

Extended release formulation of pudafensine

Technical field

5 The present invention relates to extended release formulations comprising the compound pudafensine or a pharmaceutically acceptable salt thereof as disclosed herein.

Background

10 Pudafensine (the compound exo 7 [(8 azabicyclo[3.2.1]octan-3-yl)oxy]-3 methoxy-chromen-2-one also known as IP2015) is a mono-amine re-uptake inhibitor under clinical development. In the nervous system, the compound increases levels of the neurotransmitters; dopamine and serotonin, which has utility in treatment of central nervous system disorders.

15 Given the compound's effect on the central nervous system, it is necessary that oral formulations exhibit a robust release profile. To date, no known solid formulations of the compound have been shown to produce an effective release of the compound. The compound suffers from low solubility, which poses a challenge both in the manufacture
20 of such formulations and for the oral administration of the compound.

In some applications, it would be highly desirable to provide formulations capable of sustained compound release over extended periods, without compromising the absorption of the compound or the delivery of a therapeutically effective dose to the
25 patient.

Accordingly, there is a strong un-met need for solid forms that can ensure a consistent and robust release of pudafensine while providing an acceptable exposure of the compound to achieve a pharmacological effect without side effects for the patient.
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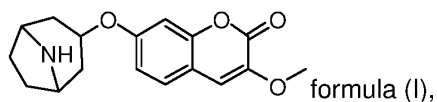
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Summary

The inventors have surprisingly found specific formulations of pudafensine that can provide extended release of pudafensine while maintaining the overall exposure of the compound in humans. The formulations according to the present disclosure provide an increase in $t_{\max}$ and a reduction in the peaks and variability of the plasma concentration of pudafensine without sacrificing overall exposure of the compound in plasma. This is highly advantageous in the clinical application of pudafensine since it allows for an extended presence of pudafensine in a subject without compromising the therapeutic efficacy due to a loss in exposure, whilst avoiding the presence of adverse events.

Thus, in one aspect, the present disclosure provides for a composition comprising pellets, said pellets comprising or consisting of:

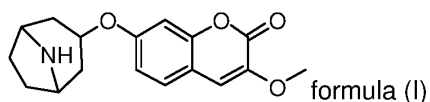
- a) a pellet core;
- b) a drug layer covering the core, the drug layer comprising a compound of formula (I)



- c) a barrier coating layer comprising a film forming agent wherein said layer covers the drug layer b), and
- d) an extended release layer comprising one or more extended release polymer(s); wherein said extended release layer covers the barrier coating in c).

In one aspect, the present disclosure provides for a unit dosage form comprising the composition described herein.

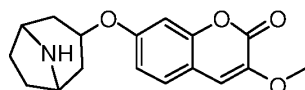
In one aspect, the present disclosure provides for a method of obtaining a therapeutically effective plasma concentration of a compound of formula (I)



in a subject, wherein the $t_{\max}$ of the compound of formula I is between 4 and 12 hours, said method comprising oral administration of a composition as described herein.

In one aspect, the present disclosure provides for a method of preparing a composition comprising pellets, the method comprising:

- a) providing pellet core,
- b) providing a drug layer solution comprising a compound of formula (I)



thereof;

- c) coating the drug layer solution onto the pellet core to form a drug layer;
- d) providing a barrier coating solution comprising a film forming agent;
- e) coating the barrier coating solution on top of the drug layer in c) to obtain a barrier coating layer;
- f) providing an extended release solution comprising one or more extended release polymer(s)
- g) coating the extended release solution on to the barrier coating layer in e) to obtain an extended release layer.

Description of Drawings

Figure 1: Dissolution rate of IR pellets and IR capsules having 10 mg or 5 mg of pudafensine. **A, B:** IR pellets 10 mg pudafensine; **C:** IR capsules 5 mg pudafensine; **D:** IR pellets 5 mg pudafensine. Further details given in Example 2.

Figure 2: Dissolution rate of ER pellets and ER capsules having 10 mg or 5 mg of pudafensine. **A, B:** ER pellets 10 mg pudafensine; **C:** ER pellets 5 mg pudafensine; **D:** ER capsules 5 mg pudafensine. Further details are given in Example 2.

Figure 3: Concentration of pudafensine in plasma of humans after administration of pudafensine as extended release formulation, immediate release formulation and an aqueous solution.

Figure 4: Data from a Phase IIb study with the compound IP2015 in ED patients show their response to question Q3 of the international index of erectile function scale 15 (IIEF-15): When you attempted intercourse, how often were you able to penetrate (enter) your partner during the last week?

Figure 5: Data from a Phase IIb study with the compound IP2015 in ED patients show their response to question Q4 of the International Index of erectile function scale 15 (IIEF-15): During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

- 5 Figure 6: Data from a Phase IIb study with the compound IP2015 in ED patients show their overall response to questions of the International Index of erectile function scale 15 (IIEF-15).

Definitions

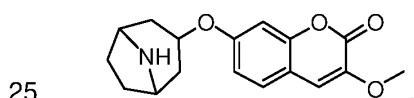
- 10 “C_{max}” is a term used in pharmacokinetics to refer to the maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administered and prior to the administration of a second dose.

“t_{max}” is the term used in pharmacokinetics to describe the time at which the C_{max} is observed.

- 15 As used herein the terms “inert core” and “inert sphere” refer to a pharmaceutically acceptable core for use in pharmaceutical formulations which core is inert. For example, the “inert core” or “inert sphere” refers to a pharmaceutically acceptable pellet that does not contain a drug substance.

- 20 “Pharmaceutically acceptable” means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

By “pudafensine,” “IP2015” or “compound I” is meant the compound of formula I. The compound of formula I is:



- The term “pharmaceutically acceptable salt” of a compound refers to a salt that is pharmaceutically acceptable, as defined herein, and preferably possesses the desired pharmacological activity of the parent compound. Pharmaceutically acceptable salts include acid addition salts formed with inorganic acids; or formed with organic acids; or salts formed when an acidic proton present in the parent compound either is replaced by a metal ion; or coordinates with an organic or inorganic base.
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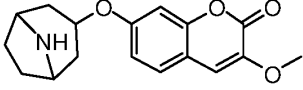
As used herein, "formulation" is the result of combining different substances, including the active ingredient, to produce a final product.

As used herein, the term 'weight of the pellets' refers to the total weight of the pellets including the drug layer, barrier coating layer and extended release layer within the composition, *e.g.*, the total weight of the components comprising the pellet core, drug layer, barrier coating layer, extended release layer, any other layer on the pellet. In capsule formulations, this does not include the weight of the capsule shell.

Detailed description

The present disclosure provides for a composition comprising pellets, said pellets comprising or consisting of:

- a) a pellet core;
- b) a drug layer covering the core, the drug layer comprising a compound of formula (I)

 formula (I), or a pharmaceutically acceptable salt thereof;

- c) a barrier coating layer comprising a film forming agent wherein said layer covers the drug layer b), and
- d) an extended release layer comprising one or more extended release polymer(s); wherein said extended release layer covers the barrier coating in c).

Composition

Pellets offer a high degree of flexibility in the design and development of oral dosage forms. Microcrystalline cellulose pellets (MCC) and sugar are well-known materials in pellet technology to use as core materials. Water-insoluble inert pellet cores are made of microcrystalline cellulose or silica, while water-soluble inert pellet cores are composed of sugar, such as sucrose, xylitol, mannitol, and lactose; starch or salts. Both material classes show desirable characteristics, such as a narrow particle size distribution, sphericity, and surface smoothness and may be used according to the invention. A person of skill in the art will be able to determine suitable materials and suppliers of spheres suitable as core for pellets of the compositions according to the present disclosure.

In one embodiment, the pellets comprise an inert pellet core. In one embodiment, the pellet core comprises or consist of microcrystalline cellulose (MCC). MCC is a commercially available chemical (CAS 9004-34-6) and its pellets are commercially available in multiple size ranges, for example Cellet® or Celphere™.

- 5 The size of the pellet core may be any suitable size, for example at least 100 µm. Different size of pellet cores may be used, for example pellet cores with sizes from 100 µm to 1500 µm, such as from 100 µm to 500 µm, such as from 500 µm to 1000 µm or from 1000 µm to 1500 µm.

- 10 Methods to coat pellet compositions are well known in the art. They can both start from a solution, dispersion or powder that is coated onto the pellets layer by layer. Well-established methods to coat pellets are for example: a fluidized bed technology, by compression coating, wüster coating, pan coating, centrifugal or rotor coating.

- 15 In one embodiment, the drug layer further comprises a binder. Binders are used to avoid the sticking of the drug on the pellets and provide uniform coating on the pellets. The binder is mixed with the drug in a solution and then coated onto the inert pellets. It was surprisingly found that the presence of a binder, such as HPMC, in the coating solution allowed for homogeneous coating of pudafensine on to the inert pellet coat despite the compound's low solubility.

- 20 Known binders are for example sucrose, starch, hydroxypropyl methyl cellulose (HPMC) hydroxypropyl cellulose (HPC), gelatin or polyvinylpyrrolidone. Thus, in one embodiment, the binder is: sucrose, starch, hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), gelatin, polyvinylpyrrolidone (PVP); polyalkylene glycols or polyalkylene oxides, such as polyethylene oxide (PEO); or mixtures thereof.

- 25 In one embodiment, the binder is hydroxypropyl methyl cellulose (HPMC). HPMC (CAS number 9004-65-3) is a cellulose derivative wherein some free hydroxyl groups in cellulose have been substituted with hydroxypropyl and methyl groups, different grades of HPMC having different multiple weight, degree hydroxypropyl or methyl groups and viscosities are commercially available and suitable for use in formulation development.

