0-24h} / 24h) / C_{max}$				
0.43	0.65	0.70	0.63	0.31
0.56	0.63	0.67	0.64	0.30
0.51	0.53	0.63	0.72	0.24
0.52	0.58	0.60	0.69	0.26
0.58	0.47	0.64	0.67	0.24
0.39	0.54	0.49	0.58	0.25
0.42	0.46	0.56	0.61	0.24
0.43	0.72	0.48	0.55	0.25
0.66	0.51	0.80	0.68	0.24
0.51	0.62	0.66	0.73	0.41
0.48	0.56	0.74	0.61	0.20
0.49	0.74	0.76	0.69	0.18
0.63	0.67	0.72	0.79	0.37
0.67	0.63	0.38	0.57	0.32
0.59	0.63	0.67	0.79	0.27
0.49	0.53	0.74	0.72	0.29
0.47	0.68	0.61	0.62	0.25
0.50	0.60	0.62	0.51	0.31
0.52	0.67	0.63	0.65	0.26
-	0.73	0.68	0.79	0.22
-	-	0.56	0.61	0.23
-	-	0.70	0.81	-
Mean				
0.52	0.61	0.64	0.67	0.27
Min				
0.39	0.46	0.38	0.51	0.18
Max				
0.67	0.74	0.80	0.81	0.41

Figures 1 to 3 show the mean plasma concentration versus time profiles for hydrocodone, hydromorphone and norhydrocodone after single dose administration by dose group (0-42h).

Safety Results

No severe, significant, or serious adverse events were reported during the study. The frequency of adverse event observations did not appear to be related to treatment. Overall, adverse events were mild or moderate in intensity and were, except for a few, expected opioid effects. No safety concerns with respect to the clinical laboratory tests, vital signs, and ECGs were raised.

Discussion

The median T_{max} for the four Egalet® formulations were almost identical and between 4.50 hours (treatment A & C) and 4.75 (treatment B & D), whereas the median T_{max} for Norco 10/325 was 1.00 hour.

NORCO® 10/325, when dosed in half nominal dosage of the Egalet® formulations gave rise to a C_{max} of 81661 pmol/mL, slightly higher than the C_{max} (76870 pmol/mL) obtained for treatment A, the Egalet® formulation resulting in the highest C_{max}. As expected, when dose-normalized and tested for equivalence the ratios of least-square means were below 50% for all Egalet® formulations which indicate the prolonged and slower release from the Egalet® tablets.

For treatment A, a fairly constant and high concentration is maintained until the 10 hours post-dose time-point, after which the concentration drops exponentially. For treatment B a bi-exponential decline in hydrocodone concentration is observed, with a slow decrease between C_{max} and the 15-hour time-point, and a faster decline thereafter. Both treatment A and treatment B might be relevant candidates to consider for a twice daily dosage regimen.

For treatment C and D, which both have the same geometry, but different chemical compositions, the mean concentration-time-curves display an almost identically pattern. These two formulations have extremely prolonged in-vivo profiles, with fairly constant hydrocodone concentrations until the 24 hours post-dose time-point, after which elimination occurs. Surprisingly, both release profiles provide once-daily dosing characteristics.

When dose-normalized, all Egalet® formulations were found to provide the same total hydrocodone exposure as Norco 10/325. CI's for point-estimates for Egalet® treatments A and B did include 100%; CI's for treatment A ranging from approximately 95%-103% and for Treatment B ranging between 97-107%. Point-estimates for treatment C and D were below 100%, lowest for formulation C, but point estimates and corresponding 90% confidence limits were all within 80-125% acceptance limits, and thus considered equivalent. AUC equivalence was also found for metabolites.

Both treatment A and B have relevant release characteristics for twice daily dosing.

Treatment C and D provide in-vitro release profiles for developing a once-daily hydrocodone tablet. Treatment D (formulation B1) seem most promising based on the slightly higher AUC point-estimates and confidence limits found for this treatment. Further and more importantly, treatment D offers the possibility for developing higher dosage-strength, which can be relevant especially for the segment of opioid tolerant pain patients.

Compared with NORCO® 10/325 (immediate-release (IR) formulation), all Egalet® test (prolonged-release (PR)) formulations produced a more gradual rise and a more sustained elevation of plasma concentrations for hydrocodone and the active metabolites hydromorphone and norhydrocodone. Amongst the tested Egalet® formulations they are both a candidate for a formulation bioequivalent to immediate release Norco® (treatment A) with a more sustained profile suitable for twice daily dosing and two candidates for a once daily formulation of hydrocodone (Treatment C and D). In addition there were no safety concerns raised with any of the treatments.

Steady state Pharmacokinetics simulation

The individual patient data from study HC-EG-001 were simulated to Steady state to derive the steady state parameters of the Egalet® hydrocodone formulations tested and to assess the individual ranges for C_{24}/C_{max} supporting the use of Egalet® Hydrocodone for administration with 24 hours interval.

Method for SS simulation

The individual steady state data in the time interval [0h, 24h] were estimated as a sum of two components a) the sample values in the [0h, 24h] interval and b) estimated tail values in the interval [24h, infinity], e.g. the estimated value at 1 hour on day 2, 3, 4 etc. This corresponds to the superimposition principle. The tail was assumed to follow the standard one-compartment elimination (i.e. exponential function), and was estimated based on sample data from 24-42 hours for Hydrocodone and derivatives.

The estimated tails after 42h were less than 20% of total area and were included in the modelling.

For Hydrocodone the reference dose was 10 mg while test-doses were 20 mg. No dose normalisation was performed as this would have given large differences in estimated peaks.

Results

Table 6: Summary of Steady State Parameters

		Peak	Trough	Trough/Peak	T_{max}
		(pmol/mL)	(pmol/mL)	Ratio	(Hours)
Treatment	N	20	20	20	20
A 6.0mm	Mean	82873	12136	0.14	6.25
	Median	82296	11931	0.14	4.75
	Range	54340-111354	4620-25139	0.06-0.27	4.50-10.00
A 7.5mm	N	20	20	20	20
	Mean	75908	20241	0.26	5.38
	Median	74781	19423	0.27	4.50
	Range	51907-107306	5954-33512	0.11-0.37	2.50-15.00
A 9.0mm	N	22	22	22	22
	Mean	67119	26909	0.40	5.25
	Median	65726	27115	0.42	4.75
	Range	43067-109224	4626-41216	0.08-0.52	3.50-10.00
B 9.0mm	N	22	22	22	22
	Mean	68359	29121	0.42	4.52
	Median	66746	26434	0.42	4.50
	Range	38985-107507	12482-48370	0.30-0.56	3.00-7.00
Reference	N	20	20	20	20
	Mean	86525	3368	0.04	1.05
	Median	83719	2855	0.03	1.00
	Range	54982-137908	1324-7698	0.02-0.08	0.67-2.00

Figure 4 shows an estimated steady state hydrocodone curve

Conclusions

Especially from the formulation A chemistry (see Table 16 herein below) (treatment A, B and C) it is shown that within the same chemical composition the technology allows a certain space for designing the profile of the plasma curve of the active drug. A relatively short Egalet® formulation with a relatively wide release area (A1, 6mm length) provides a fast release rate and a C_{max} and AUC equivalent to the immediate release comparator product Norco®. The profile patterns are similar for the

metabolites. A longer geometry with a smaller area exposed for release at the open ends of the Egalet® formulation provides a lower C_{max} and release over a longer period providing a more sustained plasma profile.

T_{max} is not affected by the geometry changes of the Egalet® formulation. What determines the maximum length of the Egalet® formulation is the possibility of loosing AUC, if bioavailability of the active drug substance decreases in the lower intestines, e.g. if there is no or only little colon absorption, or if the Egalet® shell (coating) is simply excreted with a remainder of the matrix and active drug substance inside. With the formulation A3 (9mm length) there is no sign that the maximum length has been reached as AUC as Bioequivalence criterias with the immediate release formulation has been met on $AUC_{(0-t)}$ and $AUC_{(0-inf.)}$ Formulation B1 (9mm length) is a different chemical composition than A and is relased with the same rate as A3. B1 is is slightly preferable for a once daily formulation as it provides a marginally higher C_{24}/C_{max} ratio and less variability than A3.

Example 2

A randomised, comparative, open-label, crossover, phase I study evaluating single dose pharmacokinetic profiles of various egalet® oxycodone 40 mg test formulations versus OxyContin® in healthy volunteers using naltrexone blockade under fasting conditions

The study is also referred to as OC-EG-001 herein.

Objectives

The objective of this study was to find the optimal geometry of the Egalet® oxycodone 40 mg comparable to the pharmacokinetic plasma profile of OxyContin®.

The secondary objective of this study was to evaluate the safety and tolerability of Egalet® oxycodone 40 mg controlled-release dosage units in healthy subjects.

Rationale

1) Optimisation of the dosage regimen for patients suffering from moderate-to-severe pain by offering a controlled-release formulation for dosing twice a day or only once a day.
2) Providing a drug preferably classified as abuse resistant, lowering the potential of its abuse.

Design

The study was a single centre, open-label, single-dose, randomised, 4-way crossover, comparative Phase I study, performed under fasting conditions in accordance with regulatory requirements of bioequivalence limits (80-125% confidence interval) in 16 healthy subjects.

In this study the PK profiles of single doses of three different geometries (6.0 mm, 7.5 mm and 9.0 mm) of Egalet® oxycodone 40 mg tablets were evaluated and compared to a marketed, reference listed drug, OxyContin® 40 mg. This study was necessary for the further development adjustments needed to optimize and finalize the Egalet® oxycodone formulation corresponding to either a twice daily controlled release formulation or a once-daily formulation.

Primary pharmacokinetic analyses were performed with measurements of oxycodone plasma concentrations and secondary analysis of the active metabolites noroxycodone and oxymorphone plasma concentrations.

Table 7 Treatments

Treatment regimens	**Co-administration**
Treatment A (test 1, 6.0 mm): 1 x 40 mg Egalet® oxycodone	Nalrexone 1 x 50 mg 12 and 1 hour prior to dosing of treatment regimen A-D
Treatment B (test 2, 7.5 mm): 1 x 40 mg Egalet® oxycodone	Nalrexone 1 x 50 mg 12 and 1 hour prior to dosing of treatment regimen A-D
Treatment C (test 3, 9.0 mm): 1 x 40 mg Egalet® oxycodone	Nalrexone 1 x 50 mg 12 and 1 hour prior to dosing of treatment regimen A-D
Treatment D (reference): 1 x 40 mg OxyContin® (containing oxycodone)	Nalrexone 1 x 50 mg 12 and 1 hour prior to dosing of treatment regimen A-D

The composition of the formulations is given in Example 3, Table 12 herein below.

Methodology

For each period, subjects were confined to the clinical research facility from at least 14 hours prior to drug administration and were discharged from the clinic at least 48 hours after study drug administration. The treatment phases were separated by washout periods of 7 days.

In each period, subjects were administered a single oral dose of one of the three Egalet® oxycodone 40 mg or OxyContin® (as one 40 mg controlled release tablet), in accordance with the subjects' randomization sequence under fasting conditions. 50 mg Naltrexone was co-administered (to alleviate or avoid opioid side effects) in opioid-naïve subjects as presented in Table 7.

Restrictions

During the confinement, subjects were served controlled meals. On Day 1, subjects were served a controlled lunch no less than 4 hours post-dose, an evening meal approximately 9 hours post-dose, and an evening snack approximately 13 hours post-dose.

With the exception of the volume administered at the time of dosing, fluids were not permitted from 1 hour before dosing to 1 hour after dosing, but water was permitted *ad libitum* at all other times.

Subjects abstained from food or drink containing xanthine derivatives or xanthine-related compounds and energy drinks from 48 hours prior to drug administration until after the last sample collection of each period, alcohol-based products from 24 hours prior to admission until after the last sample collection of each period, and food or beverages containing grapefruit or pomelo products, and natural health products from 7 days prior to drug administration until after the last sample collection of each period. Subjects abstained from food containing poppy seeds for 24 hours prior to admission of each period.

Vigorous physical activity was prohibited at all times during the confinement.

Sample collection

In each period, all blood samples were drawn into blood collection tubes (1 x 4 mL) containing potassium EDTA K2; prior to drug administration and 0.333, 0.667, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 20.0, 24.0, 30.0, 36.0, and 48.0 hours post dose.

When deemed appropriate by the clinical staff, and as agreed upon by the subject, a dead-volume intravenous catheter was used for blood collection to avoid multiple skin punctures; collections were performed via direct venipuncture, otherwise.

Pharmacokinetic Parameters

The following PK parameters were calculated and summarised by standard non-compartmental methods for oxycodone plasma concentrations, noroxycodone and oxymorphone plasma concentrations respectively. The PK endpoints were calculated individually for each subject and treatment for the plasma concentrations obtained on Days 1-3 (0 – 48h) within each period.

1) $AUC_{(0-t)}$: area under the concentration-time curve from time zero to the last non-zero concentration: The area under the concentration-time-curve from time 0h until the last concentration sample at time 48h, AUC_{0-t}., were calculated by the linear trapezoidal

method, using the actual sampling time points. If the last blood sample was taken less than 48 hours after drug administration, the 48h values were extrapolated using the terminal elimination rate constant, Kel as described below. If the last sample was taken after 48 hours, a 48h value was estimated by interpolation. Intermediate missing values remained missing (equivalent to interpolating between neighbouring points when calculating AUC). Intermediate values below the limit of quantification (LOQ) were assigned a value of LOQ/2, while trailing values below LOQ were assigned a value of zero.

2) $AUC_{(0\text{-}inf)}$: area under the concentration-time curve from time zero to infinity (extrapolated): was determined for profiles that did not return to zero within 48 hours. $AUC_{(0\text{-}inf)}$, was calculated as the sum of $AUC_{0\text{-}t}$ and Ct Primary bioequivalence analysis of Oxycodoneel where Ct was the last sample above LOQ.

3) C_{max}: maximum observed concentration: were derived from the samples 0 - 48h after drug administration. Actual sampling time points were used for T_{max}.

4) Residual area: calculated as $100*(1- AUC_{(0\text{-}t)} / AUC_{(0\text{-}inf)})$.

5) T_{max}: time of observed C_{max}: were derived from the samples 0 - 48h after drug administration. Actual sampling time points were used for T_{max}.

6) $T_{½}$ el: elimination half-life was found by $Ln(2)/K_{el}$.

7) K_{el}: elimination rate constant: was the slope of the terminal part of the log-concentration-time-curve and was found using log-linear regression. The final three plasma concentrations above LOQ were included in the calculation as a minimum. However, the log-linear plots of plasma concentration were inspected and a different selection of data points could have been chosen to ensure that the time period represented the terminal elimination phase. Actual time values were used.

8) MRT: Mean residence time; was calculated as

$MRT_{0\text{-}inf} = AUMC_{0\text{-}inf} / AUC_{0\text{-}inf}$, where

$AUMC_{0\text{-}inf} = AUMC_{0\text{-}t} + t*Ct/K_{el} + Ct/(K_{el})2$,

and where $AUMC_{0-t}$ was the area under the first moment curve from time 0 until the last valid measurement at the time point t. Ct was the last valid plasma concentration found at this time point, t.

9) AUC_{0-12} and AUC_{0-24}: were calculated by utilisation of the linear trapezoidal method in the same way as for AUC_{0-t}.