- 30 In one embodiment, the drug layer comprises the binder in an amount from 0.5% to 10% by weight of the composition or by weight of the pellets, such as from 0.5% to 5%, such as from 1% to 5%, such as from 2% to 5%, such as 2%, 3%, 4% or 5% by weight of the composition or by weight of the pellets. Particularly, in one embodiment the drug layer

comprises the binder, as described herein, in an amount from 0.5% to 10% by weight of the pellets, such as from 0.5% to 5%, such as 2%, 3%, 4% or 5% by weight of the pellets.

In one embodiment, the drug layer comprises HPMC in an amount from about 0.5% to about 10% by weight of the composition or by weight of the pellets . In one embodiment, the drug layer comprises HPMC in an amount from about 1% to 5% by weight of the composition or by weight of the pellets, such as about 2%, 3%, 4% or 5% by weight of the composition or by weight of the pellets. Particularly, in one embodiment the drug layer comprises HPMC, as described herein, in an amount from 0.5% to 10% by weight of the pellets, such as from 0.5% to 5%, such as 2%, 3%, 4% or 5% by weight of the pellets.

In one embodiment, the drug layer comprises additional excipients such as pH modifiers and/or stabilizers. The inventors unexpectedly found that the addition of sodium sulphite (also known as sodium sulphite or Na_2SO_3 , CAS number 7757-83-7) in the drug layer increased the dissolution rate of pudafensine from the drug layer. Thus, in one embodiment the drug layer further comprises sodium sulphite.

The pH modifier, the stabilizer or the sodium sulphite may be present for example in an amount from about 0.05 % to about 1.5 % by weight of the composition or the pellets, such as for example from 0.05 % to 0.5 % by weight, such as from 0.5 % to 1.0% by weight, such as for example 1.0 % to 1.5 % by weight of the composition or by weight of the pellets. In one embodiment, the stabilizer or the sodium sulphite is present in an amount from about 0.05% to about 1.5% by weight of the pellets.

In one embodiment, the sodium sulphite is present in an amount of about 0.3 % to 0.8% by weight of the pellets. In one embodiment, the sodium sulphite is present in an amount of about 0.5% by weight of the pellets.

In one embodiment, the compound of formula I, or a pharmaceutically acceptable salt thereof is present in an amount from about 0.5% to about 5 % by weight of the total composition or by weight of the pellets. For example, the compound of formula I may be present in an amount from 0.5 % to 1 %, such as from 1 % to 2 %, such as from 2 % to 3 %, such as from 3 % to 4 %, such as from 4 % to 5 % by weight of the total composition or by weight of the pellets. In one embodiment, the compound of formula I may be present from 2.5% to 3.5% by weight of the composition or by weight of the pellets.

In one embodiment, the compound of formula I, or a pharmaceutically acceptable salt thereof, is present in an amount from about 0.5% to about 5% by weight of the pellets. For example, the compound of formula I is present in an amount from 0.5 % to 1 %, such

as from 1 % to 2 %, such as from 2 % to 3 %, such as from 3 % to 4 %, such as from 4 % to 5 % by weight of the pellets. In one embodiment, the compound of formula I is present in an amount from 2.5% to 3.5% by weight of the pellets.

5 The pellets according to the present disclosure comprise in one embodiment a barrier coating between the drug layer and the extended release layer, said barrier coating comprising a film-forming agent. Film forming agents may be a polymer able to form a film and may be aided by the presence of plasticizers and stabilizers. Examples of known film forming agents in the art are cellulose derivatives, polyacrylates, polymethacrylates or copolymers of acrylate and methacrylate and polyvinylalcohol (PVA). The barrier
10 coating may help with reducing swelling of the pellets.

In one embodiment, the film-forming agent is HPMC. In one embodiment the HPMC is as described herein.

The film-forming agent may be present in the barrier coating in an amount from 0.5 % to about 5% by weight of the composition or by weight of the pellets. In one embodiment,
15 the barrier coating comprises the film-forming agent in an amount from 0.5% to 5% by weight of the pellets.

Thus, in one embodiment, the barrier coating comprises HPMC in an amount from 0.5 % to about 5% by weight of the composition or by weight of the pellets. The amount of HPMC in the barrier coating may be for example from 1% to 4%, such as from 1% to
20 2%, such as from 2% to 3%, such as from 3% to 4% by weight of the composition or by weight of the pellets. In one embodiment, the barrier coating comprises HPMC in an amount from about 1% to 4% by weight of the composition or by weight of the pellets. Particularly, in one embodiment the barrier coating comprises HPMC, as described herein, in an amount from 0.5% to 5% by weight of the pellets, such as from 0.5% to 5%,
25 such as 2%, 3%, 4% or 5% by weight of the pellets.

The extended release layer comprises at least one extended release polymer. The extended release polymer may be for example a hydrophobic polymer that is permeable when in contact with water. Examples of extended release polymers may be for example,
30 cellulose derivatives that have been modified with hydrophobic groups, such as short alkyl groups or other hydrophobic polymers such as synthetic polyacrylates derivatives with hydrophobic groups such as short alkyl groups.

In one embodiment, the at least one extended release polymer is ethylcellulose. Ethylcellulose (EC, CAS number: 9004-57-3) is a cellulose derivative wherein some free hydroxyl groups in cellulose have been substituted with ethyl groups, different grades of

EC having different molecular weight, degree of substitution with ethyl groups and viscosities are commercially available and suitable for use in formulation development. EC is a hydrophobic polymer that is insoluble but permeable in aqueous media and contributes to pH independent drug release.

5 In one embodiment, the at least one extended release polymer is present in an amount from 0.5% to about 10% by weight of the composition or by weight of the pellets. Particularly, in one embodiment, the extended release layer comprises the extended release polymer in an amount from 0.5 % to about 10% by weight of the pellets.

10 Thus, in one embodiment, the extended release layer comprises ethylcellulose in an amount from about 0.5% to about 10% by weight of the composition or by weight of the pellets, such as from about 1% to about 10%, such as from about 2% to about 10%, such as from about 3% to about 10%, such as from about 3% to about 4%, such as from about 4% to about 5%, such as from about 5% to about 6%, such as from about 6% to about 7%, such as from about 7% to about 8%, such as from about 8% to about 9%, such as from about 9% to about 10% by weight of the composition or by weight of the pellets. For
15 example, the extended release layer may comprise ethylcellulose in an amount from about 1% to about 5%, such as from about 2% to about 5% by weight of the composition or by weight of the pellets. In one embodiment, the extended release layer comprises ethylcellulose as described herein in an amount from 1% to about 10% by weight of the pellets, such as from about 2% to about 5% by weight of the pellets.
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The extended release layer comprises in one embodiment an additional film forming agent, such as a film forming agent as described herein above for the barrier coating layer. The presence of a film forming agent aids in forming the extended release layer and may also further contribute to the extended release properties of the formulation. In
25 one embodiment, the extended release layer further comprises HPMC.

The film forming agent may be present in the extended release layer in an amount from 0.5 % to about 5% by weight of the composition or by weight of the pellets. Particularly, in one embodiment the extended release layer comprises the film forming agent in an amount from 0.5% to about 5% by weight of the pellets.

30 Thus, in one embodiment, the extended release layer comprises HPMC in an amount from 0.5 % to about 5% by weight of the composition or by weight of the pellets. The amount of HPMC in the extended release layer may be for example from 1% to 4%, such as from 1% to 2%, such as from 2% to 3%, such as from 3% to 4% by weight of the composition or by weight of the pellets. In one embodiment, the extended release layer

comprises HPMC in an amount from about 1% to 4% by weight of the composition or by weight of the pellets. In one embodiment, the extended release layer comprises HPMC as described herein, in an amount from 0.5% to about 5% by weight of the pellets.

5 In one embodiment, the extended release layer comprises an extended release polymer as described herein, such as ethylcellulose in an amount from 0.5 to 10% and a film forming agent as described herein, such as HPMC, in an amount from 0.5% to 5%.

10 In one embodiment, the extended release layer further comprises a plasticizer. The plasticizer may aid in enhancing the flexibility and plasticity of the film or layer. It may do so by making polymer more pliable and softer. Suitable plasticizers are known to someone of skill in the art. For example, in one embodiment the plasticizer is selected from: esters derived from citric acid, such as triethyl citrate or tributyl citrate; acetylated monoglycerides; esters of phthalic acid; polyethylene glycol or derivatives thereof; and sorbitol or mixtures thereof.

15 In one embodiment, the extended release layer further comprises triethyl citrate. In one embodiment the triethyl citrate acts as a plasticizer.

20 In one embodiment, the extended release layer comprises the plasticizer in an amount from about 0.05% to about 5%, such as from 0.1% to about 3% by weight of the composition or by weight of the pellets. In one embodiment, extended release layer comprises the plasticizer in an amount from about 0.05% to about 5%, such as from 0.1% to about 3% by weight of the pellets.

25 In one embodiment, the extended release layer further comprises an antitacking agent. Antitacking agents are added to prevent the formation of lumps in solid form and easing packaging, transport and/or flowability. Suitable antitacking agents are known to someone of skill in the art. For example, in one embodiment the antitacking agent may be selected from: stearates or fatty acid salts of calcium or magnesium, talc, silica, silicates or combinations thereof.

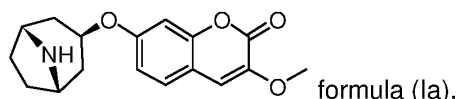
In one embodiment, the extended release layer further comprises magnesium stearate.

30 In one embodiment, the extended release layer comprises the antitacking agent, such as magnesium stearate in an amount from about 0.05% to about 5%, such as from 0.1% to about 3% by weight of the composition or by weight of the pellets.

In one embodiment, the extended release layer further comprises one or more additional excipients selected from:

- i. a film forming agent as described herein above;
- ii. a plasticiser as described herein above; and
- 5 iii. an antitacking agent as described herein above.

In one embodiment, the compound of formula I is according to formula Ia



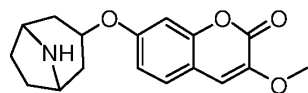
or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound is Exo-7-[(8-azabicyclo[3.2.1]octan-3-yl)oxy]-3-methoxy-chromen-2-one or a pharmaceutically acceptable salt thereof.