11) Proportion $AUC_{(0-Tmax)}$: was calculated as
Proportion $AUC_{(0-Tmax)} = 100 * AUC_{0-Tmax} / AUC_{0-inf}$

12) Protraction index (AUC_{0-24h} / 24h) / C_{max} was calculated for each individual with regard to the hydrocodone concentration profile

Pharmacokinetic Methods

Numerical data was presented in summary tables by number of subjects, arithmetic mean (geometric mean and CV where applicable), median, standard deviation, minimum and maximum. Categorical data is presented by number and percent of subjects as well as number events (where applicable).

All calculations of endpoints, analyses and presentation of endpoints were carried out in SAS version 9.1 (Statistical Analysis System) or later versions. Analysis datasets were derived from the study data and was adhere to the CDISC ADaM standard (Clinical Data Interchange Standard Consortium Analysis Data Model).

For the oxycodone AUC_{0-48}, AUC_{0-inf}, and C_{max} primary PK parameters, the ratio between test treatments A, B, and C compared to treatment D (reference) were, after log transformation, estimated in a mixed linear model as

$$\text{Log (Endpoint)} = \text{Treatment} + \text{Period} + \text{Subject} + \text{random error},$$

Where treatment (A, B, C, or D) and period were fixed effects and subject was a random effect.

The estimation included all valid PK data from all treatments for each comparison. Treatment sequence was included as a fixed effect in the above model.

The ratios of means (A/D, B/D, and C/D) were calculated with 90% geometric confidence intervals based on least squares means. The treatment difference and corresponding confidence interval were back-transformed, thus yielding ratio estimates. Hence, the CI was evaluated against the range (0.80; 1.25).

Other endpoints were tabulated.

Pharmacokinetic Results

28 subjects were screened for this study and upon completion of all screening procedures a total of 16 healthy, adult non-smokers were enrolled in the study, of which 9 completed all treatment groups.

Table 8: Primary Analysis of Oxycodone, Noroxycodone and Oxymorphone (Bioequivalence), Full PK data set:

		Test / Reference						
		Test		**Reference**				
		N	Mean	n	Mean	Ratio (%)	90% CI	P-value
Oxycodone								
6.0 mm vs Reference	$AUC_{(0-48h)}$ (nmol*h/L)	12	574.7	11	547.8	104.9	(95.8,115.0)	0.3790
	$AUC_{(0-inf)}$ nmol*h/L)	12	575.0	11	549.6	104.6	(95.3,114.8)	0.4162
	C_{max} (nmol/L)	12	45.4	11	52.2	87.0	(79.0, 95.8)	0.0201
7.5 mm vs Reference	$AUC_{(0-48h)}$ (nmol*h/L)	12	526.6	11	547.8	96.1	(87.6,105.5)	0.4756
	$AUC_{(0-inf)}$ nmol*h/L)	12	529.1	11	549.6	96.3	(87.6,105.8)	0.4992
	C_{max} (nmol/L)	12	37.4	11	52.2	71.7	(65.0,79.1)	<.0001
9,0 mm vs Reference	$AUC_{(0-48h)}$ (nmol*h/L)	11	534.9	11	547.8	97.7	88.9, 107.3	0.6711
	$AUC_{(0-inf)}$ nmol*h/L)	11	542.6	11	549.6	98.7	89.7, 108.7	0.8222
	C_{max} (nmol/L)	11	31.4	11	52.2	60.1	54.5, 66.4	<.0001
Noroxycodone								
6.0 mm vs Reference	$AUC_{(0-48h)}$ (nmol*h/L)	12	606.6	11	576.3	105.3	(97.8,113.3)	0.2469
	$AUC_{(0-inf)}$ nmol*h/L)	12	612.8	11	586.5	104.5	(97.3,112.3)	0.3064
	C_{max} (nmol/L)	12	37.3	11	38.3	97.4	(90.9,104.3)	0.5175
7.5 mm vs Reference	$AUC_{(0-48h)}$ (nmol*h/L)	12	508.2	11	576.3	88.2	(81.8,95.1)	0.0082

	$AUC_{(0\text{-}inf)}$ nmol*h/L)	12	519.1	11	586.5	88.5	(82.3, 95.2)	0.0084
	C_{max} (nmol/L)	12	28.9	11	38.3	75.6	(70.5, 81.1)	<.0001
9,0 mm vs Reference	$AUC_{(0\text{-}48h)}$ (nmol*h/L)	11	540.1	11	576.3	93.7	(86.9,101.1)	0.1575
	$AUC_{(0\text{-}inf)}$ nmol*h/L)	11	565.9	11	586.5	96.5	(89.6,103.9)	0.4185
	C_{max} (nmol/L)	11	38.3	11	25.6	67.0	(62.4, 71.9)	<.0001
Oxymorphone								
6.0 mm vs Reference	$AUC_{(0\text{-}48h)}$ (nmol*h/L)	12	9.6	11	11.5	83.6	(69.5,100.6)	0.1100
	$AUC_{(0\text{-}inf)}$ nmol*h/L)	11	14.9	9	16.4	90.8	(78.0,105.6)	0.2829
	C_{max} (nmol/L)	12	0.7	11	0.8	87.5	(76.9, 99.5)	0.0882
7.5 mm vs Reference	$AUC_{(0\text{-}48h)}$ (nmol*h/L)	12	9.2	11	11.5	80.1	(66.3, 96.7)	0.0551
	$AUC_{(0\text{-}inf)}$ nmol*h/L)	11	14.8	9	16.4	90.1	(77.3,104.9)	0.2506
	C_{max} (nmol/L)	12	0.6	11	0.8	75.7	(66.4, 86.3)	0.0012
9,0 mm vs Reference	$AUC_{(0\text{-}48h)}$ (nmol*h/L)	11	10.4	11	11.5	90.4	(74.7,109.5)	0.3778
	$AUC_{(0\text{-}inf)}$ nmol*h/L)	10	18.7	9	16.4	113.9	(97.5,133.0)	0.1635
	C_{max} (nmol/L)	11	0.5	11	0.8	70.6	(61.9, 80.6)	0.0001

Table 9 Endpoints for Oxycodone

Treatment	6.0 mm	7.5 mm	9.0 mm	Reference
$AUC_{(0-48h)}$(nmol*h/L):				
Mean	586	537	562	569
Min, Max	462 – 880	402 – 693	384 – 774	403 – 806
$AUC_{(0-inf)}$(nmol*h/L):				
Mean	587	540	571	571
Min, Max	461 – 882	414 – 695	387 – 778	405 – 811
C_{max} (nmol):				
Mean	46	38	33	54
Min, Max	32 - 59	27 – 56	23 – 45	39 – 79
Residual area (Pct.):				
Mean	0	1	1	0
Min, Max	0 – 0	0 – 3	0 – 7	0 – 1
T_{max} (h):				
Mean	4.9	4.4	4.2	2.2
Min, Max	2.5 - 10.0	2.0 - 6.0	1.0 - 6.0	0.7 – 4.0
$T_{(1/2)}$(h):				
Mean	4.5	5.2	5.7	5.2
Min, Max	3.5 - 5.5	4.1 - 10.3	3.7 - 12.5	4.2 - 6.3
Elimination rate (1/h):				
Mean	0.16	0.14	0.13	0.14
Min, Max	0.13 - 0.20	0.07 - 0.17	0.06 - 0.19	0.11 - 0.17
MRT (h):				
Mean	10.0	11.9	15.6	10.1
Min, Max	8.1 - 11.6	9.2 - 14.0	13.1 - 21.7	9.5 - 10.7
Proportion $AUC_{(0-Tmax)}$ (Pct.):				
Mean	26	20	15 (7)	12
Min, Max	11 – 50	9 - 30	3 - 25	2 – 24

The protraction index was determined, and the data below in table 10 are derived from the oxycodone concentration profile obtained in the individuals, which participated in this study.

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Table 10 Protraction index

6 mm	7.5 mm	9 mm	Reference
$(AUC_{0-24h} / 24h) / C_{max}$			
0.48	0.56	0.64	0.47
0.48	0.50	0.50	0.38
0.48	0.47	0.55	0.41
0.45	0.46	0.53	0.32
0.60	0.58	0.56	0.44
0.52	0.63	0.48	0.37
0.59	0.52	0.68	0.50
0.54	0.68	0.53	0.46
0.51	0.58	0.63	0.33
0.51	0.59	0.51	0.47
0.51	0.56	0.54	0.49
0.55	0.53	0.54	-
0.62	-	-	-
Mean			
0.53	0.55	0.56	0.42
Min			
0.45	0.46	0.48	0.32
Max			
0.62	0.68	0.68	0.50

Figures 5 to 7 show the mean plasma concentration versus time profiles for oxycodone, oxymorphone and noroxycodone after single dose administration by dose group (0-48h)

Safety results

No severe, significant, or serious adverse events were reported during the study. The most frequently occurring adverse events were expected or procedure-related and were mild or moderate in intensity

Discussion

From, the descriptive summaries of $AUC_{(0-48)}$ and $AUC_{(0-inf)}$ in Table 8 and 9, it was clear that the reference group had similar values of $AUC_{(0-48)}$ and $AUC_{(0-inf)}$ compared to the values for the test tablets hence the 90% confidence intervals for the ratios of means for $AUC_{(0-48)}$ and $AUC_{(0-inf)}$ for all three tablet sizes/geometries were contained within the interval 80-125.

The level of C_{max} decreased with increasing size of the tablets. The pattern was repeated for the metabolites; noroxycodone and oxymorphone. However, the 90%

confidence intervals for C_{max} were not contained in the interval 80-125 for any of the tablets sizes.

The elimination rate was almost the same for all four treatment groups. Mean MRT increased with increasing size of the tablet, with the reference group matching the 6.0 mm group. The mean proportion of AUC $_{(0\text{-}Tmax)}$ decreased with increasing size of the tablet, as with $AUC_{0\text{-}48}$ and C_{max}.

Hence, bioequivalence of the three test formulations compared to reference was not obtained on the basis of this trial. The ratio for C_{max} showed a clearly decreasing trend with increasing size of tablets. It was indicated that the 6.0 mm tablet was closest to the reference tablet, as the 90% confidence intervals for C_{max} were 79.0 - 95.8 and that the 9.0 mm tablet had the most sustained profile, with a potential for QD (once daily) dosing.

Steady State pharmacokinetic simulation

As the data demonstrate that administration with an interval of 24 hours most probably is suitable for these pharmaceutical compositions, an explorative simulation was applied on the data to emulate a steady state scenario.

Method for SS simulation

The individual steady state data in the time interval [0h, 24h] were estimated as a sum of two components a) the sample values in the [0h, 24h] interval and b) estimated tail values in the interval [24h, infinity], e.g. the estimated value at 1 hour on day 2, 3, 4 etc. This corresponds to the superimposition principle. The tail was assumed to follow the standard one-compartment elimination (i.e. exponential function), and was estimated based on sample data from 24-48 hours for Oxycodone and derivatives.

The estimated tails after 48h were less than 20% of total area except in some cases for oxymorphone which showed large variation in sample data. All profiles where the tail estimation was possible were included in the modelling.

Steady state Results

Table 11 Summery of Steady State parameters

			Peak	Trough	Trough/Peak	T_{max}
Analyte	**Treatment**		**(ng/mL)**	**(ng/mL)**	**Ratio**	**(Hours)**
Oxycodone	Reference	N	11	11	11	11
		Mean	58.78	6.39	0.11	2.20
		Median	60.29	5.89	0.11	2.50
		Range	41.31-85.57	4.35-9.81	0.09-0.14	0.67-4.0
	Test 6.0 mm	N	13	13	13	13
		Mean	48.04	4.44	0.09	4.89
		Median	43.57	3.92	0.08	5.00
		Range	33.80-60.94	1.56-7.91	0.04-0.17	2.50-10.0
	Test 7.5 mm	N	12	12	12	12
		Mean	42.22	6.95	0.17	4.38
		Median	40.47	6.30	0.16	4.75
		Range	34.22-58.74	2.62-11.08	0.07-0.32	2.00-6.0
	Test 9.0 mm	N	11	11	11	11
		Mean	42.42	13.86	0.33	4.23
		Median	39.73	12.30	0.31	4.50
		Range	31.38-58.58	9.31-19.84	0.25-0.43	1.00-6.0

Figure 8 shows an estimated steady state oxycodone curve.

From figure 8 it is seen that the concentration profile curve of oxycodone flattens with an increase of size of the tablet and an increase in the tablet size caused a decrease in C_{max}.

The individual steady state data [0h, 24h] is estimated as sum of observed data in the [0h, 24h] interval and estimated tail values [24h, infinity]. Peak and trough derived from these individual steady state data. The tails were estimated by standard one-compartment terminal elimination approach.

The pattern of increasing Trough/C_{max} ratio with increasing length for mean oxycodone plasma concentrations is similar for the active metabolites mean noroxycodone and mean oxymorphone plasma.

Conclusions

The curve demonstrates that the Egalet® technology is capable of controlling the release by adjusting the geometry of the tablet hence prolonging the release of drug.

It is commonly known that enterohepatic cycling causes a multiple peak phenomenon in the concentration-time profiles. Since this was not observed for oxycodone, the once daily profile is triggered by the technology feature of the Egalet® oxycodone formulation rather than enterohepatic re-cycling.

The through/C_{max} index rises with the length of the tablet hence the 9mm appears to demonstrate a profile sufficiently prolonged to provide sustained efficacy for a long time i.e. 24 hours.

The main outcome of the study lead to the conclusion that the three test formulations were equivalent to the reference formulation in regards to the amount of oxycodone absorbed (AUC) but not the rate of absorption mainly represented by the C_{max}.

Treatment A (6.0 mm) was the closest to the OxyContin® tablet profile and Treatment C (9.0 mm) had the most sustained profile with a potential for once daily dosing.

The explorative pharmacokinetic analysis of steady state simulations showed clear evidence of technology controlled release dependence.

Example 3

Compostions

The tablets preferably used in by the present invention and notably in Examples 1 and 2 are a combination of a matrix polymer system and a water-impermeable, essentially non-erodible shell (coating) partly covering this matrix. The active drug substance is dispersed and/or dissolved in the matrix.

The active drug substance is released substantially by surface erosion. The erosion of the matrix occurs when water diffuses into the matrix at a constant rate, leading to polymer hydration, swelling, disentanglement and dissolution.

A cylindrical shaped shell (coating) with a well defined surface area in both ends of the tablet leads to constant dissolution because of a constant release area. Accordingly, a zero-order release mechanism can be obtained. The shell (coating) is only very slowly degradable and passes intact through the GI tract and is excreted with feces. Interestingly, for tablets with a given length extended release over a pre-defined period of time is achieved, thus tablets with a length of in the range of 8 to 10 mm preferably 9 mm to 9.5 mm provide in vivo efficacy for 24 hours as disclosed in Examples 1 and 2.

Geometry

By varying the size of the tablet and the thickness of the shell (coating), and thereby the matrix weight and size of the erosion area controlled release properties can by varied, Thus the release area defines the rate of which drug is released, and the length of the matrix defines the duration of the release of drug. It is thus possible to use the same matrix composition for all strengths that is needed. The present invention discloses that tablets with a length of 8 to 10 mm are particularly useful for once daily administration. The tablet may be comprised of a round or elliptical cylinder, i.e. the shell (coating) encompasses the entire length of the core. By varying the length of the tablet, keeping the volume fixed, it is possible to vary dissolution time with a fixed matrix composition. Thus the duration of the release depend on the length of the composition. The rate of release (mg/h) may depend on the release area. To increase the strength of a pharmaceutical composition without changing the duration of the dissolution process, the length is kept constant while the area may be increased proportionally with the dose. This technology enables formulations with different release properties without changing chemistry of the formulation.

The release rate can also be altered by varying matrix composition. For example the dissolution rate of the matrix depends on ingoing components solubility, hydration rate and disentanglement rate among other properties. Accordingly, the dissolution rate may be increased by choosing hydrophilic or low molecular weight components in the matrix.

Table 12 discloses a preparation according to the invention controlling release by tablet length. These preparations were used in Example 2.

The composition was prepared by two component injection molding. The matrix volume was 125 mm^3 and the length was 6 mm, 7.5 mm and 9 mm, respectively.

Table 12

Component	Function	Quantity per unit (mg)	% w/w
Matrix			
Oxycodone hydrochloride	Active ingredient	40.0	26.8
Polyethylene oxide 200,000	Carrier	38.4	25.7
Polyethylene oxide 300,000	Carrier	29.9	20.0
Poloxamer 188	Co-carrier, Plasticizer	14.9	10.0
Poloxamer 407	Co-carrier, Plasticizer	20.9	14.0
Butylhydroxytoluene	Antioxidant, Stabilizer	0.07	0.5
Eudragit L100-55	Carrier, Stabilizer	4.48	3.0
Total, matrix		148.7	100.0
Shell (coating)			
Ethylcellulose	Coat material	84.2	87.0
Cetostearyl alcohol	Plasticizer	10.1	12.0
Titanium dioxide	Colorant	0.97	1.0
Total, shell (coating)		96.8	100.0
Total		245.4	

The release time in an in vitro study (tested in an USP 2 apparatus at 50 rpm and pH 6.8) is proportional to the length of the tablet. The release is shown in Table 13.

Table 13

	Release time (release)
6 mm length (batch no. 08-0088-114)	405 min (94 %)
7.5 mm length (batch no. 08-0089-114)	510 min (88 %)
9 mm length (batch no. 08-0090-114)	600 min (88 %)

The releationship between release time and tablet length is shown in Figure 9.

Table 14 discloses compositions designated formulation A and B.

The compositions were prepared by two component injection molding. Two different formulations with different compositions were tested. Both formulations showed the same dissolution properties as tested in an USP 2 apparatus at 50 rpm and pH 6.8 (see figure 10). The two formulations were tested in two different tablet shapes: round (formulation A) and elliptical (formulation B). Formulation B was tested in different sizes, systematically varying volume and release area. It was found that the release duration did not vary with volume, area or shape, but appears to be dependent on the length. The dose was released proportionally to the release area, such that each composition released the complete dose (100%) at the same timepoint.

Table 14

Components	**Amount per tablet (% w/w)**		**Function**
	Form. A	**Form. B**	**--**
Matrix	100	100	
Morphine sulfate pentahydrate	16.0	51.5	Active ingredient
Polyethylene oxide 200 000	71.4	-	Carrier, release modifier
Polyethylene oxide 300 000		32.0	Carrier, release modifier
Poloxamer 188		13.4	Co-carrier, Plasticizer
Mannitol	10.0	3.0	Release modifier and stabilizer
Butylated hydroxytoluene (BHT)		0.1	Antioxidant, Stabilizer
Vitamin E Polyethylene Glycol Succinate (TPGS)	2.6	-	Stabilizer

Components	Amount per tablet (% w/w)		Function
	Form. A	Form. B	--
Shell (coating)	100	100	
Ethylcellulose	87.0	87.0	Coat material
Cetostearyl alcohol	12.0	12.0	Plasticizer
Titanium dioxide	1.0	1.0	Coloring agent, UV stabiliser

Table 15

Shape	Batch no.	Length (mm)	Volume (mm^3)	Release area (mm^2)	Dose (mg)
Round	08-0141-066	9	150	16.67	30
Ellipse	08-0140-066	7,5	42.08	5.61	30
ellipse	08-0138-066	7,5	89.94	11.99	60
ellipse	08-0137-066	7,5	150.2	20	100
Ellipse	08-0139-066	7,5	300.02	40	200

Table 16 and 17 shows preparations according to the invention controlling the release by tablet length. These preparations were used in the study described in Example 1.

Compositions were prepared by injection molding. Two formulations were prepared: a medium load composition tested in three different tablet lengths and a high load formulation tested in 9 mm length unit of half the volume. The medium load formulations were shown to release in dissolution test (USP 2, pH 6.8, 50 RPM) with durations that were proportional to the tablet length. The high load formulation was adjusted by chemical formulation to a release time that was intermediate of the medium formulation release times.

In conclusion the release time can be adjusted both by tablet length.

Table 16 Formulation A1-A3

Component	**Function**	**Formulation A1 20 mg medium load 6.0 mm, length**		**Formulation A2 20 mg medium load 7.5 mm, length**		**Formulation A3 20 mg medium load 9 mm, length**	
		Quantity per unit		Quantity per unit		Quantity per unit	
		(mg)	(% w/w)	(mg)	(% w/w)	(mg)	(% w/w)
Matrix							
Hydrocodone bitartrate	Active ingredient	20	13.6	20	13.6	20	13.6
Polyethylene oxide 200,000	Carrier	77.8	52.9	77.8	52.9	77.8	52.9
Polyethylene oxide 300,000	Carrier	14.7	10.0	14.7	10.0	14.7	10.0
Poloxamer 188	Co-carrier, Plasticizer	23.5	16.0	23.5	16.0	23.5	16.0
Poloxamer 407	Co-carrier, Plasticizer	5.9	4.0	5.9	4.0	5.9	4.0
Butylhydroxytoluene	Antioxidant, Stabilizer	0.7	0.5	0.7	0.5	0.7	0.5
Mannitol	Carrier, Stabilizer	4.4	3	4.4	3	4.4	3
Total, matrix		147	100	147	100	147	100
Shell (coating)							
Ethylcellulose	Coat	80.9	87	95.7	87	145.3	87
Cetostearyl alcohol	Plasticizer	11.2	12	13.2	12	20.0	12
Titanium dioxide	Colorant	0.93	1	1.1	1	1.7	1
Total, shell (coating)		93	100	110	100	167	100
Total		240	200	257	200	314	200

Table 17 Formulation B1

Component	**Function**	**20 mg high load (9.0 mm length)**	
		Quantity per unit	
		(mg)	% w/w
Matrix			
Hydrocodone bitartrate	Active ingredient	20.0	26.2
Polyethylene oxide 200,000	Carrier	40.7	53.3
Polyethylene oxide 300,000	Carrier	7.6	10.0
Poloxamer 188	Co-carrier, Plasticizer	7.6	10.0
Butylhydroxytoluene	Antioxidant, Stabilizer	0.4	0.5
Total, matrix		76.3	100.0
Shell (coating)			
Ethylcellulose	Coat material	79.8	87.0
Cetostearyl alcohol	Plasticizer	11.0	12.0
Titanium dioxide	Colorant	0.9	1.0
Total, shell (coating)		91.7	100
Total		168	200

Table 18

Formulation	**A1**	**A2**	**A3**	**B1**
Parameter	**6.0 mm length 08-0188-113**	**7.5 mm length 08-0189-113**	**9.0 mm length 08-0190-113**	**9.0 mm length 08-0191-113**
Release area (mm^2)	20,8	16.6	13.8	7
Dimensions (mm)				
Length	6.0	7.5	9.0	9.0
Short diameter	4.7	4.3	4.4	3.4
Long diameter	9.4	8.5	8.3	5.6

Figure 12 shows the release times for hydrocodone versus tablet length.

Example 4

A single-period, multiple-dose, single-centre, phase I trial evaluating the steady-state pharmacokinetic profile of Egalet® morphine 30 mg (Formulation A) controlled extended release dosage unit in healthy volunteers using naltrexone blockade.

The content of the Egalet® morphine 30 mg (Formulation A) controlled extended release dosage unit used in this study is described in detail in Example 3 herein above in Table 14. The shape was of the formulation used in this study was a round, 9,0 mm long and a volume of 150 mm^3 and a cross section area of 8,335 mm^2.

This study is also referred to as MP-EG-003 herein.

One objective was to evaluate the steady-state pharmacokinetic profile of Egalet® morphine 30 mg (Formulation A) controlled release dosage unit administered once daily for 10 consecutive days under fasting conditions.

This was a single-centre, non-comparative, multiple-dose, phase I trial, performed under fasting conditions. Subjects were confined to the Clinical Research Facility from

at least 14 hours before the first study drug administration (evening of Day -1, when the first administration of co-medication [naltrexone] was given) and were discharged from the clinic on Day 11, after the 36.0-hour post-dose blood draw. Subjects came back for all subsequent blood draws on Days 12, 13, 14, and 15. Naltrexone is an opioid receptor antagonist.

Number of subjects enrolled, randomised and completed the study was: 18 (8 females and 10 males).

Subjects had to be healthy, adult non-smokers, aged ≥ 18 and ≤ 55 years; body mass indices ≥ 18.0 and < 30.0 kg/m2. All subjects had to be in compliance with the inclusion and exclusion criteria described in the protocol and were judged eligible for enrolment in this study based on medical and medication histories, demographic data (including sex, age, race, body weight [kg], height [cm], and BMI [kg/m2]), vital signs measurements (including pulse oxymetry), a 12-lead ECG, a physical examination, a urine drug screen, an alcohol breath test, a pregnancy test, and clinical laboratory tests (hematology, biochemistry, urinalysis, HIV, hepatitis C [HCV] antibodies, and hepatitis B surface antigen [HBSAg]).

Table 19 Treatment

	Study Drug	**Co-medication**
Name	Egalet® morphine Formulation A	Naltrexone hydrochloride (Revia®)
Unit dose	30 mg	50 mg
Regimen	single dose of 1 x 30 mg controlled release dosage unit by oral administration for 10 consecutive days (Days 1 to 10)	single dose of 1 x 50 mg film coated tablet by oral administration on the following days: Day -1, 12 hours before the first morphine administration; Days 1 through 10: 1 hour before each morphine administration; Day 11: approximately 24 hours after the last morphine administration (immediately prior to next dose)

The following pharmacokinetic parameters were calculated for morphine: AUC_{0-24h}, T_{max}, steady state C_{max}, steady state C_{min}, PTF, AUC_{0-inf}, $T_{½ el}$, and K_{el}.

The pharmacokinetic parameters listed above were also calculated for morphine-3-glucuronide and morphine-6-glucuronide.

Additional pharmacokinetic parameters were MRT, HVD and $T_{75\%Cmax}$ (for morphine only)

Also the protraction index was calculated for each individual with regard to the morphine concentration profile

Safety: Adverse events, vitals signs (including pulse oxymetry) and ECG measurements, and standard laboratory evaluations.

A single arm, non-comparative study, formal statistical analyses were not performed for the PK endpoints. Endpoints are summarized and represented by N, arithmetic and geometric mean, median, standard deviation, minimum and maximum.

The attainment of steady state was assessed based on log-transformed pre-dose plasma concentrations of morphine recorded on Days 4 to 10. In a repeated measures model with subject and day as factors, Day 10 concentration was compared to Days 4 to 9, respectively. The first day with a non-significant difference to Day 10 is considered steady state. Mean and individual curves of untransformed pre-dose plasma concentrations versus time (Days 4 to 11) were produced. The steady state analysis was repeated exploratively including time since physical activity and time since last bowel movement as covariates in the model.

Results

Figure 13 shows the mean steady state morphine plasma concentration versus time curve (0-24h).

Steady state was obtained already after 4 days of administration of the Egalet® morphine 30mg (Formulation A) extended release dosage unit. 4 days was the earliest

investigated time point and thus steady state may possibly have been reached even earlier. Both the mean and individual concentration vs. time profiles seem to demonstrate that the Egalet® morphine (Formulation A) dosage unit offers at least a twice daily and preferably also a once daily treatment for most subjects, by providing steady morphine concentration throughout the 24 hours for most subjects. For some subjects, however, the morphine concentration decreases and reaches a relatively low level at the 24h time point. The co-administration of naltrexone may have marginally influenced the PK-profiles and some of the PK endpoints. No severe, significant, or serious adverse events were reported during the study.

Table 20 Pharmacokinetics - morphine

Enrolled subjects	18
AUC_{0-24h}(nmol*h/L)	
Geom. mean	353
Min, Max	176 – 795
T_{Max}(h)	
Geom. mean	1.54
Min, Max	0.50 - 5.05
C_{Max} (SS)(nmol/L)	
Geom. mean	31.6
Min, Max	14.1 - 59.3
C_{Min} (SS)(nmol/L)	
Geom. mean	6.9
Min, Max	1.6 - 23.4
C_{24} (SS)(nmol/L)	
Geom. mean	12,52
Min, Max	2,19-27,3

SS=steady state

Also the Protraction index was determined, and the data below in Table 21 are derived from the steady state profiles obtained in the individuals, which participated in this study.

Table 21 Protraction index

	$(AUC_{0-24h} / 24h) / Cmax$
	0.36
	0.34
	0.39
	0.36
	0.39
	0.34
	0.30
	0.35
	0.35
	0.36
	0.39
	0.35
	0.40
	0.29
	0.42
	0.39
	0.47
Mean	0.37
Min	0.29
Max	0.47

Example 5

A SINGLE-CENTRE, SINGLE-DOSE, RANDOMISED, OPEN-LABEL, 5-WAY CROSSOVER, DOSE-LINEARITY STUDY OF EGALET® MORPHINE 30, 60, 100 AND 200 mg CONTROLLED-RELEASE DOSAGE UNITS IN HEALTHY VOLUNTEERS USING NALTREXONE BLOCKADE UNDER FASTING CONDITIONS

This study is also referred to as MP-EG-005 herein.

Objectives

The primary objective of this study was to evaluate dose-linearity of the four strengths of Egalet® Morphine controlled-release dosage units of Formulation B.

Rationale

1) Optimisation of the dosage regimen for patients suffering from moderate-to-severe pain by offering a controlled-release formulation for dosing only once a day that can be developed in high strengths.

2) Demonstration of dose proportionality between 4 different geometries of the egalet® morphine corresponding to 30, 60, 100 and 200mg morphine sulfate.

Design

This was a single centre, open-label, single-dose, randomised, 5-way crossover, comparative bioavailability study, performed under fasting conditions to evaluate dose-linearity of the four strengths of Egalet® Morphine of Formulation B,

Evaluation of safety and tolerability to controlled-release dosage units included adverse events (i.e., seriousness, severity, and relationship), vital signs and clinical laboratory parameters.

Sample collection

Measurements of morphine plasma concentrations and secondary analysis with morphine-3-glucuronide and morphine-6-glucuronide plasma concentrations were performed at the following timepoints: pre-dose and 0.333, 0.667, 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 15.0, 18.0, 21.0, 24.0, 30.0, 36.0, and 48.0 hour post-dose.

Treatments

In each treatment period, subjects were administered a single oral dose of either Egalet® Morphine of Formulation B (dosage unit of 30, 60, 100, or 200 mg) or Formulation A (two tablets of 30 mg) controlled-release dosage units on Day 1, in accordance with the subjects' randomization sequence. The content of the formulations are described in Table 14 herein above. The geometry of the formulations are described in Table 15 herein above,

The treatment periods were separated by a washout of 7 days.

- Treatment A: 1 x 30 mg Egalet® Morphine controlled-release dosage unit of Formulation B (length 7.5 mm) (08-0140-066).
- Treatment B: 1 x 60 mg Egalet® Morphine controlled-release dosage unit of Formulation B (length 7.5 mm) (08-0138-066).
- Treatment C: 1 x 100 mg Egalet® Morphine controlled-release dosage unit of Formulation B (length 7.5 mm) (08-0137-066).

- Treatment D: 1 x 200 mg Egalet® Morphine controlled-release dosage unit of Formulation B (length 7.5 mm) (08-0139-066).
- Treatment E: 2 x 30 mg Egalet® Morphine controlled-release dosage units of Formulation A (length 9 mm) (08-0141-066).