In one embodiment, the pharmaceutically acceptable salt of the compound of formula (I) or formula (Ia) is a hydrochloride salt.

In one embodiment, the composition is an extended release (ER) composition of the compound of formula I. The extended release composition provides for an increase of $t_{\max}$ of the compound of formula I.

Thus, in one embodiment the present disclosure provides for a composition which is an extended release composition of an active ingredient consisting of a compound of formula I,

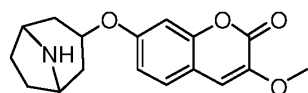


composition comprising pellets, said pellets comprising or consisting of:

- a) an inert pellet core comprising microcrystalline cellulose (MCC);
- b) a drug layer comprising: the compound of formula (I), or a pharmaceutically acceptable salt thereof, in an amount of about 0.5% to about 5% by weight of the total composition or by weight of the pellets and HPMC in an amount of about 0.5% to about 5% by weight of the total composition or by weight of the pellets, wherein the drug layer covers the inert core;
- c) a barrier coating layer comprising HPMC in an amount of about 0.5% to about 5% by weight of the total composition or by weight of the pellets, wherein the barrier coating layer covers the drug layer b); and

- d) an extended release layer comprising ethyl cellulose in an amount of about 0.5 to 10% by weight of the total composition or by weight of the pellets, wherein the extended release layer covers the barrier coating layer c).

5 In one embodiment the present disclosure provides for a composition which is an extended release composition of an active ingredient consisting of a compound of formula I,



formula (I), or a pharmaceutically acceptable salt thereof, the composition comprising pellets, said pellets comprising or consisting of:

- a) an inert pellet core comprising microcrystalline cellulose (MCC);
- 10 b) a drug layer comprising: the compound of formula (I), or a pharmaceutically acceptable salt thereof, in an amount of about 0.5% to about 5% by weight of the pellets and HPMC in an amount of 0.5% to about 5% by weight of the pellets, wherein the drug layer covers the inert core;
- 15 c) a barrier coating layer comprising HPMC in an amount of about 0.5% to about 5% by weight of the pellets, wherein the barrier coating layer covers the drug layer b); and
- d) an extended release layer comprising ethyl cellulose in an amount of about 0.5 to 10% by weight of the pellets, wherein the extended release layer covers the barrier coating layer c).

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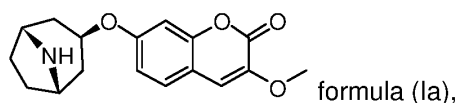
In one embodiment, the drug layer further comprises other excipients such as pH modifiers or stabilizers, as described herein. In one embodiment, the drug layer further comprises sodium sulphite as described herein.

25 In one embodiment, the extended release layer further comprises one or more additional excipients selected from:

- i. a film forming agent selected from the group consisting as described herein;
- ii. a plasticiser selected as described herein; and
- iii. an antitacking agent as described herein.

30 In one embodiment, the extended release layer further comprises HPMC as described herein.

In one embodiment, the compound of formula I is according to formula Ia



or a pharmaceutically acceptable salt thereof.

5 In one embodiment, the compound is exo 7 [(8 azabicyclo[3.2.1]octan-3-yl)oxy]-3-methoxy-chromen-2-one or a pharmaceutically acceptable salt thereof.

In one embodiment, the composition according to the present disclosure comprises an amount of the compound of formula I of about 0.5 mg to about 30 mg, such as from 1 mg to 20 mg, such as from 1 mg to about 16 mg, such as 1 mg to about 10 mg, such as from 2 mg to about 10 mg, such as from 3 mg to about 10 mg, such as from 4 mg to about 10 mg. For example, the composition may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg of the compound of formula I.

Dosage form

15 The present disclosure provides for dosage form, such as a pharmaceutical dosage form, comprising the composition as described herein. In one embodiment, the dosage form is a unit dosage form. Methods to manufacturing dosage forms, including suitable excipients and materials will be known to the skilled artisan.

20 The unit dosage form or the pharmaceutical dosage form is in one embodiment a solid dosage form. In one embodiment, the unit dosage form or the pharmaceutical dosage form is a capsule.

Dosage forms are designed to facilitate the safe and effective delivery of active compounds to patients.

25 Thus, in one embodiment, the composition according to the present disclosure is in the form of a unit dosage form or a pharmaceutical dosage form. In one embodiment, the composition according to the present disclosure is a capsule.

In one embodiment, the composition is for oral administration . As demonstrated by the examples, the compositions according to the present disclosure provide for extended release of pudafensine after oral administration, while maintaining exposure of pudafensine.

Extended release

The inventors have surprisingly shown that the compositions according to the present disclosure provide for extended release of pudafensine in the gastrointestinal tract after oral administration.

5 In one embodiment, the composition provides a pharmacokinetic profile having a single mean average plasma concentration peak upon oral administration.

The examples demonstrate that compositions according to the present disclosure are able to reduce $C_{\max}$ of the compound of formula I after oral administration compared to administration of an aqueous solution of an equivalent amount of the compound of
10 formula I.

In one embodiment, the composition reduces $C_{\max}$ of the compound of formula I upon oral administration. In one embodiment, $C_{\max}$ is reduced by at least 10%, such as at least 20% compared to an aqueous solution of an equivalent amount of the compound of formula I upon oral administration.

15 In one embodiment, the composition provides for a $C_{\max}$ of the compound of formula I upon oral administration from 5.0 ng/mL to 12.0 ng/mL, such as from 6.0 ng/mL to 10.0 ng/mL, such as from 6.0 ng/mL to 8.0 ng/mL. In one embodiment, the composition provides for a mean $C_{\max}$ of the compound of formula I upon oral administration from 6.0 ng/mL to 10.0 ng/mL, for example from 6.0 ng/mL to 7.0 ng/mL, or from 7.0 ng/mL to 8.0
20 ng/mL, or from 8.0 ng/mL to 9.0 ng/mL, or from 9.0 ng/mL to 10.0 ng/mL.

The examples also demonstrate that compositions according to the present disclosure are able to increase $t_{\max}$ of the compound of formula I after oral administration compared to administration of an aqueous solution of an equivalent amount of the compound of
25 formula I.

In one embodiment, the composition increases $t_{\max}$ of the compound of formula I compared to an aqueous solution of an equivalent amount of the compound of formula I after oral administration. In one embodiment, $t_{\max}$ is increased at least 60 minutes, such as increased 90 minutes, such as increased 120 minutes, such as increased 180
30 minutes, such as increased 210 minutes.

In one embodiment, the composition according to the present disclosure provides for a $t_{\max}$ of the compound of formula I from about 4 to 12 hours, such as from 5.5 hours to 8.5 hours after oral administration. For example, the composition provides for a $t_{\max}$ of the compound of formula I of 5.5, 6.0, 6.5, 7.0, 7.5, 8.0 or 8.5 hours.

One unexpected effect of the composition according to the present disclosure is the ability to provide extended release by increasing $t_{\max}$ without reducing exposure of the drug in humans and mammals. The exposure of a drug reflects the total amount of drug that reaches the systemic circulation and remains available for action. Thus, adequate exposure of the drug is crucial to achieve the desired pharmacological effects.

It would have been expected that by extending the release time, and thus the period pudafensine remains in the gastrointestinal tract, the exposure to the compound would be reduced due to phenomena hindering absorption, such as excretion, degradation, or reduced absorption in lower sections of the gastrointestinal tract. In contrast, the exposure of pudafensine after oral administration of the extended release compositions according to the present disclosure was found to be comparable to the exposure provided by an equivalent amount of the compound in solution.

The exposure of a substance may be measured as the “area under the curve” or “AUC” of the compound in the bloodstream. As it is well-known in the art, this may be calculated by plotting the concentration of the drug in the bloodstream against time and determining the integral of the resulting curve, also known as the “area under the curve” or “AUC.”

The amount of drug in the bloodstream may be detected at different time-points by well known methods in the art such as HPLC, LC/MS, ELISA, or other suitable analytical methods. Methods to calculate the integral of the plot are also well known to some one of skill in the art. The integral of the plot, or area under the curve, may be calculated within a specific time interval, such as within the first 24, 48, or 72 hours. In general, the term “AUC_{0-t}” refers to the area under the curve for the first “t” hours, for example as in “AUC₀₋₂₄” referring to the area under the curve within the first 24 hours. The term “AUC_{0-inf}” or “AUC_{inf}” refers to the area under the curves where the last point for integration has been extrapolated to infinity.

Thus, in one embodiment, the composition according to the present disclosure provides for an AUC₀₋₇₂ of the compound of formula I upon oral administration of at least 85%, such as at least 90% of the AUC₀₋₇₂ of an aqueous solution of an equivalent amount of the compound of formula I upon oral administration.

In one embodiment, the composition according to the present disclosure provides for an AUC_{0-inf} of the compound of formula I upon oral administration of at least 85%, such as at least 90% of the AUC_{0-inf} of an aqueous solution of an equivalent amount of the compound of formula I upon oral administration.

In one embodiment, the composition provides for an AUC_{0-inf} of the compound of formula I upon oral administration from 100 to 500 h·ng/mL, such as AUC_{0-inf} from 160 to 460 h·ng/mL, or AUC_{0-inf} from 250 to 350 h·ng/mL, such as AUC_{0-inf} of about 300 h·ng/mL.

5 In one embodiment, the composition provides for mean AUC_{0-inf} of the compound of formula I upon oral administration from 200 h·ng/mL to 400 h·ng/mL, such as mean AUC_{0-inf} from 250 h·ng/mL to 350 h·ng/mL.