To alleviate or avoid opioid side effects that are expected in opioid-naïve subjects, naltrexone was administered as a 1 x 50 mg tablet with approximately 120 mL of water approximately 12 hours before morphine administration (Day -1), approximately 1 hour before morphine administration (Day 1), and approximately 24 hours post- morphine administration (Day 2).

Methodology

A total of 39 healthy, adult non-smokers signed the study-specific informed consent form and were confined for Period 1; of these subjects, 35 (18 males and 17 females) were enrolled and dosed in the study; 31 of these enrolled subjects completed the study. Prior to entering the trial, subjects completed all screening procedures. Upon arrival at the clinical facility for the confinement (Day -1) and once eligibility had been confirmed, subjects were sequentially allocated a two-digit subject number that corresponded to the randomisation scheme.

All subjects received standardised meals throughout during their confinements, not less than 4 hours post-dose, approximately 9 hours post-dose, and an evening snack approximately 13 hours post-dose. With the exception of the volume administered at the time of the administration of morphine, fluids were not permitted from 1 hour before dosing to 1 hours post-morphine dose, but water was permitted ad libitum at all other times.

A urine drug screen and an alcohol breath test were performed for all subjects upon admission to the clinical unit for each period.

Female subjects of childbearing potential and who had sexual intercourse with a non-sterile male partner were required to use a method of contraception from 14 days prior to study drug administration until 7 days following the last drug administration.

Data were evaluated descriptively only, as defined in the statistical analysis plan (SAP).

Pharmacokinetic Parameters

The following PK parameters were calculated and summarised by standard non-compartmental methods for morphine plasma concentrations, morphine-3-glucuronide plasma concentrations, and morphine-6-glucuronide plasma concentrations. The morphine-3-glucuronide plasma concentrations and morphine-6-glucuronide plasma concentrations were included for supportive information.

1) AUC_{0-t}: area under the concentration-time curve from time zero to the last non-zero concentration
2) AUC_{0-inf}: area under the concentration-time curve from time zero to infinity (extrapolated)
3) C_{max}: maximum observed concentration
4) Residual area: calculated as $100*(1- AUC_{0-t} / AUC_{0-inf})$.
5) T_{max}: time of observed C_{max}
6) $T_{½ el}$: elimination half-life
7) K_{el}: elimination rate constant
8) MRT: mean residence time
9) Proportion of AUC before T_{max}

Pharmacokinetic Methods

The PK endpoints were calculated individually for each subject and dose based on the plasma concentrations obtained on Days 1-3 (0 – 48h) within each period.

AUC_{0-t}

The area under the concentration-time-curve from time 0h until the last concentration sample at time 48h, AUC_{0-t}., were calculated by the linear trapezoidal method, using the actual sampling time points. If the last blood sample was taken less than 48 hours after drug administration, the 48h values were extrapolated using the terminal elimination rate constant, K_{el} as described below. If the last sample was taken after 48 hours, a 48h value was estimated by interpolation. Intermediate missing values remained missing (equivalent to interpolating between neighbouring points when calculating AUC). Intermediate values below the limit of quantification (LOQ) were assigned a value of LOQ/2, while trailing values below LOQ were assigned a value of zero.

AUC_{0-inf}

The area under the concentration-time-curve from time 0h until infinity was determined for profiles that did not return to zero within 48 hours. AUC_{0-inf}, was calculated as the sum of AUC_{0-t} and C_t/K_{el} where Ct was the last sample above LOQ.

T_{max} and C_{max}

T_{max} and C_{max} were derived from the samples 0 - 48h after drug administration. Actual sampling time points were used for T_{max}.

Residual area:

Calculated as 100 * (1- AUC_{0-t} / AUC_{0-inf})

$T_{1/2\ el}$:

The elimination half-life $T_{½}$ was found by Ln(2)/K_{el},(for calculation of K_{el} refer to the below)

K_{el}:

The elimination rate constant, K_{el} was the slope of the terminal part of the log-concentration-time-curve and was found using log-linear regression. The final four plasma concentrations above LOQ were included in the calculation as a minimum. However, the log-linear plots of plasma concentration were inspected and a different selection of data points could have been chosen to ensure that the time period represented the terminal elimination phase. Actual time values were used.

MRT:

The mean residence time was calculated as

$$MRT_{0-inf} = AUMC_{0-inf} / AUC_{0-inf}, \text{ where}$$
$$AUMC_{0-inf} = AUMC_{0-t} + t*C_t/K_{el} + C_t/(K_{el})^2,$$

and where $AUMC_{0-t}$ was the area under the first moment curve from time 0 until the last valid measurement at the time point t. C_t was the last valid plasma concentration found at this time point, t.

$\%AUC_{0-Tmax}$

The proportion of AUC before T_{max} was found by 100 * ($AUC_{0\text{-}Tmax}$ / $AUC_{0\text{-}inf}$)

Pharmacokinetic Results

As displayed in Figure 14, below, there was a clear increase in the concentration of morphine with the increase in dosage. The curves of 1 x 60 mg Egalet® Morphine Formulation B and 2 x 30 mg Egalet® Morphine Formulation A were very close together, however during the first 8 hours, the plasma concentration of 1 x 60 mg Egalet® Morphine Formulation B was slightly higher than that of the 2 x 30 mg Egalet® Morphine Formulation A.

There was a very small bump in the mean profiles at 24 hours. However, this was more pronounced in some of the individual plots and could be a result of a hepatic recirculation or a naltrexone-derived increase in morphine absorption.

Also the metabolites morphine-3-glucuronide and morphine-6-glucuronide concentrations were proportional between strengths.

Individual plasma concentration profiles for each subject showed consistency across profiles for morphine, morphine-3-glucuronide, and morphine-6-glucuronide concentrations within each subject.

For morphine, these relationships are also presented in Table 22, displaying a slightly greater than two-fold increase of the $AUC_{0\text{-}48}$ when the dose was doubled. It was also shown that the $AUC_{0\text{-}48}$ for the 60 mg Egalet® Morphine Formulation B was higher than the $AUC_{0\text{-}48}$ for the 2 x 30 mg Egalet® Morphine Formulation A. The results for C_{max} displayed the same pattern as the results for $AUC_{0\text{-}48}$ and the results for $AUC_{0\text{-}48}$ and C_{max} was confirming the patterns displayed by Figure 14. The relationship between dosage and $AUC_{0\text{-}inf}$ was the same as for $AUC_{0\text{-}48}$.

Table 22 Endpoints for Morphine

Treatment	**30 mg Form B**	**60 mg Form B**	**100 mg Form B**	**200 mg Form B**	**2x30 mg Form A**
$AUC_{(0-48h)}$(nmol*h/L):					
Mean	300	681	1175	2437	618
Min – Max	110 – 535	364 – 1127	756 - 2189	1371 - 4176	203 - 1008
C_{max} (nmol):					
Mean	19	43	73	168	35
Min – Max	8 - 40	23 - 69	38 - 138	71 - 277	16 - 72
$AUC_{(0-inf)}$(nmol*h/L):					
Mean	381	823	1355	2702	728
Min – Max	117 – 1668	414 - 2582	784 - 2795	1483 - 4528	209 - 1324
Residual area (Pct.):					
Mean	13	13	11	9	13
Min – Max	0 - 74	1 - 75	2 - 44	0 - 20	1 - 43
T_{max} (h):					
Mean	3	3	3	4	4
Min – Max	1 – 6	1 – 5	1 - 10	1 - 10	0 - 24
$T_{(1/2)}$(h):					
Mean	17	17	14	13	14
Min – Max	4 - 129	5 - 134	7 - 47	5 - 20	6 - 31
Elimination rate (1/h):					
Mean	0.06	0.06	0.06	0.06	0.06
Min – Max	0.01 - 0.17	0.01 - 0.13	0.01 - 0.10	0.03 - 0.14	0.02 - 0.12
MRT (h):					
Mean	27	29	24	21	25

Min – Max	9 - 178	14 - 186	13 - 61	12 - 29	9 - 49
Proportion $AUC_{(0\text{-}Tmax)}$ (Pct.):					
Mean	12	9	11	15	12
Min – Max	1 - 36	1 - 20	1 - 28	2 - 33	1 - 54

For morphine-3-glucuronide and morphine-6-glucuronide plasma concentrations, the relationship between dosage and $AUC_{0\text{-}48}$, $C_{max,}$ and $AUC_{0\text{-}inf}$ was the same as for the morphine plasma concentrations. The pattern of the residual area and the elimination rate for morphine-3-glucuronide and morphine-6-glucuronide concentrations was also similar as to that of morphine. For both morphine-3-glucuronide and morphine-6-glucuronide concentrations, the mean T_{max} was 4 hours.

Primary PK Analysis (Dose-linearity)

From the descriptive summaries of $AUC_{0\text{-}48}$ and C_{max} in Table 23, it was clear that a dose response relationship was present for $AUC_{0\text{-}48}$ and C_{max}.

Table 23 Primary Analysis of Morphine (Dose-Linearity)

	Coefficient for log-dose	Estimate	Std.Err.	90% Confidence Interval Lower	Upper
Full PK Data Set:					
$AUC_{(0-48h)}$ (nmol*h/L)	B	1.1171	0.02281	1.0792	1.1550
$AUC_{(0-inf)}$ (nmol*h/L)	B	1.0806	0,03317	1.0225	1.1358
C_{max}	B	1.1365	0.02297	1.0983	1.1747
Completers Only:					
$AUC_{(0-48h)}$ (nmol*h/L)	B	1.1185	0.02310	1.0801	1.1569
$AUC_{(0-inf)}$ (nmol*h/L)	B	1.0826	0.03376	1.0265	1.1387
C_{max}	B	1.1349	0.02310	1.0965	1.1733

The coefficient (beta) for log-dose was estimated in a mixed linear model including period as a fixed effect and subject as a random effect.
The analyses for completers only are regarded as exploratory.

Table 23 presents the analysis of dose-linearity for morphine concentration for AUC_{0-48} and C_{max}.

The table showed that dose-linearity could be assumed as the 90% confidence interval for β was fully contained within the interval 0.80- 1.25 for AUC_{0-48}, AUC_{0-inf} as well as for C_{max}, both for the full PK analysis set and for completers only. The estimates of coefficient for the log-dose, β, for the three parameters ranged from 1.08 to 1.14. This indicated that the bio-availability increased slightly more than proportionally with dose. However, since the confidence intervals were within the regulatory acceptance limits, this slight deviation was not considered clinically important.

The analysis of morphine-3-glucuronide and morphine-6-glucuronide concentrations confirmed the results for the morphine plasma concentration, as all 90% confidence

intervals were contained within the interval 0.80-1.25 and all estimates of β were slightly larger than 1.

Bioequivalence of 1x60 mg Formulation B versus 2x30 mg Formulation A

From Table 22, it was apparent that the mean values for AUC and C_{max} in the 60 mg Egalet® Morphine Formulation B treatment group and 2 x 30 mg Egalet® Morphine Formulation A treatment group were similar, but with slightly higher values for the 60 mg Egalet® Morphine Formulation B treatment group.

The results of the secondary analysis of morphine are presented in Table 24 and the estimated ratios of means for AUC_{0-48h} and AUC_{0-inf} were 110.2 and 111.6, respectively. The estimated ratio for C_{max} was 121.7. The 90% confidence intervals for AUC_{0-48h} and AUC_{0-inf} lay within the boundaries of 0.80 and 1.25; however the upper limit of the 90% confidence intervals for C_{max} exceeded the 1.25 boundary value. Hence, bioequivalence was not demonstrated. Both AUC_{0-48h} and C_{max} were statistically significantly different from 100 on a 5% level as a minimum. The results were confirmed by the analyses of the completers only and the analysis of subjects with a residual area less than 20%. Moreover, the ratio was statistically significantly different from 100 on a 5% level.

The estimated ratios and associated 90% confidence intervals reflected the results of morphine concentration. However, for the morphine-3-glucuronide concentration, AUC_{0-inf} and C_{max} were statistically significantly different from 100 on a 5% level and the 90% confidence interval for analysis of subjects with a residual area less than 20% was contained within 0.80 – 1.25. It should be noted that the upper boundary of the 90% confidence interval for C_{max} was below the 133% limit, which was the upper limit of a widened acceptance interval of 75-133%, as mentioned in guidelines.
The estimated ratios and associated 90% confidence intervals for morphine-6-glucuronide concentration reflected the results of the morphine concentration. However, in this analysis, the ratio between Egalet® Morphine Formulations A and B for all endpoints except AUC_{0-48h} were statistically significantly different from 100.

Table 24 Secondary Analysis of Morphine (Bioequivalence)

	Means		Form B / Form A		
	Form. B (1x60 mg)	**Form. A (2x30mg)**	**Ratio**	**90 % CI**	**p-value**
Full PK data set:					
$AUC_{(0-48h)}$ (nmol*h/L)	642.3	583.0	110.2	(102.7, 118.2)	0.0235
$AUC_{(0-inf)}$ (nmol*h/L)	755.2	676.8	111.6	(100.9, 123.5)	0.0749
C_{max} (nmol/L)	40.5	33.3	121.7	(113.0, 131.2)	<.0001
Completers only:					
$AUC_{(0-48h)}$ (nmol*h/L)	654.7	591.3	110.7	(103.0, 119.1)	0.0218
$AUC_{(0-inf)}$ (nmol*h/L)	772.2	693.6	111.3	(100.2, 123.7)	0.0945
C_{max} (nmol/L)	41.1	33.4	122.9	(113.8, 132.8)	<.0001
PK set-tail less 20%:					
$AUC_{(0-inf)}$ (nmol*h/L)	714.4	624.9	114.3	(104.6, 125.0)	0.0141

Endpoints are log-transformed before analysis, and results are transformed back and presented as ratios. The model includes period and treatment as fixed effects and subject as a random effect.

Estimates and comparisons are based on the full model with all treatments included.

The mean is the geometric mean estimated from the model.

Exploratory Secondary Analysis of Bioequivalence of 1x30 mg Formulation B versus 1x30 mg Formulation A

The results in Table 25 showed that for all endpoints based on morphine plasma concentrations, the 90% confidence for the estimated ratio of means lay within the boundaries of 0.80 to 1.25 and none of the ratios were statistically significantly different from 100. Hence, bioequivalence could be assumed to have been demonstrated.

Table 25 Exploratory Secondary Analysis of Morphine (Bioequivalence) - 1x30 mg Formulation B versus 1x30 mg Formulation A

	Means		Form B / Form A		
	Form. B (1x30 mg)	Form. A (1x30mg)	Ratio	90 % CI	p-value
Full PK data set:					
$AUC_{(0-48h)}$ (nmol*h/L)	277.8	291.5	95.3	(88.9, 102.2)	0.2551
$AUC_{(0-inf)}$ (nmol*h/L)	326.5	338.4	96.5	(87.3, 106.7)	0.5569
C_{max} (nmol/L)	18.0	16.6	108.2	(100.5, 116.6)	0.0811
Completers only:					
$AUC_{(0-48h)}$ (nmol*h/L)	282.2	295.7	95.5	(88.8, 102.6)	0.2899
$AUC_{(0-inf)}$ (nmol*h/L)	332.6	346.8	95.9	(86.3, 106.6)	0.5114
C_{max} (nmol/L)	18.3	16.7	109.4	(101.3, 118.2)	0.0547
PK set-tail less 20%:					
$AUC_{(0-inf)}$ (nmol*h/L)	296.8	312.4	95.0	(86.5, 104.2)	0.3604

Formulation A (1*30mg) is derived by dividing AUC and C_{max} by 2 - since two tablets were administered.