In one embodiment, the composition according to the present disclosure provides:

- 10 a) an AUC_{0-72} or an AUC_{0-inf} of the compound of formula I upon oral administration of at least 85%, such as at least 90% of the AUC_{0-72} or the AUC_{0-inf} of an aqueous solution of an equivalent amount of a compound of formula I upon oral administration, and
- b) a t_{max} of the compound of formula I from about 4 to 12 hours, such as from about 5.5 to about 8.5 hours upon oral administration.

15 The compositions according to the present disclosure provide for an extended release of the compound of formula I. An extended release may be characterized by the dissolution rate of the active ingredient from the composition. A person of skill in the art is aware of methods to determine dissolution rate of solid dosage forms, such as according to the US Pharmacopeia, such as with a USP-I or a USP-II apparatus, with suitable methods of detection of the active ingredient such as HPLC, LC/MS or ELISA.

20 In one embodiment, the composition releases the compound of formula I at a rate of: 35-70% released within the first 2 hours; 60-95% released after 4 hours and a full release after 8 hours as measured in a USP-I or a USP-II apparatus at pH 6.8 at 37 °C.

In one embodiment, the composition releases the compound of formula I at a rate of:

- 25 i. 35-70% of the compound released within the first 2 hours, such as 40-65% release within the first 2 hours;
- ii. 60-95% released after 4 hours, such as 75-85% released after 4 to 6 hours, such as after 4 hours, 5 hours or 6 hours; and
- iii. full release after 8 hours

as measured in a USP-I or a USP-II apparatus at pH 6.8 at 37 °C.

30

In one embodiment, the composition releases the compound of formula I at a rate of:

- i. 35-70% of the compound released within the first 2 hours, such as 40-65% release within the first 2 hours;
- ii. 60-95% released after 4 hours, such as 75-85% released after 4; and
- 5 iii. full release after 8 hours

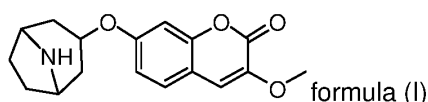
as measured in a USP-I or a USP-II apparatus at pH 6.8 at 37 °C.

Thus, in one aspect the present disclosure provides for an immediate release composition of a compound of formula (I), said composition providing a pharmacokinetic profile upon administration characterized by having one or more of:

- 10 • $C_{\max}$ of the compound of formula I upon oral administration from 5.0 ng/mL to 12.0 ng/mL, such as from 6.0 ng/mL to 10.0 ng/mL, such as from 6.0 ng/mL to 7.0 ng/mL,
- a $t_{\max}$ of the compound of formula I from about 4 to 12 hours, such as from 5.5 hours to 8.5 hours after oral administration,
- 15 • an $AUC_{0-\infty}$ of the compound of formula I upon oral administration from 160 to 450 h·ng/mL, such as $AUC_{0-\infty}$ from 250 to 350 h·ng/mL, such as $AUC_{0-\infty}$ of about 300 h·ng/mL.

20 In one embodiment, said immediate release composition comprises the compound of formula (I), a pellet core, a binder, pH modifiers or stabilizers as described herein in the section "A composition".

In one aspect, the present disclosure provides for method of obtaining a therapeutically effective plasma concentration of a compound of formula (I)



25 in a subject, wherein the $t_{\max}$ of the compound of formula I is between 4 and 12 hours, such as between 5.5 to about 8.5 hours, said method comprising oral administration of a composition as described herein or the unit dosage as described herein.

In one embodiment, the method provides for an AUC_{0-72} or an $AUC_{0-\infty}$ of the compound of formula I upon oral administration of at least 85%, such as at least 90% of the AUC_{0-72} or the $AUC_{0-\infty}$ of an aqueous solution of an equivalent amount of a compound of formula I upon oral administration

30

In one embodiment, the subject is a human.

Method of preparation

In one aspect, the present disclosure provides for a method of preparing a composition comprising pellets, the method comprising:

- 5 a) providing pellet core,
 b) providing a drug layer solution comprising a compound of formula (I)
- COC(=O)C1=C(C(=C2C(=C1)OC(=O)C2)C=C3C(=CC=C3)OCC4CNC4)C=C2
- formula (I), or a pharmaceutically acceptable salt thereof;
- c) coating the drug layer solution on to the pellet core to form a drug layer;
- d) providing a barrier coating solution comprising a film forming agent;
- 10 e) coating the barrier coating solution on top of the drug layer in c) to obtain a barrier coating layer;
- f) providing an extended release solution comprising one or more extended release polymer(s)
- g) coating the extended release solution on to the barrier coating layer in e) to obtain
- 15 an extended release layer.

In one embodiment of the method, the pellet core, the drug layer, the barrier coating, or the extended release layer are as described herein in the section "Composition".

- 20 In one embodiment of the method, the drug layer solution comprises a film forming agent or a stabilizer according as described herein in the section "Composition".

In one embodiment of the method, the drug layer solution comprises a solvent or dispersant, wherein said solvent or dispersant comprises or consist of an aqueous solution.

- 25 In one embodiment of the method, the barrier coating solution comprises a solvent or dispersant, wherein said solvent or dispersant comprises or consists of an aqueous solution.

In one embodiment of the method, the extended release layer solution further comprises a film forming agent, a plasticizer and/or an antitacking agent as described herein in the section "Composition".

- 30 In one embodiment of the method, the extended release layer solution comprises a solvent or dispersant, wherein said solvent or dispersant comprises or consist of an aqueous solution comprising an organic solvent, such as isopropanol.

In one embodiment of the method, the composition is as defined herein in the section "Composition".

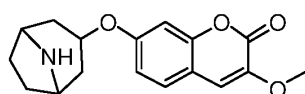
In one aspect, the present disclosure provides for a composition obtained by the method described herein.

5 Items

1. A composition comprising pellets comprising or consisting of:

- a) a pellet core;
b) a drug layer covering the core, the drug layer comprising a compound of formula (I)

10



formula (I), or a pharmaceutically acceptable salt thereof,

- c) a barrier coating layer comprising a film forming agent, wherein said layer covers the drug layer b), and

15

- d) an extended release layer comprising one or more extended release polymer(s); wherein said extended release layer covers the barrier coating in c).

2. The composition according to item 1, wherein the drug layer further comprises a binder selected from the group consisting of cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC); polyalkylene glycols; such as polyethylene glycol (PEO) and polyvinyl pyrrolidone (PVP), hydroxypropyl cellulose and gelatin.

20

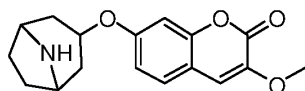
3. The composition according to any one of the preceding items, wherein the binder is HPMC.

25

4. The compound according to any one of the preceding items, wherein the film forming agent is selected from the group consisting of hydroxypropyl methyl cellulose (HPMC), cellulose derivatives, polyacrylates, polymethacrylates and copolymers of acrylate and methacrylate and polyvinylalcohol (PVA).

30

5. The composition according to any one of the preceding items, wherein the barrier coating layer comprises HPMC in an amount of about 0.5% to about 5 % by weight of the composition or by weight of the pellets.
- 5 6. The composition according to any one of the preceding items, wherein the one or more extended release polymer(s) are present in an amount of about 0.5% to about 10 % by weight of the composition or by weight of the pellets.
- 10 7. The composition according to any one of the preceding items, wherein the extended release polymer is ethylcellulose.
8. The composition according to any one of the preceding items, wherein the extended release layer further comprises a film forming agent.
- 15 9. The composition according to any one of the preceding items, wherein the extended release layer further comprises HPMC.
10. The composition according to any one of the preceding items, wherein the extended release layer further comprises HPMC in an amount from 0.5% to about 5% by weight of the composition or by weight of the pellets.
- 20 11. The composition according to any one of the preceding items, wherein the pellet core consists of or comprises spheres made of a material selected from the group consisting of: microcrystalline cellulose (MCC); sugars, such as sucrose, xylitol, mannitol, and lactose; starch, silica, tartaric acid, and calcium carbonate.
- 25 12. The composition according to any one of the preceding items, wherein the composition is an extended release composition of an active ingredient consisting of a compound of formula I,



- 30 formula (I), or a pharmaceutically acceptable salt thereof, the composition comprising pellets comprising or consisting of:
- a) an inert pellet core comprising microcrystalline cellulose (MCC);
- b) a drug layer comprising: the compound of formula (I) or a pharmaceutically acceptable salt thereof in an amount of about 0.5% to about 5% by weight
- 35 of the total composition or by weight of the pellets and HPMC in an amount

of 0.5% to about 5% by weight of the total composition or by weight of the pellets,

wherein the drug layer covers the inert core;

- 5 c) a barrier layer comprising HPMC in an amount of about 0.5% to about 5% by weight of the total composition or by weight of the pellets, wherein the barrier coating layer covers the drug layer b); and
- d) an extended release layer comprising ethyl cellulose in an amount of about 0.5 to 10% by weight of the total composition or by weight of the pellets, wherein the extended release layer covers the barrier coating layer c).

10 13. The composition according to any one of the preceding items, wherein $t_{\max}$ of the compound of formula I is from about 4 to 12 hours, such as from 5.5 to 8.5 hours after oral administration.

15 14. The composition according to any one of the preceding items, wherein after oral administration the composition provides:

- 20 a) an AUC_{0-72} or an $AUC_{0-\infty}$ of at least 85% of the AUC_{0-72} or $AUC_{0-\infty}$ of an aqueous solution of an equivalent amount of a compound of formula I after oral administration, and
- b) a $t_{\max}$ of the compound of formula I from about 5.5 to 8.5 hours.

25 15. A unit dosage form comprising the composition according to any one of the preceding items.

Examples

Example 1: Preparation of formulations

Aim

30 To describe the preparation of compositions according to the present disclosure.

Materials and Methods

Materials. Microcrystalline cellulose spheres (Celphere CP-507 particle size range 500-710 μm), sodium sulphite anhydrous, hydroxypropylmethyl cellulose (HPMC, Methocel E5 premium LV), Ethyl cellulose (Ethocel STd. 7 Premium), Triethyl citrate dihydrate (Ph.

Eur), Magnesium stearate (Ligamed 2V) NF and pudafensine monohydrate monohydrochloride salt.

5 **Drug layered pellets.** Sodium sulphite, HPMC 5cps and pudafensine (previously sifted through a mesh size # 60) are mixed in purified water then stirred to get uniform dispersion. Then the solution is coated onto the inert pellet core (Celphere CP-507) in a fluidized bed (GPCG 1.1 bowl, Gun nozzle size: 1.2 mm, ADP size: type B).

10 **Barrier coated pellets.** HPMC is mixed in purified water and stirred to obtain a uniform dispersion. The solution is coated onto the drug layered pellets (GPCG 1.1 bowl, Gun nozzle size: 1.2 mm, ADP size: type B)

15 **Extended release pellets.** HPMC, Ethyl cellulose, triethyl citrate and magnesium stearate (sifted through a mesh size # 60) are mixed in purified water and stirred to get a uniform dispersion. The solution is coated onto the barrier coated pellets in a fluidized bed (GPCG 1.1 bowl, Gun nozzle size: 1.2 mm, ADP size: type B).

20 **Encapsulation.** Encapsulation of the composition was done by filling the required amount of pellets to obtain the desired dose into a Swedish Orange Capsule, size 0. For example, amounts of pellets equivalent to 5 mg or 10 mg of pudafensine free base were loaded onto the capsules.

The drug substance pudafensine was used as a monohydrate and monohydrochloride salt. Hence the quantity per bottle, or capsule or administration is calculated based on the amount of free base.

The samples were prepared:

- 25
 - Immediate release (IR) compositions, corresponding to drug layered pellets with and without encapsulation as in Table 1.
 - Extended release compositions (ER), corresponding to extended release pellets, with and without encapsulation as in Table 2.
 - A drug-in-bottle (DiB) solution having IP2015 dissolved in water for injection

30 having 50 mg/mL of Hydroxypropyl 2-beta cyclodextrin (HP β CD) as solubility enhancer.

Table 1. Composition of IP2015 immediate release (IR) pellets

		IP2015 IR pellets		
S. No	Purpose	Ingredients	Qty (g)	% w/w
		Drug layering		
1	Core pellets	Celphere CP-507	1400.0	92.729
2	Drug substance	IP2015 ^a	48.37	3.204
3	Binder	HPMC E5 (Methocel E5 premium LV)	53.40	3.537
4	pH modifier/alkalizer	Sodium sulphite anhydrous	8.00	0.530
5	Dispersant	Purified Water	q.s	q.s
		Total	1509.6	100.000

^aThe drug substance is a monohydrate and monohydrochloride salt. The quantity of free base may be calculated by analysis of anhydrous and solvent-free basis, by methods well known in the art. For the present batch 60 mg of free base correspond to 72 mg of drug substance.

5

Table 2. Composition of IP2015 extended release (ER) pellets

Table 1: Composition of IP2015 Extended Release (ER) pellets				
IP2015 ER pellets				
S. No	Purpose	Ingredients	Qty (g)	% w/w
Drug layering				
1	Core pellets	Celphere CP-507	1400.0	83.762
2	Drug substance	IP2015 ^a	48.37	2.894
3	Binder	HPMC E5 (Methocel E5 premium LV)	53.40	3.195
4	pH modifier/alkalizer	Sodium sulphite anhydrous	8.00	0.479
5	Dispersant	Purified Water	q.s	q.s
Drug layering sum			1509.6	90.330
HPMC Barrier Coating				
6	-	IP2015 layered pellets	1509.6	90.330
7	Film forming agent for seal coating	HPMC E5 (Methocel E5 premium LV)	42.80	2.561
8	Dispersant	Purified water	q.s	q.s
HPMC Barrier layer sum			1552.6	92.891
Extended release layer				
9	-	Barrier coated pellets	1552.6	92.891
10	Extended release polymer	Ethocel Std. 7 Premium (Ethyl cellulose)	53.05	3.174
11	Film former	HPMC E5 (Methocel E5 premium LV)	53.05	3.174
12	Plasticiser	Triethyl citrate dihydrate (Ph. Eur)	3.712	0.222
13	Antitacking agent	Magnesium stearate (Ligamed 2V) NF	9.012	0.539
14	Dispersant	Isopropanol pharmacopeial grade	q.s	q.s
Total weight of ER coated pellets			1671.4	100.000

^aThe drug substance is a monohydrate and monohydrochloride salt. The quantity of free base may be calculated by analysis of anhydrous and solvent-free basis, by methods well known in the art. For the present batch 60 mg of free base correspond to 72 mg of drug substance.

In addition, two similar ER compositions (ER1 and ER2) were prepared in an analogous manner with the following parameters in the extended release layer:

- ER1: 5% HPMC, 5% ethyl cellulose
- ER2: 5% HPMC, 7.5 ethyl cellulose

5

Solubility tests

Solubility of IP2015 was determined in both aqueous and non-aqueous vehicles. In non-aqueous liquids, the solubility was visually confirmed in progressive dilutions. The solubility of IP2015 in pH specific aqueous solutions was evaluated, the solubility was visually confirmed, and the content was evaluated by HPLC.

10

Table 3. Solubility of IP2015 in different media.

Vehicle	Solubility (mg/ml)	Inference (Ph.Eur)
Ethanol	<1	Very slightly soluble
N,N-dimethyl acetamide	<1	Very slightly soluble
Dimethyl sulfoxide	5 to 10	Slightly soluble
N-methyl-2-pyrrolidone	<1	Very slightly soluble
Propylene glycol	1 to 5	Slightly soluble
Polyethylene glycol 400	<1	Very slightly soluble
Glycerine	<1	Very slightly soluble
pH 1.2 HCl (0.1N)	0.017	Very slightly soluble
pH 3.0 Citrate buffer	0.839	Very slightly soluble
pH 4.0 Citrate buffer	0.849	Very slightly soluble
pH 3.0 Acetate buffer	1.173	Slightly soluble
pH 4.5 Acetate buffer	0.981	Very slightly soluble
pH 5.8 Potassium Phosphate buffer	0.104	Very slightly soluble
pH 6.8 Potassium Phosphate buffer	0.146	Very slightly soluble
pH 7.5 Potassium Phosphate buffer	0.084	Very slightly soluble
Purified Water	0.738	Very slightly soluble

Results

15

As seen from table 3, IP2015 has solubility lower than 1 mg/mL in aqueous solutions across physiological pH. It was unexpectedly found that the presence of the binder in the solution allowed for a homogeneous and consistent distribution of IP2015 in the drug layer. In contrast, when a solubility enhancer was used to improve the solubility of IP2015, such as hydroxypropyl 2-beta cyclodextrin (HPβCD), the concentration of the compound was not enough to form a good drug layer.

20

Example 2: IP2015 release in solution*Aim*

To study the release of IP2015 for compositions according to the present disclosure.

5 *Materials and Methods*

The dissolution profile of IP2015 IR pellets (part finished IMP) and IP2015 IR capsules is determined using 0.1N HCl Buffer.

Dissolution conditions IR samples:

10

Parameter	Condition
Media	0.1N HCl buffer
Volume	900 mL
Apparatus	USP-I (Basket)
RPM	50
Temperature	37.0° + 0.5°C
Sampling volume	10 mL
Time points	5, 10, 15, 30 min

Dissolution conditions ER samples:

The dissolution profile of IP2015 ER pellets (part finished IMP) and IP2015 ER capsules is determined as following:

15

Parameter	Condition
Media	pH 6.8 phosphate buffer
Volume	900 mL
Apparatus	USP-I (Basket)
RPM	50
Temperature	37.0° + 0.5°C
Sampling volume	10 mL

Dissolution samples are being analyzed with a gradient reverse phase HPLC method, The mobile phase is buffer solution (0.1% orthophosphoric acid and water): acetonitrile (85:15). The detection is by DAD.

20

To study the effect of sodium sulphite, two different samples of pellets were prepared according to example 1, with and without sodium sulphite. The dissolution rate of samples corresponding to 5 mg of IP2015 from the pellets without encapsulation was studied.

To study the effect of encapsulation, the dissolution rate of IP2015 from both encapsulated and non-encapsulated pellets was assessed using samples corresponding to 5 mg of IP2015, prepared according to example 1. For comparison, dissolution of non-encapsulated samples corresponding to 10 mg of IP2015 was also assessed.

Results

The dissolution profile of samples with and without sodium sulphite is shown in Table 4. Table 4. Drug release from 5 mg IP2015 IR pellet samples with and without sodium sulphite.

Time / min	Drug release (%)	
	with Na ₂ SO ₃	without Na ₂ SO ₃
5	96	103
10	97	107
15	98	108
20	99	108
30	99	108
45	99	108
60	99	108

Impact of sodium sulphite on the dissolution profile was observed. The dissolution profiles of scale-up batches, which had sodium sulphite in the drug layering coating, showed a faster dissolution profile compared to a scale-up batch, which doesn't have sodium sulphite in the drug layering coating.

Figure 1 shows the release profile of IP2015 IR pellets and capsules . The dissolution profile is as expected. The IP2015 IR capsule fulfil the requirements for an immediate release oral dosage form with 80% released after 10 min and > 90% released after 20 min.

Figure 2 shows the release profile of IP2015 ER pellets and capsules . The dissolution profile is as expected. The IP2015 ER capsule fulfils the requirements for the extended release with 35-70% released within the 2 hours; 70-90% released after 4 hours and a full release after 8 hours. For comparison also pellets with 10mg of API have been tested.

Table 5 shows the release from the ER1 and ER2 pellet formulations described in example 1.

Table 5. Release from ER1 and ER2 pellets

Time / min	Drug release (%)	
	ER1	ER2
120	44	31
240	69	53
360	77	60
480	82	64
600	87	68
720	91	71
840	94	74

5 *Conclusion*

The compositions according to the present disclosure provide for adequate extended release. It was surprisingly shown that the presence of sodium sulphite enhances the release from the drug layer.