Endpoints are log-transformed before analysis, and results are transformed back and presented as ratios. The model includes period and treatment as fixed effects and subject as a random effect.

Estimates and comparisons are based on the full model with all treatments included. The mean is the geometric mean estimated from the model.

Yet another explorative analysis was comparing the 24 hour plasma concentrations of morphine from formulation B to formulation A. The ratio between 60 mg Egalet® Morphine Formulation B and 2x30 mg Egalet® Morphine Formulation A at hour 24 was 116.0% (CI: 98.5% - 136.7%), p= 0.1351.

Safety Results

A total of 105 treatment emergent adverse experiences (TEAEs) were reported by 17 of the 24 subjects who received at least one dose of the study medication (safety population). No adverse events were severe, significant, or serious.

No safety issues were observed with respect to clinical laboratory results and vital signs results.

No relevant differences were observed among the treatment groups with respect to mean values and changes from baseline for vital signs and clinical laboratory results.

Discussion

The PK profiles of single doses of four different strengths of Egalet® Morphine Formulation B have been evaluated in 35 subjects in this 5-period cross over study to assess whether dose-proportionality of Egalet® Morphine Formulation B could be demonstrated. PK profiles of a single dose of 1x 60 mg Egalet® Morphine Formulation B and 2 x 30 mg Egalet® Morphine Formulation A have been evaluated to assess bioequivalence between Egalet® Morphine Formulations B and A. In addition PK profiles of a single dose of 1 x 30 mg Egalet®Morphine Formulation B and 1 x 30 mg Egalet® Morphine Formulation A (in the form of dividing PK parameter of 2x30 mg with 2) have been evaluated.

As the 90% confidence intervals for the regression coefficient of the log-dose for AUC_{0-48h} and C_{max} were contained within the interval 0.8-1.25 for morphine, dose-linearity has been demonstrated. Since the estimated coefficient of the log-dose for AUC_{0-48h} as well as C_{max} were larger than 1 and the lower limit of the 90% confidence interval was larger than 1, there was some statistical evidence of over-proportionality. Combining these two observations, some deviation from dose proportionality was present, but in the light of the protocol defined limits, this deviation was concluded not clinically relevant. Evaluating the slight deviation from proportionality between the dose levels, table 26 gives the ratios between geometric means after adjusting for dose. It was observed that the main part of the deviation was caused by the 30 mg tablet having a lower bioavailability than the other three doses as indicated by the AUC_{0-inf}.

Table 26

Ratio of Geometric Means	60mg/30mg	100mg/60mg	200mg/100mg
AUC_{0-48}	1,16	1,03	1,04
AUC_{0-inf}	1,15	1,00	1,01
C_{max}	1,14	1,01	1,16

Evaluating morphine plasma concentration the 90% confidence intervals for the ratio of means between 1 x 60 mg Egalet® Morphine Formulation B and 2 x 30 mg Egalet® Morphine Formulation A for AUC_{0-48h} and AUC_{0-inf} were contained within the interval 80-125. However, as the upper limit of the 90% confidence intervals for the ratio of means for C_{max} exceeded 125 bioequivalence was not demonstrated.

As the dose-linearity analysis showed some evidence of over-proportionality and the analysis of bioequivalence compared 1 x 60 mg Egalet® Morphine Formulation B and 2 x 30 mg Egalet® Morphine Formulation A, an analysis comparing AUC and C_{max} of 1 x 30 mg Egalet® Morphine Formulation B to half AUC and half C_{max} of 2 x 30 mg Egalet® Morphine Formulation A was performed. All 90% confidence intervals for this analysis were contained within the interval 0.80-1.25 for morphine. This means that when assuming the two Egalet® Morphine 30 mg Formulation A tablets result in a doubling of the PK response, then bioequivalence has been demonstrated between Egalet® Morphine Formulations A and B.

The minor peak in PK profiles at 24 hours could be an influence of naltrexone as seen in earlier studies and/or as a result of hepatic recirculation.

A total of 105 TEAEs were reported by 83% (n=29) of the 35 subjects who received at least one dose of the study medication (safety population). No trend was observed with respect to overall adverse event frequencies or types of adverse events experienced with respect to dose level or treatment. No other adverse events derived from abnormal clinical laboratory results or vital signs measurements were recorded for more than one subject in any given treatment group. No notable differences were observed with respect to mean values and changes from baseline for clinical laboratory and vital signs measurements.

Conclusion

The primary objective of evaluating dose-linearity of four different strengths of Egalet® Morphine Formulation B resulted in a demonstration of dose-linearity.

No severe, significant, or serious adverse events were reported during the study. The frequency of adverse event observations was not related to dose level or treatment. The most frequently occurring adverse events were expected or procedure-related and were mild or moderate in intensity. No safety issues were observed with respect to the clinical laboratory tests and vital signs. The evaluation of safety and tolerability of Egalet® Morphine showed no notable differences between 1 x 60 mg of Formulation B (Treatment B) and 2 x 30 mg of Formulation A (Treatment E), with respect to the safety parameters collected (adverse events and vital signs).

Claims

1. A pharmaceutical composition comprising

a) a matrix composition comprising

i) an active drug substance; and

ii) at least one polyglycol

said matrix composition having a cylindrical shape optionally with tapered end(s), the length of said matrix being in the range of 7.5 to 15 mm, said matrix being surrounded by

b) a coating having one or two openings exposing at least one surface of said matrix, said coating being substantially impermeable to an aqueous medium,

wherein said composition is formulated for continued administration with in the range of 20 to 28 hours interval between individual administrations.

2. The pharmaceutical composition according to claim 1, wherein the area of the cross section of said matrix is in the range of 1 to 75 mm^2.

3. The pharmaceutical composition according to claim 1, wherein the area of the cross section of said matrix is at least 20 mm^2

4. The pharmaceutical composition according to anyone of the preceding claims, wherein the length of said matrix is in the range of 8 to 15 mm, preferably in the range of 8 to 10 mm, more preferably in the range of 9 to 9.5 mm.

5. The pharmaceutical composition according to anyone of the preceding claims, wherein the length of said matrix is in the range of 7.5 to 12 mm, preferably in the range of 7.5 to 10 mm, more preferably in the range of 7.5 to 8 mm.

6. The pharmaceutical composition according to anyone of the preceding claims, wherein the coating comprises two openings each exposing one end of the matrix.

7. The pharmaceutical composition according to any of the preceding claims, wherein a therapeutically effective response is achieved over the entire interval between administrations.

8. The composition according to anyone of the preceding claims, wherein steady state trough is at least 20%, such as at least 30%, such as at least 40%, for example at least 50% of steady state C_{max}.

9. The composition according to anyone of the preceding claims, wherein steady state trough is in the range of 30 to 80%, preferably in the range of 40 to 80% of steady state C_{max}.

10. The composition according to anyone of the preceding claims, wherein C_{min} is reached no earlier than 12 hours, preferably no earlier than 18 hours after last administration.

11. The composition according to anyone of the preceding claims, wherein the 2nd point where a concentration of 50% of steady state C_{max} is reached is at least 4 hours, preferably at least hours after last administration.

12. The composition according to anyone of the preceding claims, wherein the 1st point where a concentration of 50% of steady state C_{max} is reached is in the range of 0.5 to 2.5 hours after last administration.

13. The composition according to anyone of the preceding claims, wherein MRT is at least 11 hours, preferably at least 15 hours.

14. The composition according to anyone of the preceding claims, wherein T_{max} is in the range of 3 to 6 hours, preferably in the range of 4 to 6 hours after last administration to a steady state individual.

15. The composition according to anyone of the preceding claims, wherein the protraction index is at least 0.20, preferably at least 0.30.

16. The composition according to any one of the preceding claims, wherein the active drug substance is an analgesic.

17. The composition according to claim 16, wherein the composition is for treatment of pain in an individual in need thereof.

18. The composition according to anyone of claims 16 to 17, wherein the composition is formulated for continued administration with in the range of 20 to 28 hours interval between individual administrations and wherein pain relief is achieved over the entire interval between administrations.

19. The composition according to anyone of claims 16 to 18, wherein the analgesic is an opioid, which may be a naturally occurring, a synthetic or a semisynthetic opioid.

20. The composition according to anyone of claims 16 to 19, wherein the analgesic is selected from the group consisting of morphine, oxycodone, hydrocodone, hydromorphone, norhydrocodone oxymorphone, noroxycodone, morphine-6-glucuronode and pharmaceutically acceptable salts of any of the aforementioned.

21. The composition according to any one of claims 17 to 20, wherein said pain is chronic pain.

22. The composition according to anyone of claims 17 to 21, wherein said pain is moderate to severe.

23. The composition according to anyone of claims 17 to 22, wherein said individual is an individual suffering from cancer.

24. The composition according to anyone of claims 17 to 22, wherein said individual is an individual suffering from a severe injury.

25. The composition according to anyone of claims 17 to 24, wherein said individual is a post-surgical individual.

26. The composition according to anyone of the preceding claims, wherein each dosage of the active drug substance is in the range of 10 to 500 mg of said active drug substance.

27. The composition according to anyone of the preceding claims, wherein the polyglycol is a water soluble crystalline or semi-crystalline polymer.

28. The composition according to anyone of the preceding claims, wherein at least one polyglycol is a homopolymer.

29. The composition according to anyone of the preceding claims, wherein at least one polyglycol is a copolymer.

30. The composition according to anyone of the preceding claims, wherein the total concentration of polyglycols in the matrix composition is from 5 to 99% w/w such as from 15 to 95% w/w, for example from 30 to 90% w/w, such as from 30 to 85% w/w, for example from 30 to 80% w/w, such as from 40 to 80% w/w, for example from 45 to 75% w/w, such as from 40 to 50% w/w, for example from 45 to 50% w/w, such as from 60 to 85% w/w, for example from 60 to 80% w/w, for example from 70 to 75% w/w.

31. The composition according to anyone of the preceding claims, wherein at least one polyglycol is a polyethylene glycol and/or a polyethylene oxide.

32. The composition according to claim 31, wherein the polyethylene glycol and/or polyethylene oxide has a molecular weight of in the range of 20,000 to 700,000 daltons, such as in the range of 20,000 to 600,000 daltons, for example in the range of 35,000 to 500,000 daltons, such as in the range of 35,000 to 400,000 daltons, for example in the range off 35,000 to 300,000 daltons, such as in the range of 50,000 to 300,000 daltons, for example about 200,000 daltons, such as about 300,000 daltons.

33. The composition according to anyone of the preceding claims 1 to 31, wherein the matrix comprises at least two different polyglycols, wherein said different polyglycols are selected from the group consisting of polyethylene oxides.

34. The composition according to claim 33, wherein one PEO has an average molecular weight in the range of 150,000 to 250,000, preferably approximately 200,000 and the other PEO has an average molecular weight in the range of 250,000 to 350,000, preferably approximately 300,000.

35. The composition according to anyone of the preceding claims 28 to 34, wherein the concentration of the homopolymers in the matrix composition is in the range of 5to 90% w/w, such as in the range of 20 to 85% w/w, for example in the range of 20 to 75% w/w, such as in the range of 20 to 70% w/w for example in the range of 20 to 40% w/w, such as in the range of 30 to 85% w/w, for example in the range of about 30 to 75% w/w, such as in the range of 30 to 50% w/w, for example in the range of 30 to 40% w/w, such as in the range of 30 to 35% w/w, such as in the range of 31 to about 33% w/w, such as in the range of 50 to 85% w/w, from 60 to 80% w/w, for example in the range of 70 to 80% w/w, for example in the range of 70 to 75% w/w, such as in the range of 71 to about 73% w/w.

36. The composition according to anyone of the preceding claims 29 to 35, wherein the copolymer is a poloxamer that has an average molecular weight in the range of 2,000 to 30,000 dalton, such as in the range of 2,000 daltons to 20,000 daltons, for example in the range of 4,000 daltons to 18,000 daltons, such as in the range of 6,000 daltons to 10,000 daltons.

37. The composition according to anyone of the preceding claims, wherein the matrix comprises one or more copolymers selected from the group consisting of poloxamers.

38. The composition according to claim 37, wherein the matrix comprises only one poloxamer and has a length of in the range of 7.5 to 15 mm, preferably a length of in the range of 7.5 to 10 mm.

39. The composition according to anyone of the preceding claims 29 to 38, wherein the concentration of co-polymer in the matrix composition is in the range of 0 to 30% w/w, such as in the range of 1 to 20 % w/w, for example in the range of 2 to 10% w/w, such as in the range of 2 to 5%, w/w, such as in the range of 5 to 30% w/w, for example in the range of 5 to 20% w/w, such as in the range of 5 to 15.

40. The composition according to anyone of the preceding claims, wherein the matrix further comprises one or more gelling agent(s).

41. The composition according to any one of the preceding claims, wherein the coating is insoluble in an aqueous medium.

42. The compositions according to any one or the preceding claims, wherein the coating comprises one or more polymers selected from the group consisting of starch based polymers, cellulose based polymers, synthetic polymers and biodegradable polymers.

43. The composition according to anyone of the preceding claims, wherein the coating comprises one or more polymers selected from the group consisting of ethyl cellulose grade 20, ethyl cellulose grade 100, polylactic acid (PLA), Cornpack 200, polycaprolactone, PEO 7000000 and polyhydroxybuturate.

44. The composition according to anyone of the preceding claims, wherein the coating comprises ethyl cellulose, preferably grade 20 and/or grade 100.

45. The composition according to anyone of the preceding claims, wherein the coating comprises one or more biodegradable polymers, selected from the group consisting of polylactic acid and polycaprolactone.

46. The composition according to anyone of the preceding claims, wherein the coating comprises at least 85% polymers, wherein the polymer are selected from the group consisting of biodegradable polymers and cellulose based polymers.

47. The composition according to any one of the preceding claims, wherein the coating in addition comprises one or more plasticizers.

48. The composition according to anyone of the preceding claims, wherein the composition is designed for oral administration.

49. The composition according to anyone of the preceding claims, wherein the composition is in the form of tablets.

50. The composition according to anyone of the preceding claims, wherein the pharmaceutical composition is an injection moulded or extruded composition.

51. The composition according to anyone of the preceding claims, wherein the composition is compressed.

52. The composition according to any of the preceding claims, wherein the matrix composition has a solubility and /or release rate in ethanol that is equal to or lower than that in water.

53. The composition according to anyone of the preceding claims, wherein the composition is resistant to isolation of the active drug substance by crushing, melting and ethanol extraction.

54. The pharmaceutical composition according to anyone of the preceding claims, wherein the active drug substance is essentially not subject to entero-hepatic recirculation and the length of said matrix is in the range of 8 to 15 mm, preferably in the range of 8 to 10 mm, more preferably in the range of 9 to 9.5 mm.

55. The pharmaceutical composition according to anyone of the preceding claims, wherein the active drug substance is subject to entero-hepatic recirculation and the length of said matrix is in the range of 7.5 to 12 mm, preferably in the range of 7.5 to 10 mm, more preferably in the range of 7.5 to 8 mm.