10 Example 3: In vivo pharmacokinetics of pudafensine IR composition

Aim

To study the pharmacokinetic parameters of the compositions according to the present disclosure.

Materials and Methods

15 The pharmacokinetic profiles of different formulations of two extended release formulations (ER1 and ER2), one IR formulation (IR) and one drug-in-bottle (DiB) formulation of pudafensine as reference item were investigated in Göttingen minipigs, after single oral administration.

20 Animals were fasted prior to dosing. Each formulation was administered to the animals by a single administration; a wash-out period of 7 days was allowed after each day of dosing. A single dose of 0.5mg/kg was administered orally, by capsule, with a washout period of 7 days after each day of dosing. A single dose (0.25mL/kg) of reference item solution was administered orally, by gavage.

25 Assessment of mortality was conducted twice each day. All clinical signs were recorded at baseline and at the same time daily during the study (approximately 1-1.5, 2-2.5 and 3-3.5 hours after dosing). Fasted body weight was recorded on the day of allocation and the day before dosing.

On each day of dosing, blood samples were collected from the jugular vein (other veins were used, if necessary) at approximately the following time points: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36 and 48 hours after the first administration.

At each sampling time, at least 1.0 mL of blood was collected and transferred into tubes containing K2EDTA anticoagulant and, centrifuged at room temperature, divided in two aliquots; [Aliquot A] of approximately 250 µL and the second [Aliquot B] with the plasma remaining) and frozen at -70 ± 10°C.

The concentration of pudafensine in minipig plasma was determined via LC-MS/MS method by The Bioanalytical Department, Syngene International Ltd. During analysis, standard and quality control samples were distributed throughout each batch of study samples analysed. Plasma concentration data was used for toxicokinetic evaluation.

PK parameters were determined from the individual minipig plasma concentration versus time data by a non-compartmental analysis with uniform weighting using Phoenix® WinNonlin® validated version 8.2. The PK parameters that were calculated includes the area under the plasma concentration-time curve until last quantifiable concentration (AUC_{last}), AUC_{0-48h}, peak plasma concentration (C_{max}), time to reach peak plasma concentration (t_{max}), C_{last}, T_{last}, AUC_{inf} and terminal elimination half-life (t_{1/2}). Plasma concentrations and TK parameters are presented in ng unit.

Results

The pharmacokinetic parameters are shown in Tables 6 and 7.

Table 6. Mean pharmacokinetic parameters of pudafensine in different formulations as ER pellets.

	IR	ER1	ER2	DiB
Dose (mg/kg)	0.5	0.5	0.5	0.5
C _{max} (ng/mL)	17.026	19.124	11.682	25.135
t _{max} (h)	3.33	7.33	10.67	2.5
AUC _{0-48h} (h*ng/mL)	336.317	371.828	310.013	399.6
C _{last}	2.226	2.791	2.718	2.416
T _{last}	48	48	48	48
Half-life (h)	13.58	15.51	13.93	15.03
AUC _{last} (h*ng/mL)	336.317	371.828	310.013	399.6
AUC _{INF_obs} (h*ng/mL)	390.254	445.372	375.361	459.579

Table 7. Systemic exposure ratios of ER and IR formulations compared to DiB

	Ratio IR / DiB	Ratio ER1/DiB	Ratio ER2 / DiB
C _{max}	0.68	0.76	0.46
AUC _{0-48h}	0.84	0.93	0.78
t _{max}	1.3	2.9	4.3

5 *Conclusion*

It was surprisingly observed that the extended release formulations provided equal or higher exposure than IR formulations when compared to oral administration of DiB formulations, even while extending t_{max}. It was unexpected that even though pudafensine was exposed for longer time in the GI tract, absorbance was not reduced and exposure maintained.

Example 4. Clinical trial studying pharmacokinetics of pudafensine formulations in human.

15 *Aim*

To study the pharmacokinetics of immediate release (IR) compositions of pudafensine according to the present disclosure in humans.

Materials and Methods

20 The study is a 3-way crossover study in which pharmacokinetic parameters of pudafensine compositions according to the present disclosure were studied after oral administration. One immediate release capsule composition (IR) as disclosed in Table 1 and one extended release capsule composition (ER) as disclosed in Table 2 were used. For comparison, the results were compared to a solution of pudafensine (DiB). The compositions were prepared as described in example 1.

The study was a crossover study performed in 12 healthy subject that received single doses of 5 mg of pudafensine in different formulations with sufficient wash-out in between. After administration of the compositions, the plasma blood levels of pudafensine monitored at different timepoints.

Results

The results are shown in tables 8 and 9.

Table 8. Pharmacokinetic parameters of compositions.

		T _{lag} (h)	t _{max} (h)	C _{max} (ng/mL)	AUC _{last} (h*ng/mL)	AUC _{inf} (h*ng/mL)	AUC ₀₋₂₄ (h*ng/mL)
ER	N	12	12	12	12	9	12
	Min	0	4.13	5.58	153	168	81.5
	Median	0.25	7	6.95	251	301	118
	Max	1.08	11.93	11.4	361	454	195
IR	N	12	12	12	12	10	12
	Min	0	1.97	5.39	182	193	98.7
	Median	0	4.98	8.81	260	301	146
	Max	0	7.95	12.5	410	479	209
DiB	N	12	12	12	12	9	12
	Min	0	0.98	6.25	186	199	106
	Median	0	3.5	8.69	251	284	147
	Max	0	6.07	14.4	402	496	219

5 Table 9. Systemic exposure ratios

		C _{max}	AUC _{last}	AUC _{inf}
ER / IR ratio	N	12	12	8
	Min	0.61	0.72	0.73
	Median	0.79	0.94	0.94
	Max	1.14	1.21	1.2
	Geom. Mean (CV%)	0.797(20.83%)	0.952(15.08%)	0.957(16.76%)
ER/DiB ratio	N	12	12	7
	Min	0.65	0.74	0.77
	Median	0.8	0.98	0.87
	Max	0.96	1.18	1.15
	Geom. Mean (CV%)	0.806(12.78%)	0.955(14.56%)	0.907 (15.60%)
IR/DiB ratio	N	12	12	8
	Min	0.84	0.9	0.88
	Median	1.03	0.99	1
	Max	1.23	1.16	1.18
	Geom. Mean (CV%)	1.001(11.91%)	1.004(8.05%)	1.012(10.55%)

Conclusion

Surprisingly, it was shown that extended release pudafensine composition provides comparable exposures to equivalent amounts formulated as aqueous solution. when the C_{max} was reduced and the t_{max} was increased in the extended release formulation in
5 humans. This is highly unexpected and advantageous since it allows for safer administration of pudafensine but achieving the equivalent systemic exposure as drug-in-bottle formulations.

10 Example 5. Clinical trial studying adverse events and efficacy of treatment of erectile dysfunction with IP2015 in humans

The study investigated the effects of repeat single oral doses of IP2015 on male subjects with erectile dysfunction (ED) on ability to develop and maintain an erection, as well as safety and tolerability of single oral doses of IP2015, effects on penile rigidity and
15 tumescence during visual stimulation, effects on sperm count and motility, and any possible relationship between plasma levels of IP2015, its efficacy and safety.

*Materials and Methods*Study design

20 130 subjects were divided into 3 groups upon which the study was conducted in parallel. Each subject was dosed on four occasions with either 5 mg IP2015, 10 mg IP2015 or matched placebo. In each group, subjects were randomized evenly to each of the three study treatments and received the same treatment at each visit.

25 The study lasted approximately 8 weeks and consisted of the following:

- A screening visit (up to 21 days prior to the baseline visit)
- A baseline visit (Day -7)
- Outpatient visits on Week 1 (Day 1), Week 2, Week 3 and Week 4
- A follow-up visit a minimum of 7 to 10 days after their final dose.

30

On Day -7, and at Week 1 (Day 1), Week 2, Week 3, Week 4 and Follow-up visits, all groups were asked to complete the IIEF-15 questionnaire. Group 2 was asked to complete a Visual Stimulation Assessment using a RigiScan Plus Monitor on Day -7, Week 1 (Day 1) and Week 4. Group 2 was also required to provide blood samples for

pharmacokinetic assessment on Week 1 (Day 1) and Week 4. Group 3 was required to provide semen samples on Day -7 and Week 4.

Participants

- 5 The patients were otherwise healthy male subjects with ED as determined from an IIEF-5 score of ≤ 16 , with a body mass index of 18 to 35 kg/m² (inclusive), of any ethnic origin. Subjects were aged between 18 to 59 years, inclusive.

Dose and Mode of Administration

- 10 There were three potential study treatments of 5 mg IP2015, 10 mg IP2015 or matched placebo. In each group, subjects were randomized evenly to each of the three study treatments and received the same treatment on each visit. IP2015 or matched placebo was administered once in the morning of Week 1 (Day 1), Week 2, Week 3, and Week 4 as an oral solution in the fasted state. The dose was taken with 240 mL of water at
15 room temperature. Subjects had fasted 2 hours prior to dosing until 4 hours post-dose. Water was allowed ad libitum except for 1 hour before and 1 hour after dosing.

Evaluation

- 20 Efficacy was assessed through the International Index of Erectile Function (IIEF)-15 questionnaire. The change from baseline in responses to questions of the IIEF-15 questionnaire, including questions regarding erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction domain scores, was determined at different time points of the study. RigiScan assessments during the stimulus assessment, and sperm count and motility by semen sample collection was used for
25 efficacy evaluation. Safety was assessed through AE reporting, 12-lead ECG, vital signs, physical examinations, and clinical laboratory evaluations. Pharmacokinetics was assessed by blood sampling.