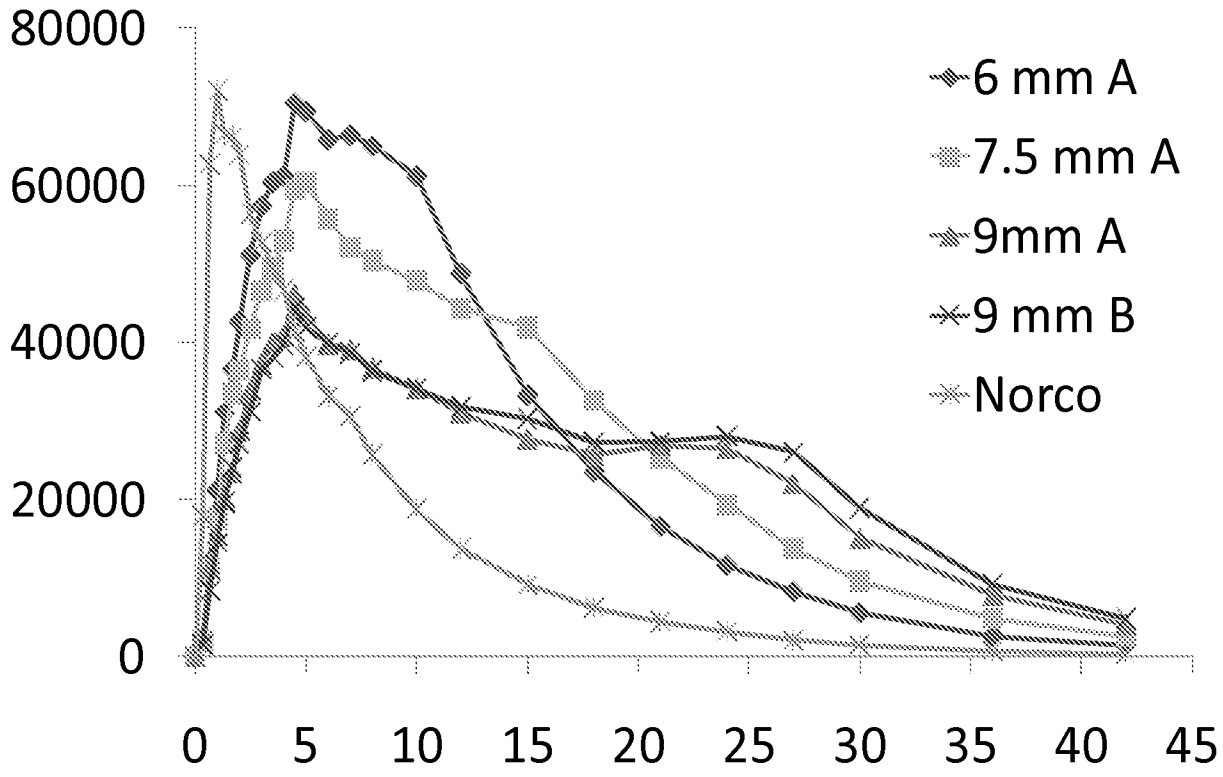
56. A method of treating a clinical condition in an individual in need thereof, said method comprising administering the pharmaceutical composition according to any one of claims 1 to 55 to an individual in need thereof.

57. The method according to claim 56, wherein said clinical condition is pain.

58. Use of the composition according to any one of claims 1 to 55 for the preparation of a medicament for treatment of a clinical condition in an individual in need thereof.

59. Use according to claim 58, wherein said clinical condition is pain.

Fig. 1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Norco

Fig. 2

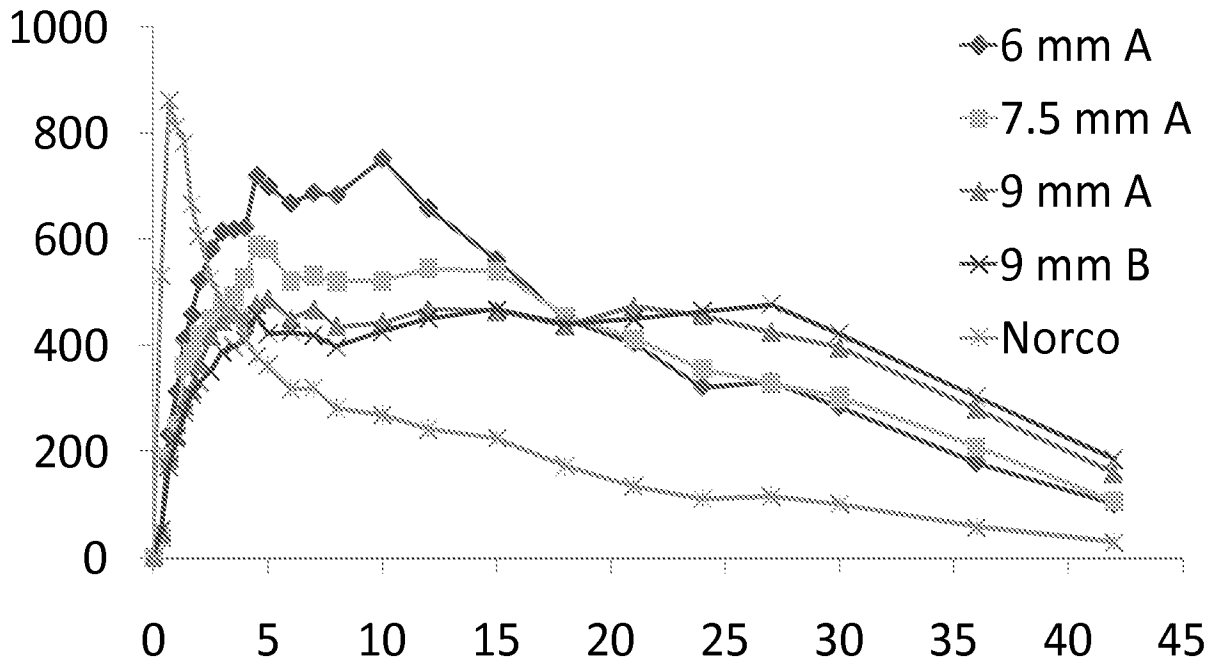
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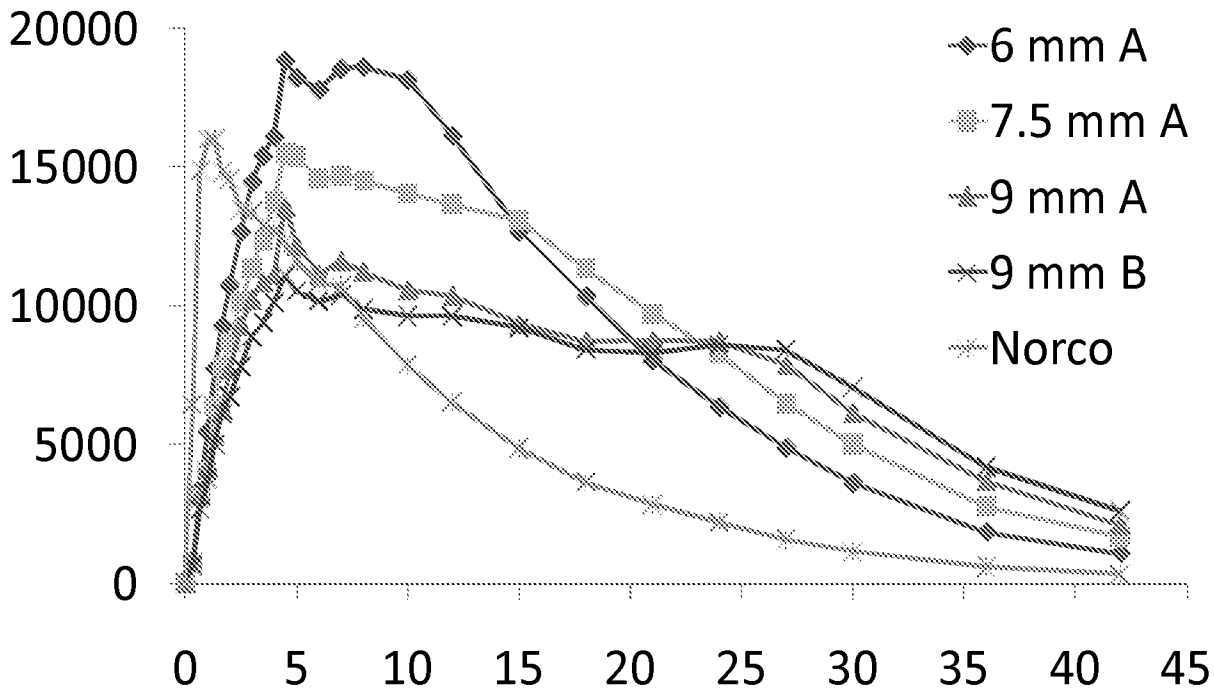
Fig. 3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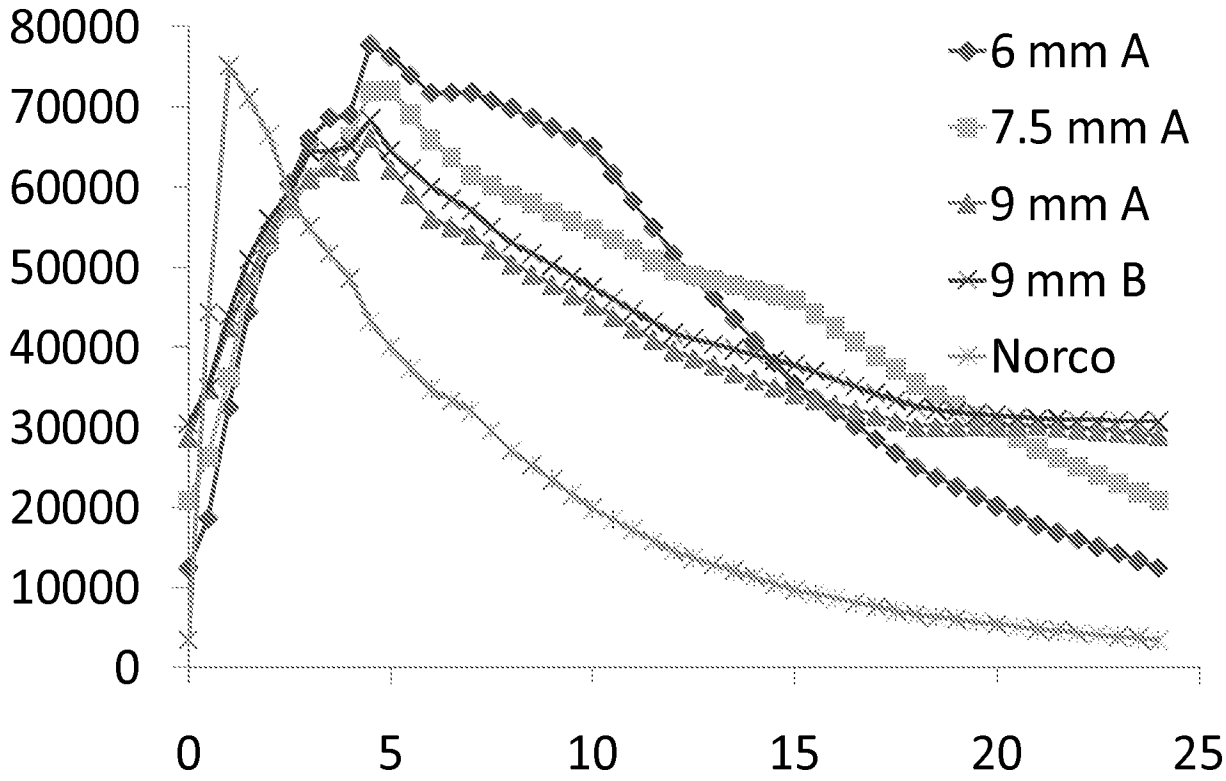
Norco

Fig. 4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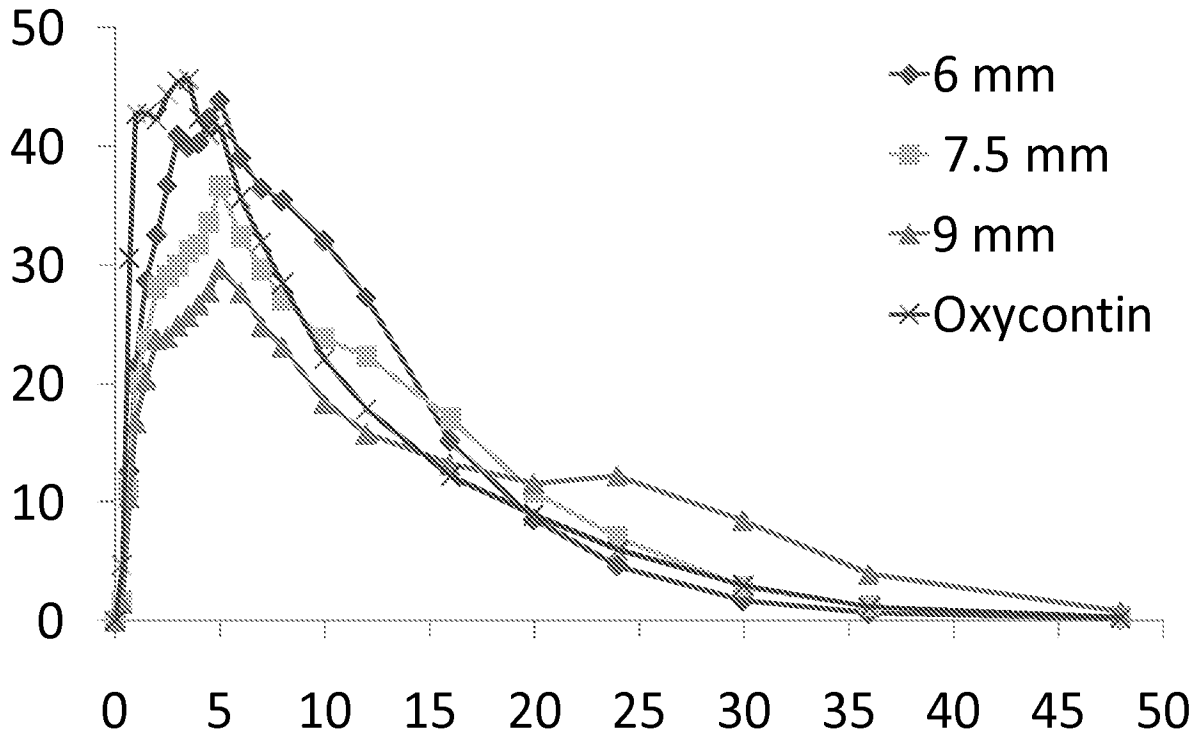
Norco

Fig. 5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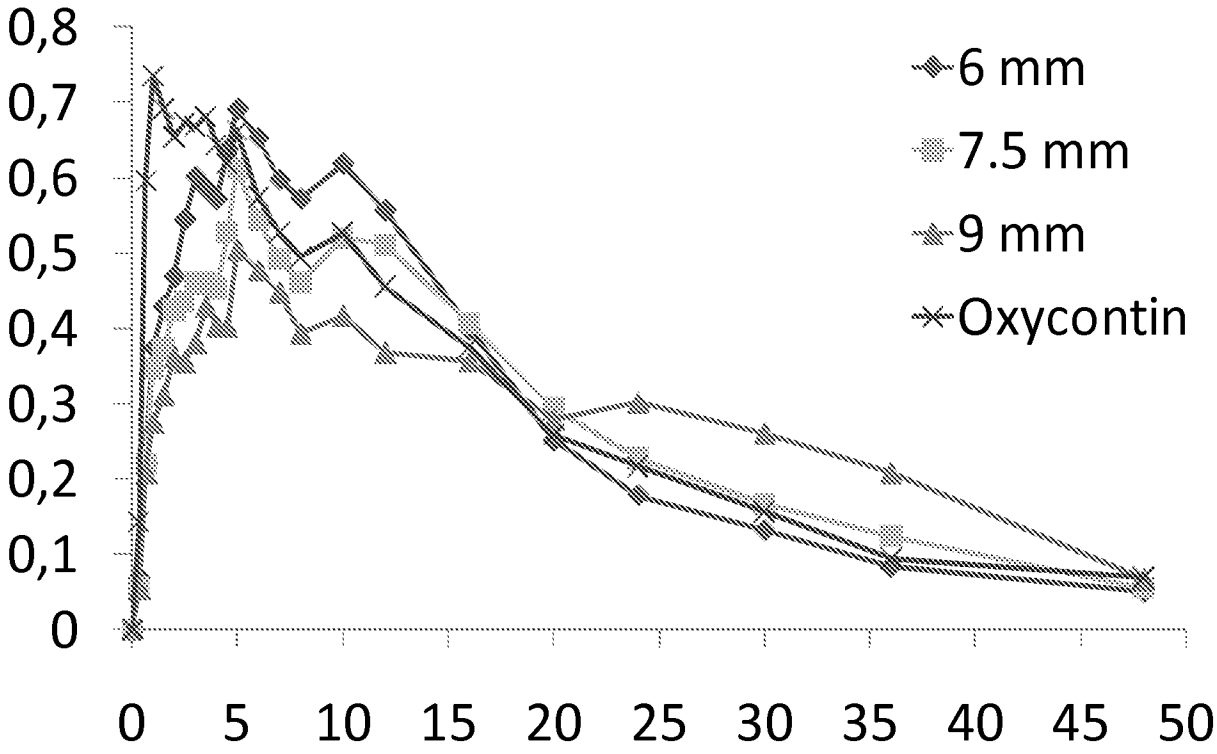
7.5 mm
9 mm
Oxycontin

Fig. 6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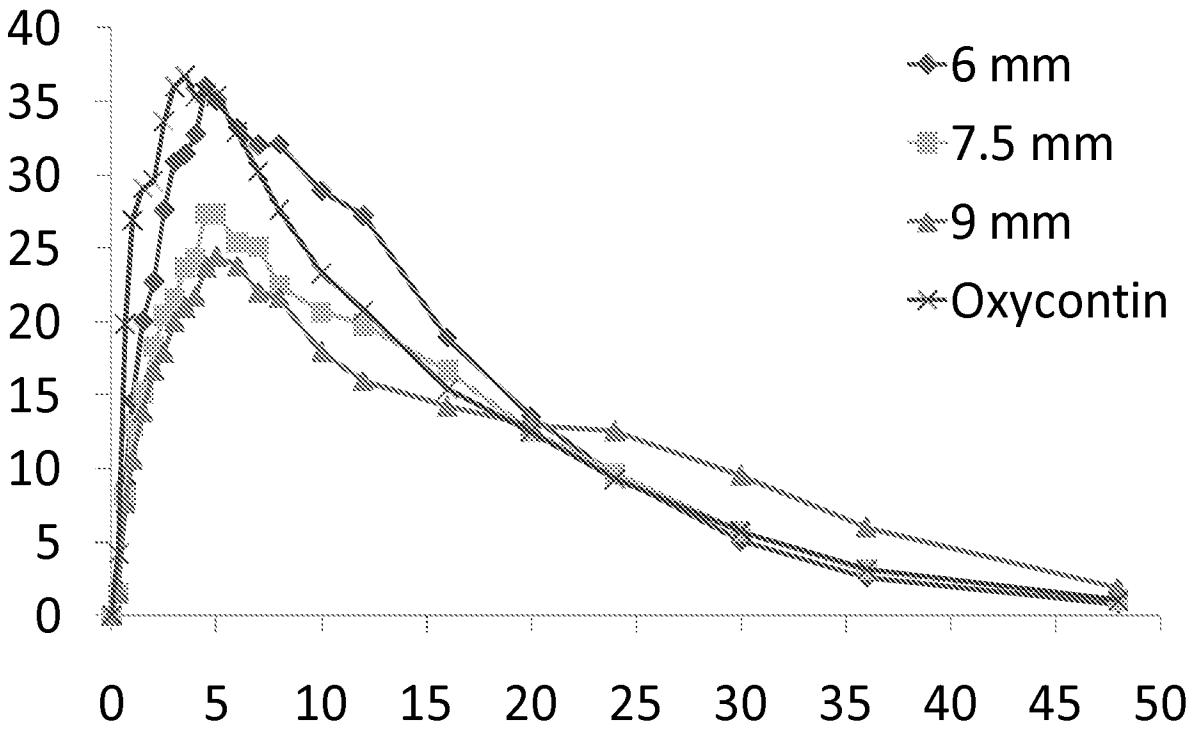
Oxycontin

Fig. 7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Oxycontin

Fig. 8

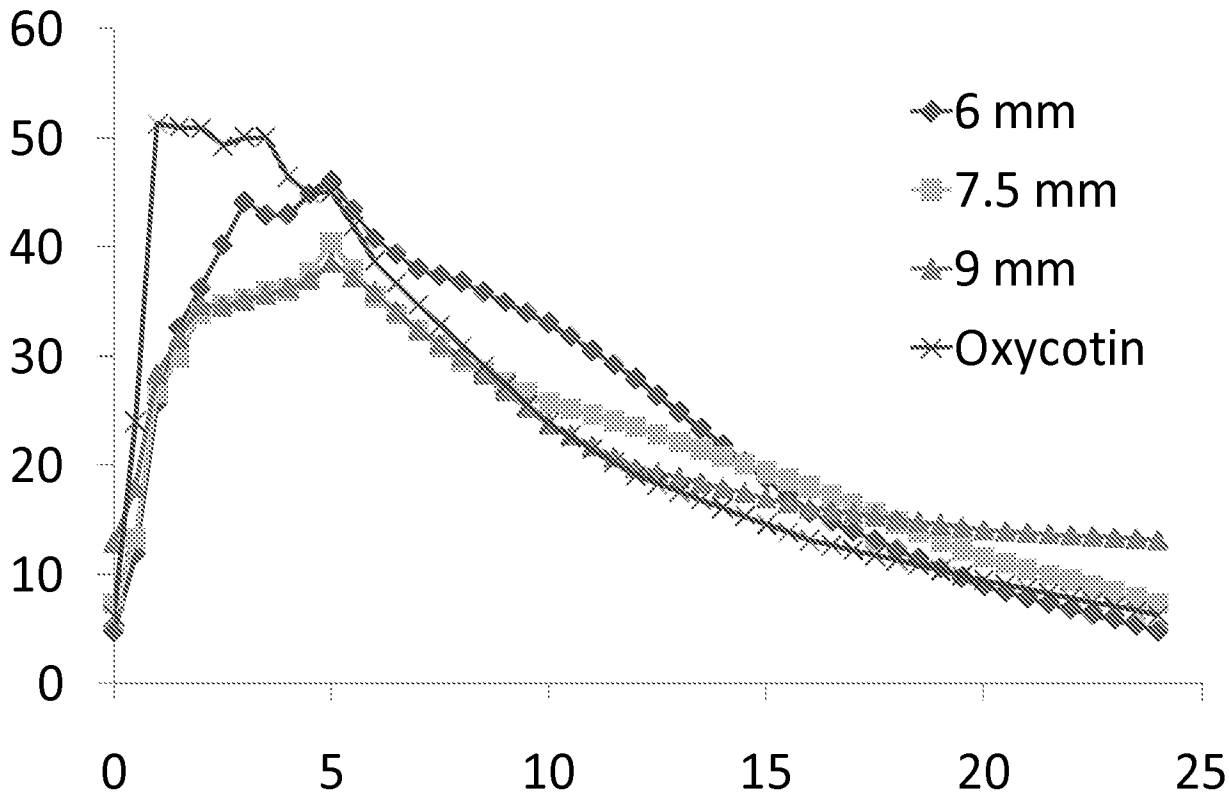


Fig. 9

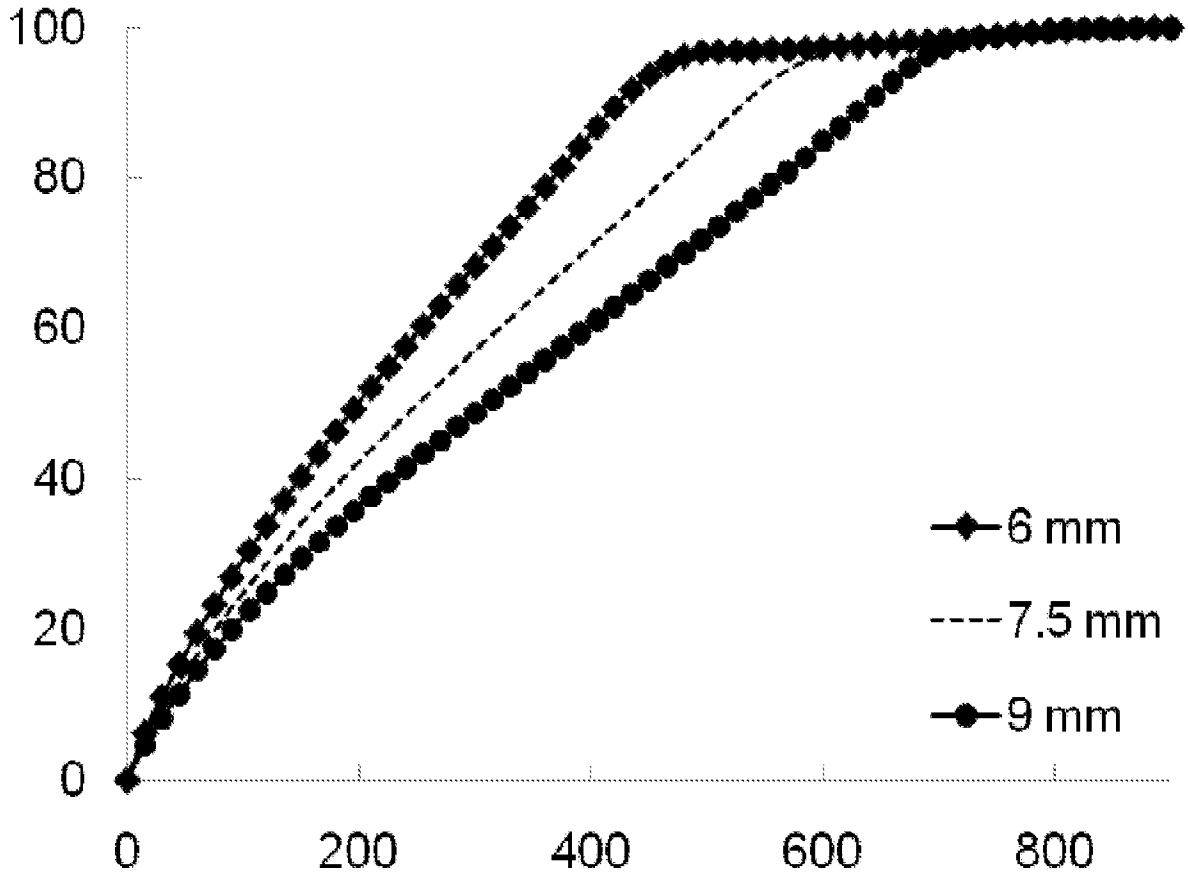
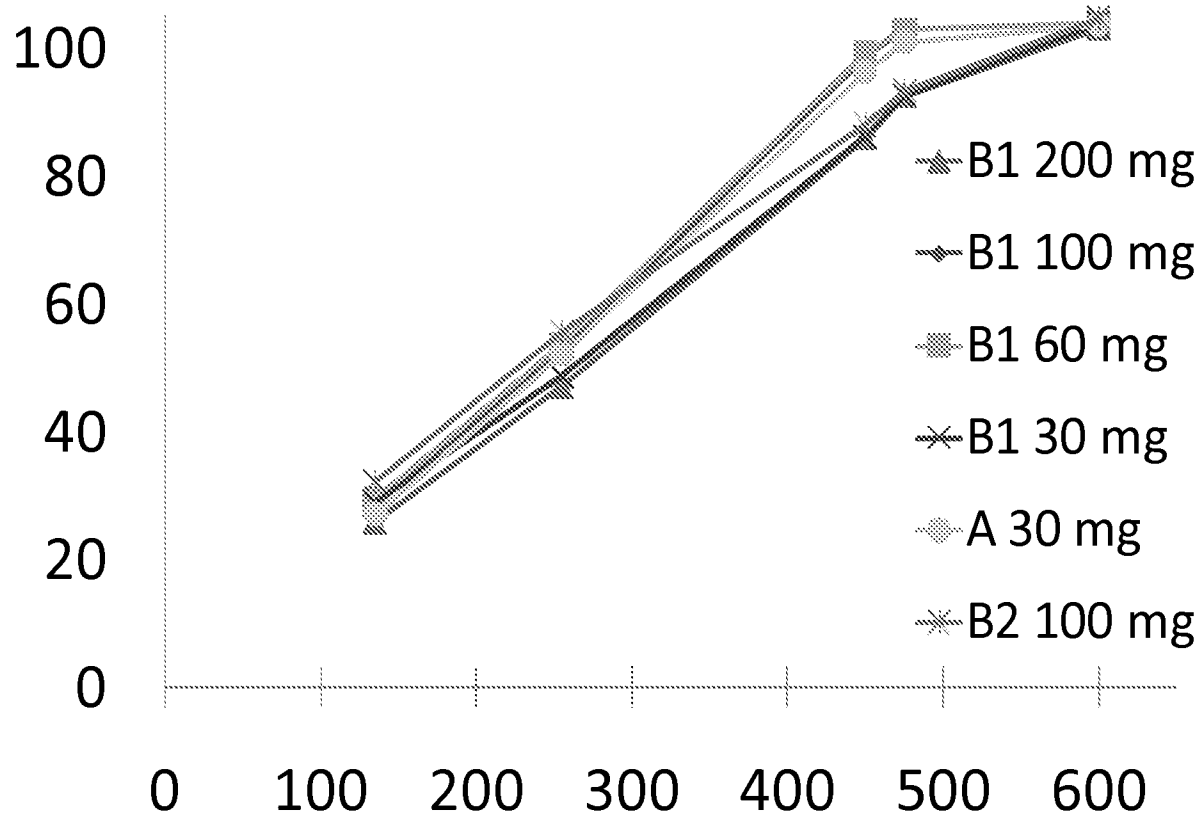