Results

30 Efficacy of IP2015

- The results for Q3 in the IIEF-15: "When you attempted intercourse, how often were you able to penetrate (enter) your partner during the last week?" are shown in Figure 4. The results for Q3 were significant for treatment with 5 mg IP2015 at week 3 versus placebo ($p=0.034$) and versus baseline ($p=0.046$). In the overall score for Q3, there was also a
35 tendency to difference versus placebo ($p=0.07$) and versus baseline ($p=0.07$).

The results for Q4 in the IIEF-15: “During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?” are shown in Figure 5. The results for Q4 show that there was a tendency to difference versus baseline (p=0.056) for the 5 mg in the overall score, though there was no difference compared to placebo (p=0.44).

The overall response to questions of IIEF-15 is shown in Figure 6, the results were significant for treatment with 5 mg IP2015 versus baseline at follow-up (p= 0.0046) and tendency versus placebo (p=0.07) and the same was the case for the overall score for 5 mg versus baseline (p= 0.0032) and tendency versus placebo (p=0.10).

In figures 4, 5 and 6, the results show the change from baseline for patients treated with four doses of placebo (n=45), 5 mg (n=42), and 10 mg (n=43) IP2015 dosed in parallel at days 1, 8, 15, and 22. The results are mean ± SE. The statistical differences were performed with Mixed Model Repeated Measures (MMRM).

Adverse events

Treatment-emergent adverse effects for the low-dose (5 mg) IP2015 were comparable to the placebo group. The TEAEs were dose-dependent, mild and moderate and slightly increased in the high dose compared to the low dose of IP2015. No severe side effects were observed at any of the doses of IP2015 (Table 10).

The results for semen analysis were complete and the treatment did not have negative effects on sperm count, motility, or morphology.

Table 10. Treatment-emergent adverse events

TEAE	IP2015 5mg, N=42	IP2015 10 mg, N=43	Placebo, N=45
Any TEAE	32 (76.2 %), 61	34 (79.1 %), 141	31 (68.9 %), 63
Related*	10 (23.8 %), 19	23 (53.5 %), 84	8 (17.8 %), 11
Mild	29 (69.0 %), 56	33 (76.7%), 132	27 (60.0%), 57
Moderate	3 (7.1%), 5	7 (16.3%), 9	6 (13.3%), 6
Severe	0	0	0
Headache	11 (26.2 %), 15	16 (37.2 %), 27	14 (31.1 %), 21
Dizziness	3 (7.1 %), 3	12 (27.9 %), 15	2 (4.4 %), 2
Nausea	1 (2.4 %), 1	8 (18.6 %), 15	1 (2.2 %), 1

Conclusion

Overall, these results, show that 5 mg doses of IP2015 are effective in treating erectile dysfunction and are safely tolerated. There was a significant effect of the 5 mg dose of IP2015 (pudafensine) on the Q3 in the IIEF-15 score compared to baseline and placebo.

5 There were tendencies regarding the overall IIEF-15 score showing a clinically significant score change of 2, which is significant for a low dose of IP2015 versus baseline and $p=0.10$ versus placebo.

Treatment-emergent adverse effects for the 5 mg dose of IP2015 were comparable to the placebo group. The TEAEs were dose-dependent, only mild and moderate effects
10 were observed. No severe TEAEs were present.

The higher efficacy, and the lower incidence of TEAEs, of the lower dose compared to the higher dose highlights the need for a solid dosage formulation of IP2015 that can produce an extended release and thus a more attractive pharmacokinetic profile for high doses of IP2015; without compromising the exposure. The compositions of the present
15 disclosure provide such an effect by reducing $C_{\max}$ and increasing $t_{\max}$ of IP2015 without reducing the systemic exposure.

Claims

1. A composition comprising pellets, said pellets comprising or consisting of:
- 5 a) a pellet core;
- b) a drug layer covering the core, the drug layer comprising a compound of formula (I)
- COC1=C(C(=O)O1)c2cc(Oc3c[nH]c4ccccc34)cc2
- 10 formula (I), or a pharmaceutically acceptable salt thereof,
- c) a barrier coating layer comprising a film forming agent, wherein said layer covers the drug layer in b), and
- 10 d) an extended release layer comprising one or more extended release polymer(s); wherein said extended release layer covers the barrier coating in c).
- 15 2. The composition according to claim 1, wherein the drug layer further comprises a binder selected from cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC); polyalkylene glycols, such as PEO, and polyvinyl pyrrolidone (PVP), hydroxypropyl cellulose and gelatin.
- 20 3. The composition according to claim 2, wherein the drug layer comprises the binder in an amount from 0.5 to 10% by weight of the pellets.
4. The composition according to any one of claims 2 to 3, wherein the binder is HPMC.
- 25 5. The composition according to claim 4, wherein the drug layer comprises HPMC in an amount from about 1% to 5% by weight of the pellets.
6. The composition according to any one of the preceding claims, wherein the drug layer further comprises additional excipients selected from: pH modifiers and/or
- 30 stabilizers.
7. The composition according to claim 6, wherein the stabilizer is sodium sulphite.

8. The composition according to any one of claims 6 to 7, wherein the pH modifier and/or the stabilizer are present in an amount from 0.05% to 1% by weight of the pellets.
- 5 9. The composition according to any one of the preceding claims, wherein the drug layer further comprises sodium sulphite is present in an amount from 0.05 % to 1% by weight of the pellets.
- 10 10. The composition according to any one of the preceding claims, wherein the pellet core consists of or comprises spheres made of a material selected from: microcrystalline cellulose (MCC); sugars, such as sucrose, xylitol, mannitol, and lactose; starch, silica, tartaric acid, and calcium carbonate.
- 15 11. The composition according to any one of the preceding claims, wherein the pellet core comprises or consists of microcrystalline cellulose (MCC).
- 20 12. The composition according to any one of the preceding claims, wherein the drug layer comprises the compound of formula I in an amount of about 0.5% to about 5 % by weight of the pellets.
- 25 13. The composition according to any one of the preceding claims, wherein the drug layer comprises the compound of formula I in an amount of from about 2.5% to 3.5% by weight of the pellets.
- 30 14. The composition according to any one of the preceding claims, wherein the barrier coating layer comprises the film forming agent in an amount between 0.5% and 5% by weight of the pellets.
- 35 15. The composition according to any one of the preceding claims, wherein the film forming agent is selected from hydroxypropyl methyl cellulose (HPMC), cellulose derivatives, polyacrylates, polymethacrylates and copolymers of acrylate and methacrylate and polyvinylalcohol (PVA).
16. The composition according to any one of the preceding claims, wherein the film forming agent is HPMC.

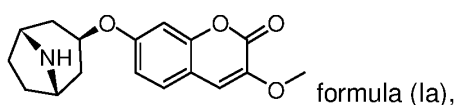
17. The composition according to any one of the preceding claims, wherein the barrier coating layer comprises HPMC in an amount of about 0.5% to about 5 % by weight of the pellets.
- 5 18. The composition according to any one of the preceding claims, wherein the barrier coating layer comprises HPMC in an amount from about 1% to 4% by weight of the pellets.
- 10 19. The composition according to any one of the preceding claims, wherein the one or more extended release polymer(s) is present in an amount of about 0.5% to about 10 % by weight of the pellets.
- 15 20. The composition according to any one of the preceding claims, wherein the one or more extended release polymer(s) is selected from: cellulose derivatives that have been modified with hydrophobic groups, such as short alkyl groups; or other hydrophobic polymers, such as synthetic polyacrylates derivatives with hydrophobic groups such as short alkyl groups.
- 20 21. The composition according to any one of the preceding claims, wherein the extended release polymer is ethylcellulose.
22. The composition according to any one of the preceding claims, wherein the extended release layer comprises ethylcellulose in an amount from about 0.5% to about 10% by weight of the pellets.
- 25 23. The composition according to any one of the preceding claims, wherein the extended release layer comprises ethylcellulose in an amount from about 1% to about 5% by weight of the pellets.
- 30 24. The composition according to any one of the preceding claims, wherein the extended release layer further comprises a film forming agent.
25. The composition according to claim 24, wherein the extended release layer comprises the film forming agent in an amount from 0.5% to about 5% by weight of the pellets.
- 35 26. The composition according to any one of claims 24 to 25, wherein the film forming agent is HPMC.

27. The composition according to any one of the preceding claims, wherein the extended release layer further comprises HPMC.
- 5 28. The composition according to any one of the preceding claims, wherein the extended release layer further comprises HPMC in an amount from 0.5% to about 5% by weight of the pellets.
- 10 29. The composition according to any one of the preceding claims, wherein the extended release layer further comprises HPMC in an amount from 1% to about 4% by weight of the pellets.
- 15 30. The composition according to any one of the preceding claims, wherein the extended release layer further comprises a plasticizer.
- 20 31. The composition according to any one of the preceding claims, wherein the extended release layer further comprises a plasticizer selected from: esters derived from citric acid, such as triethyl citrate or tributyl citrate; acetylated monoglycerides; esters of phthalic acid; polyethylene glycol or derivatives thereof; and sorbitol or mixtures thereof.
- 25 32. The composition according to any one of claims 30 to 31, wherein the plasticizer is triethyl citrate.
- 30 33. The composition according to any one of the preceding claims, wherein the extended release layer further comprises triethyl citrate.
- 35 34. The composition according to any one of the preceding claims, wherein the extended release layer further comprises an antitacking agent.
- 36 35. The composition according to claim 34, wherein the antitacking agent is selected from: stearates or fatty acid salts of calcium or magnesium, talc, silica, and silicates or combinations thereof.
- 37 36. The composition according to claim 35, wherein the antitacking agent is magnesium stearate.
- 38 37. The composition according to any one of the preceding claims, wherein the extended release layer further comprises magnesium stearate.

38. The composition according to any one of the preceding claims, wherein the extended release layer further comprises one or more additional excipients selected from:

- 5 i. a film forming agent according to claims 24 to 26; and/or
 ii. a plasticiser according to claims 30 to 33; and/or
 iii. an antitacking agent according to claims 34 to 37.

10 39. The composition according to any one of the preceding claims, wherein the compound of formula I is according to formula Ia

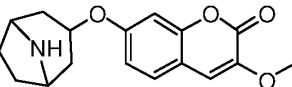


or a pharmaceutically acceptable salt thereof.

15 40. The composition according to any one of the preceding claims, wherein the compound is *exo*-7-[(8-azabicyclo[3.2.1]octan-3-yl)oxy]-3-methoxy-chromen-2-one or a pharmaceutically acceptable salt thereof.

20 41. The composition according to any one of the preceding claims, wherein the composition is an extended release (ER) composition of the compound of formula I.

42. The composition according to any one of the preceding claims, wherein the composition is an extended release composition of an active ingredient consisting of a compound of formula I,

25  formula (I), or a pharmaceutically acceptable salt thereof,
the composition comprising pellets, said pellets comprising or consisting of:

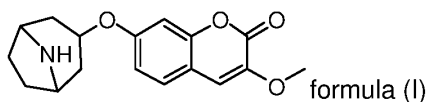
- a) an inert pellet core comprising microcrystalline cellulose (MCC);
b) a drug layer comprising: the compound of formula (I) or a pharmaceutically acceptable salt thereof in an amount of about 0.5% to about 5% by weight of the pellets and HPMC in an amount of 0.5% to about 5% by weight of the pellets,
30 wherein the drug layer covers the inert core;

- 5 c) a barrier layer comprising HPMC in an amount of about 0.5% to about 5%
by weight of the pellets, wherein the barrier coating layer covers the drug
layer in b); and
- d) an extended release layer comprising ethyl cellulose in an amount of about
0.5 to 10% by weight of the pellets, wherein the extended release layer
covers the barrier coating layer in c).
- 10 43. The composition according to claim 42, wherein the drug layer further comprises
sodium sulphite.
44. The composition according to any one of claims 42 to 43, wherein the extended
release layer further comprises one or more additional excipients selected from::
- i. a film forming agent according to claims 24 to 26; and/or
- ii. a plasticiser according to claims 30 to 33; and/or
- 15 iii. an antitacking agent according to claims 34 to 37.
45. The composition according to any one of the preceding claims, wherein the
composition comprises the compound of formula I in an amount of about 0.5 mg to
30 mg.
- 20 46. The composition according to any one of the preceding claims, wherein the
composition is in the form of a pharmaceutical dosage form or a unit dosage form.
47. The composition according to any one of the preceding claims, wherein the
composition is in the form of a solid dosage form.
- 25 48. The composition according to claim 46, wherein the unit dosage form or
pharmaceutical dosage form is a capsule.
49. The composition according to any one of the preceding claims, wherein the
composition is for oral administration.
- 30 50. The composition according to any one of the preceding claims, wherein the
composition reduces the $C_{\max}$ of the compound of formula I, wherein the $C_{\max}$ is
reduced by at least 10%, such as at least 20% compared to an aqueous solution of
35 an equivalent amount of the compound of formula I after oral administration.

51. The composition according to any one of the preceding claims, wherein the composition provides for a $C_{\max}$ of the compound of formula I upon oral administration from 5.0 ng/mL to 12.0 ng/mL, such as from 6.0 ng/mL to 10.0 ng/mL, such as from 6.0 ng/mL to 8.0 ng/mL.
52. The composition according to any one of the preceding claims, wherein the composition increases the $t_{\max}$ of the compound of formula I compared to an aqueous solution of an equivalent amount of the compound of formula I after oral administration.
53. The composition according to any one of the preceding claims, wherein the $t_{\max}$ of the compound of formula I is increased by at least 60 minutes, such as 90 minutes, such as 120 minutes, such as 180 minutes, such as 210 minutes upon oral administration compared to an aqueous solution of an equivalent amount of the compound of formula I after oral administration.
54. The composition according to any one of the preceding claims, wherein the $t_{\max}$ of the compound of formula I is from about 4 to 12 hours, such as from 5.5 to 8.5 hours after oral administration.
55. The composition according to any one of the preceding claims, wherein the composition provides for an AUC_{0-72} of the compound of formula I upon oral administration of at least 85% of the AUC_{0-72} of an aqueous solution of an equivalent amount of the compound of formula I after oral administration.
56. The composition according to any one of the preceding claims, wherein the composition provides for an $AUC_{0-\infty}$ of the compound of formula I upon oral administration of at least 85% of the $AUC_{0-\infty}$ of an aqueous solution of the compound of formula I after oral administration.
57. The composition according to any one of the preceding claims, wherein the composition provides for an $AUC_{0-\infty}$ of the compound of formula I upon oral administration from 100 to 500 h·ng/mL, such as $AUC_{0-\infty}$ from 160 to 460 h·ng/mL, or $AUC_{0-\infty}$ from 250 to 350 h·ng/mL, such as $AUC_{0-\infty}$ of about 300 h·ng/mL.

58. The composition according to any one of the preceding claims, wherein after oral administration the composition provides:
- a) an AUC_{0-72} or an AUC_{0-inf} of the compound of formula I upon oral administration of at least 85% of the AUC_{0-72} or AUC_{0-inf} of an aqueous solution of an equivalent amount of a compound of formula I after oral administration, and
 - b) a t_{max} of the compound of formula I from about 5.5 to 8.5 hours.
59. The composition according to any one of the preceding claims, wherein the composition releases the compound of formula I at a rate of:
- i. 35-70% within the first 2 hours, such as 40-65% release within the first 2 hours;
 - ii. 60-95% released after 4 hours, such as 75-85% released after 4 to 6 hours, such as after 4 hours, 5 hours or 6 hours; and
 - iii. full release after 8 hours
- as measured in a USP-I or a USP-II apparatus at pH 6.8 at 37 °C.
60. The composition according to any one of the preceding claims, wherein the composition comprises from about 0.5 mg to about 25 mg of the compound of formula (I).
61. The composition according to any one of the preceding claims, wherein the composition comprises from about 0.5 mg to 25 mg, such as about 0.5 mg, such as about 1mg, 1.5 mg, 2mg, 2.5mg, 3mg, 3.5mg, 4mg, 4.5mg, 5mg, 6mg, 7mg, 8mg, 9mg, 10mg, 11mg, 12mg, 13mg, 14mg, 15mg, 16mg, 17mg, 18mg, 19mg, 20mg, 21mg, 22mg, 23mg, 24mg or 25 mg of the compound of formula (I).
62. The composition according to any one of the preceding claims, wherein the composition comprises 5 mg or 10mg of the compound of formula (I).
63. A unit dosage form comprising the composition according to any one of the preceding claims.

64. A method of obtaining a therapeutically effective plasma concentration of a compound of formula (I)

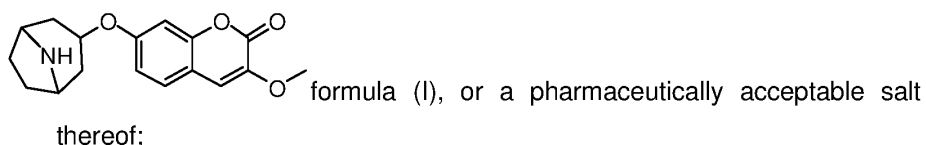


- 5 in a subject, wherein the $t_{\max}$ of the compound of formula I is between 4 and 12 hours, said method comprising oral administration of a composition according to any one of claims 1 to 62.

65. The method according to claim 64, wherein the subject is a human.

- 10 66. The method according to claims 64 to 65, wherein the AUC_{0-72} or the $AUC_{0-\infty}$ of the compound of formula I upon oral administration is of at least 85%, such as at least 90%, of the AUC_{0-72} or the $AUC_{0-\infty}$ of an aqueous solution of an equivalent amount of a compound of formula I upon oral administration.

- 15 67. A method of preparing a composition comprising pellets, the method comprising:
 a) providing pellet core,
 b) providing a drug layer solution comprising a compound of formula (I)



- 20 c) coating the drug layer solution onto the pellet core to form a drug layer;
 d) providing a barrier coating solution comprising a film forming agent;
 e) coating the barrier coating solution on top of the drug layer in c) to obtain a barrier coating layer;
 f) providing an extended release solution comprising one or more extended
 25 release polymer(s);
 g) coating the extended release solution on to the barrier coating layer in e) to obtain an extended release layer.

- 30 68. The method according to claim 67, wherein the pellet core is as described in any one of claims 10 to 11, the drug layer is as described in any one of claims 1-9 or 12-13, the barrier coating layer is as described in any one of claims 14 to 18, or the extended release layer is as described in any one of claims 19 to 38.

69. The method according to any one of claims 67-68, wherein the drug layer solution comprises a binder as described in any one of claims 2 to 5, or a pH modifier and/or a stabilizer as described in any one of claims 6 to 9.
- 5 70. The method according to any one of claims 67-69, wherein the drug layer solution comprises a solvent or dispersant, wherein said solvent or dispersant comprises or consist of an aqueous solution.
- 10 71. The method according to any one of claims 67-70, wherein the barrier coating solution comprises a solvent or dispersant, wherein said solvent or dispersant comprises or consists of an aqueous solution.
- 15 72. The method according to any one of claims 67-71, wherein the extended release layer solution comprises a film forming agent as described in any one of claims 24 to 26 or a plasticizer as described in any one of claims 30 to 33 or an antitacking agent as described in any one of claims 34 to 37.
- 20 73. The method according to any one of claims 67-72, wherein the extended release layer solution comprises a solvent or dispersant, wherein said solvent or dispersant comprises or consists of an aqueous solution comprising an organic solvent, such as isopropanol.
- 25 74. The method according to any one of claims 67 to 73, wherein the composition is as defined in any one of claims 1 to 59.
- 30 75. A composition obtained by the method according to any one of claims 1 to 74.
- 35