Fig. 10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B1 100 mg
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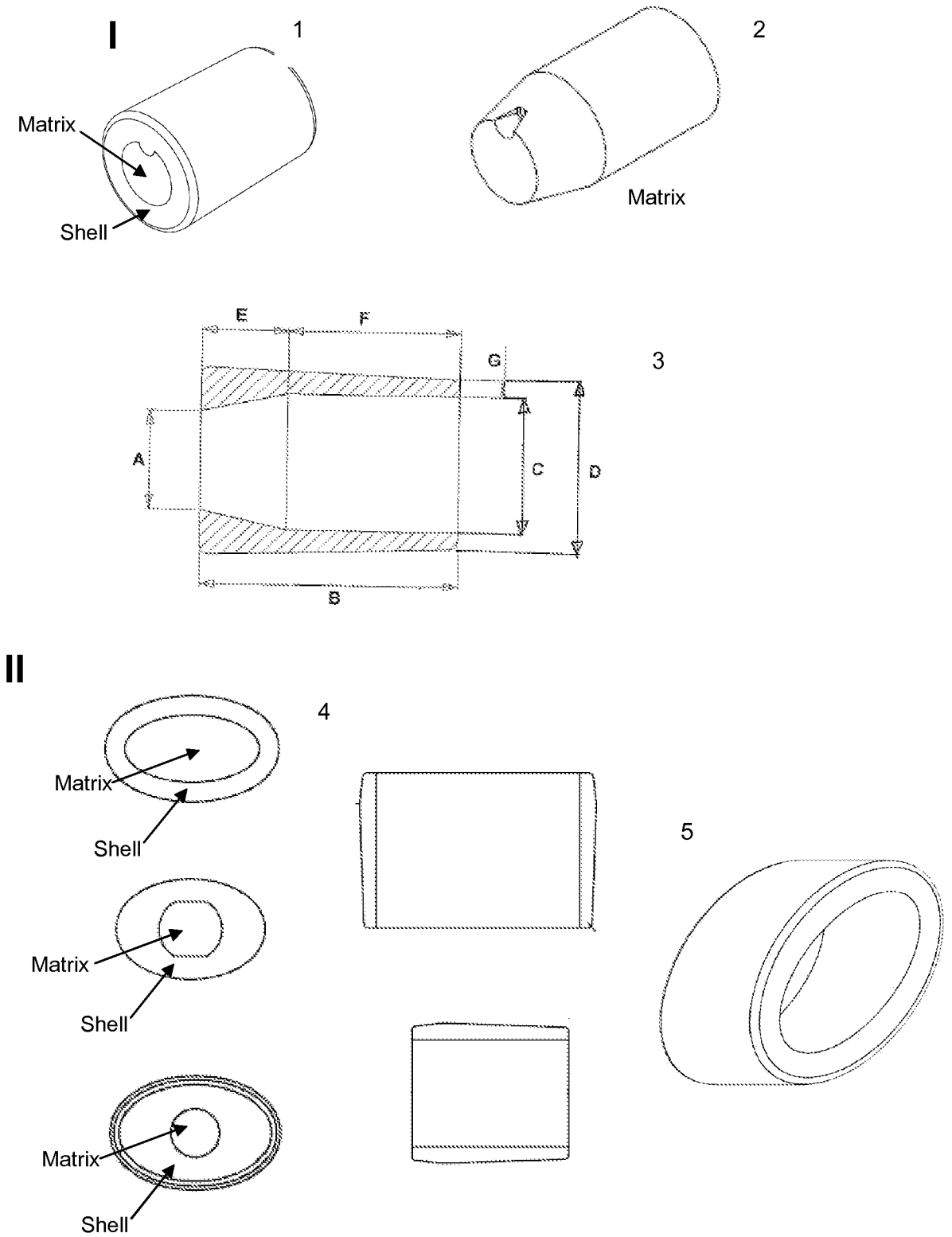
A 30 mg
B2 100 mg

Fig. 11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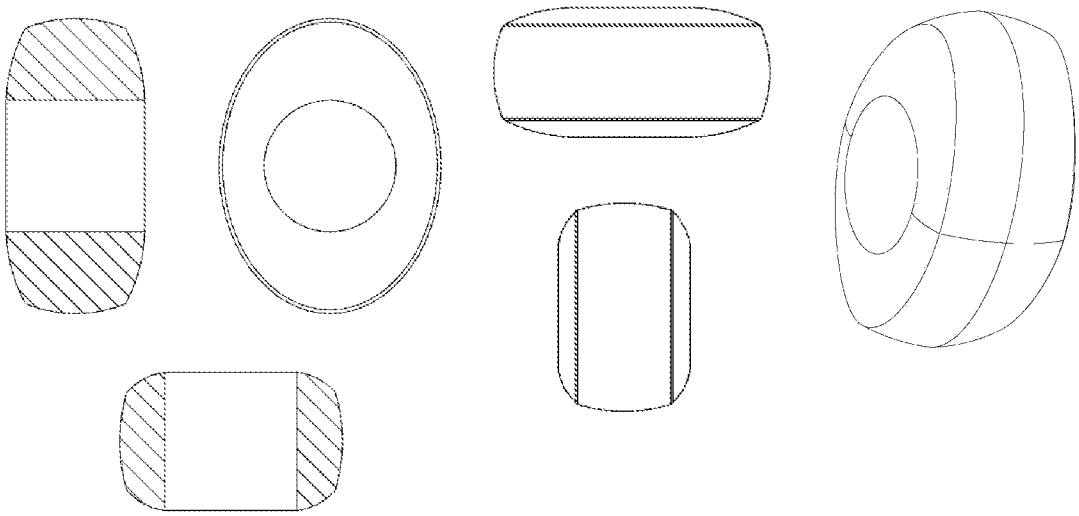
III



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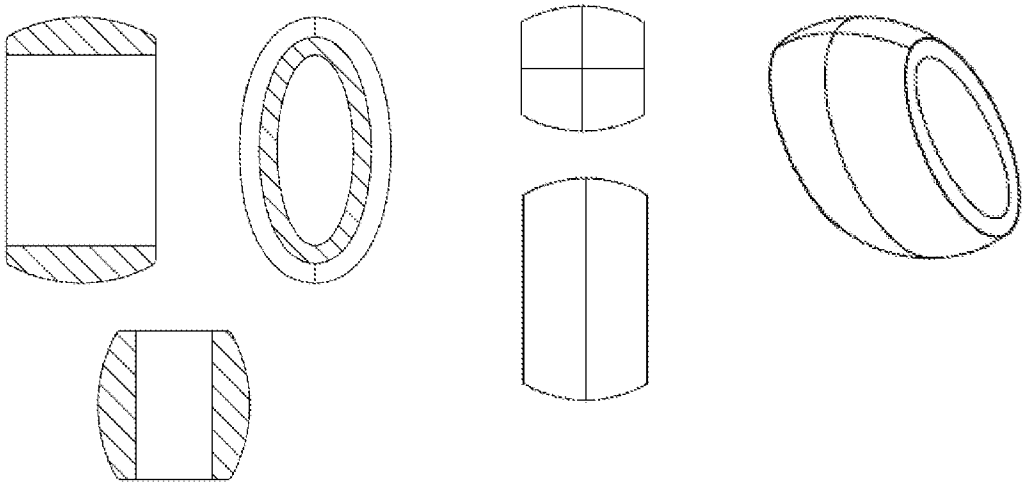

Fig. 12

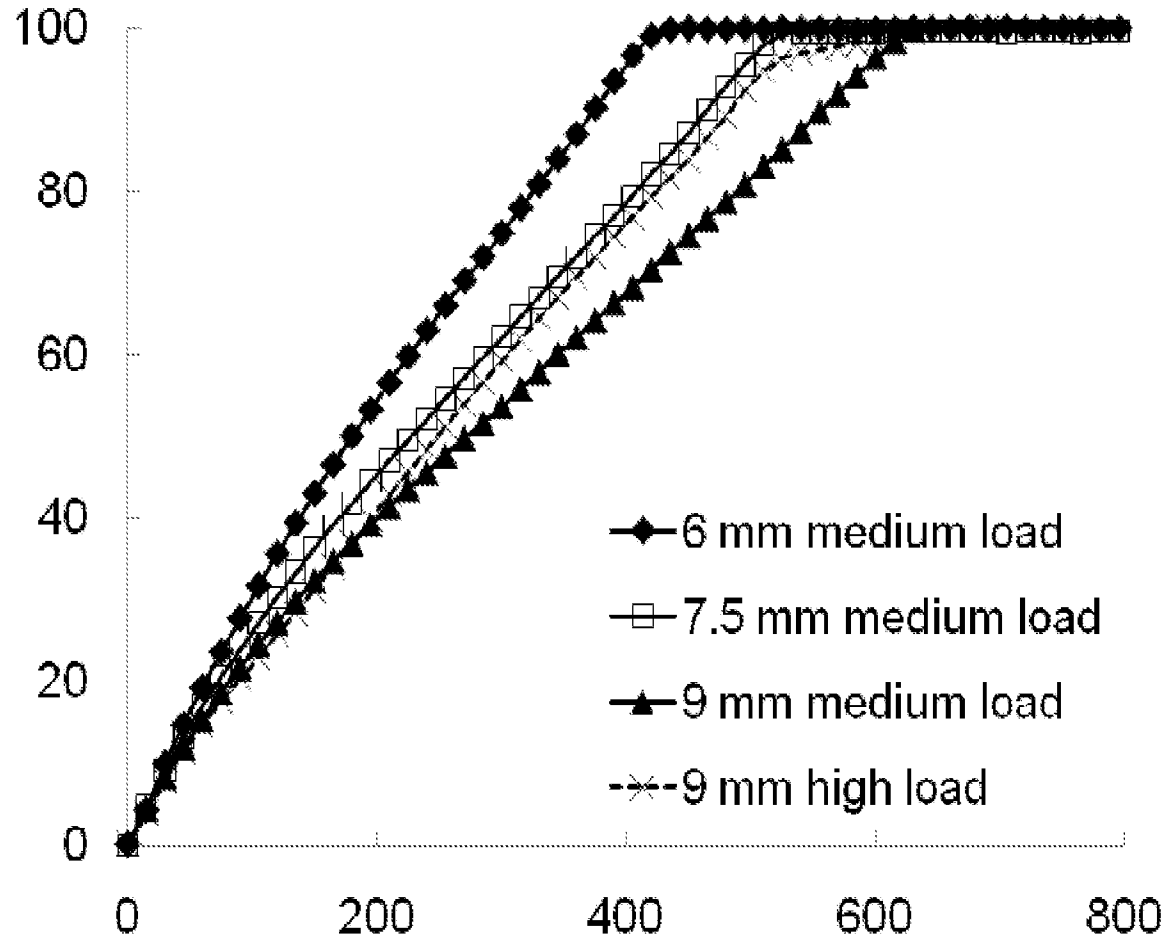
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Fig. 13

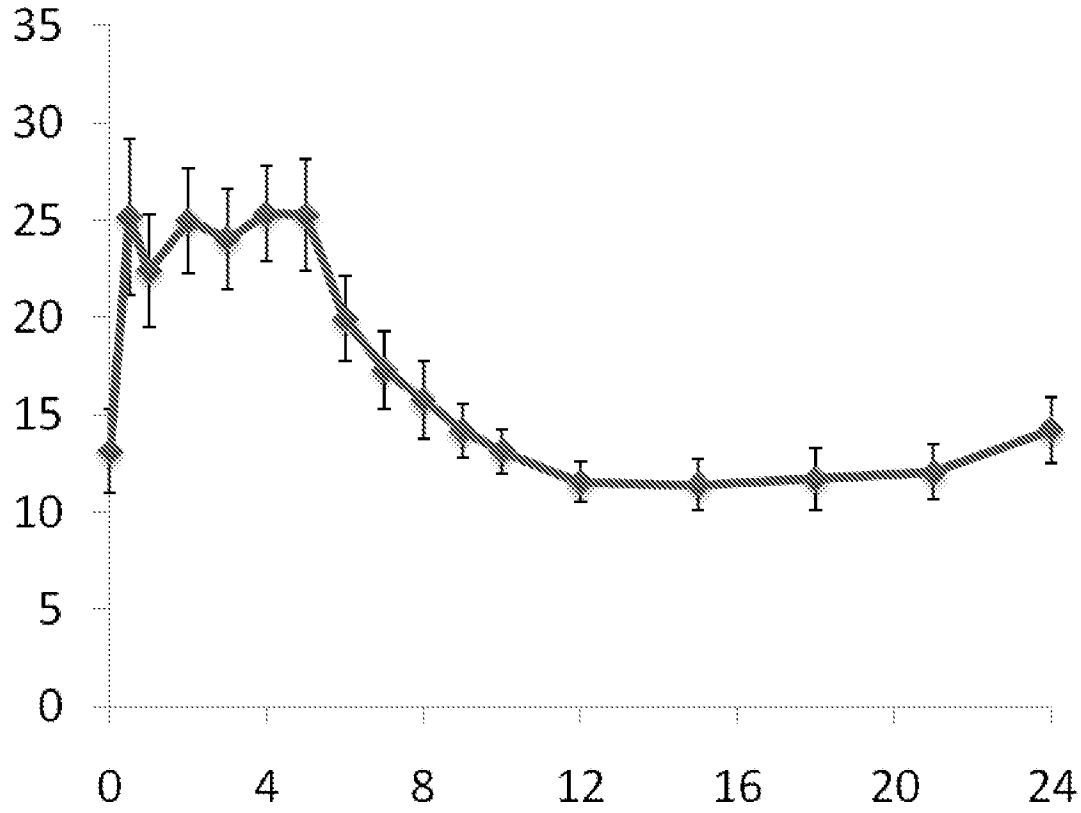
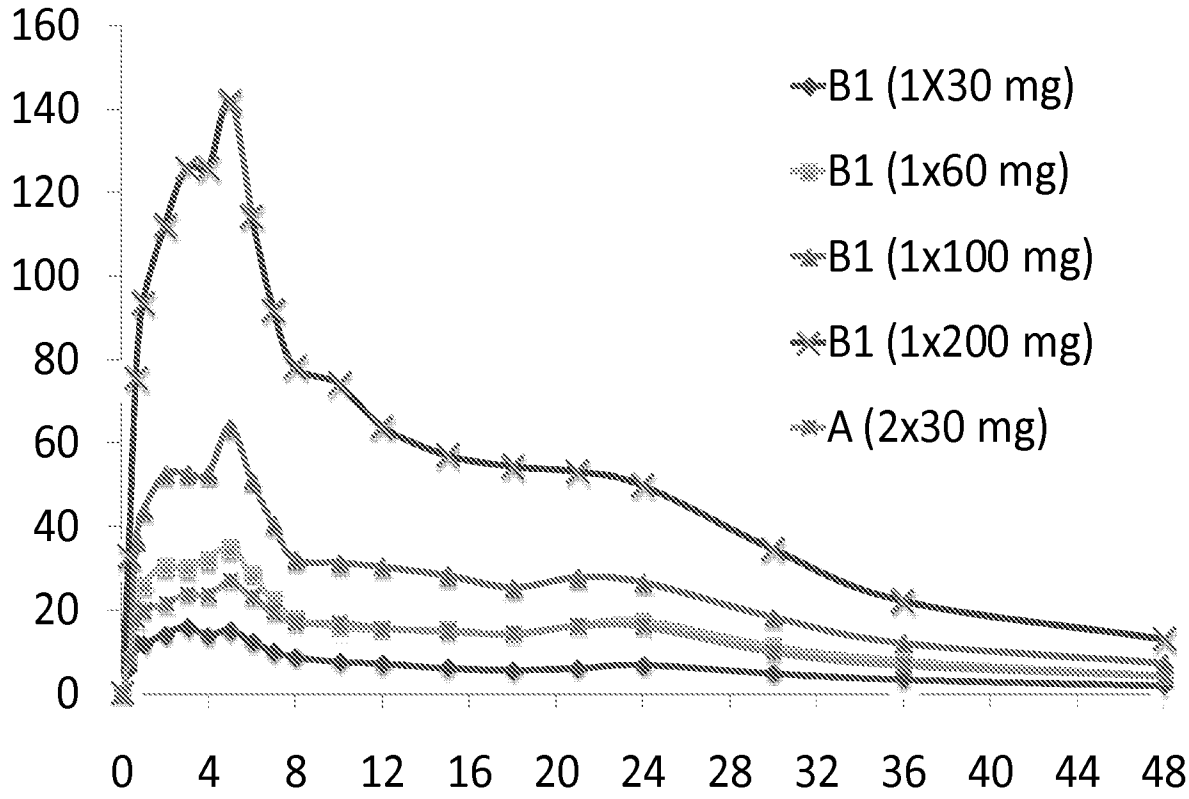


Fig. 14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B1 (1x60 mg)
B1 (1x100 mg)
B1 (1x200 mg)
A (2x30 mg)