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(54) **Title**: OSMOTIC DELIVERY DEVICE WITH MODIFIED RELEASE

(57) **Abstract**: A pharmaceutical composition comprising: a core comprising an antianginal agent, and osmotic agent, and, optionally, one or more pharmaceutically acceptable excipients; and a semipermeable membrane surrounding the core, wherein the semipermeable membrane includes at least one aperture therein through which the antianginal agent can be discharged from the pharmaceutical composition to a patient in need thereof.

OSMOTIC DELIVERY DEVICE WITH MODIFIED RELEASE

Technical field:

The present invention relates to a modified release pharmaceutical composition comprising one or more active(s) for the treatment of cardiac disorders and to a process for manufacturing the same.

Background and prior art:

It is known in the prior art that antianginal preparations are used to arrest attacks of angina pectoris. Such preparations contain active substances such as glycerol trinitrate, isosorbide dinitrate, pentaerythritol tetranitrate, and others. In addition to said active substances, these medicinal preparations contain an inert carrier which is resolved in the liquid media of the body. A typical composition comprises granules of glycerol trinitrate containing sugar, starch, and other substances as filling materials.

Further, there are antianginal preparations manufactured in the form of tablets and dragees. These also include multi-coated pills containing synthetic polymers such as polyvinyl alcohol, and a copolymer of polyvinyl alcohol and vinyl acetate, as a resolvable carrier material. Synthetic polymers are used to coat tablets or granules so that the rate of release of the active ingredient can be controlled. (e.g. FR2326933; US4012498).

One such known medicament is trimetazidine which is currently used for the prophylactic treatment of angina pectoris, in chorioretinal attacks and for the treatment of vertigo of vascular origin (Meniere's vertigo, tinnitus).

Trimetazidine or 1-(2,3,4 – trimethoxybenzyl)piperazine, being a highly aqueous soluble compound, which by maintaining the energy metabolism of the cell exposed to hypoxia or ischemia, avoids the collapse of the intracellular level of adenosine triphosphate (ATP). It

thus ensures functioning of the ion pumps and sodium-potassium transmembrane flows and maintains cellular homeostasis.

Trimetazidine dihydrochloride has, until now, been administered by the oral route at doses of from 40-60 mg/day, in the form of tablets containing 20mg of active ingredient or a drinkable solution containing 20mg of active per ml. These two forms are immediate-release forms. FR2490963 describes the immediate release tablet form. Trimetazidine dihydrochloride is rapidly absorbed and eliminated by the body, its plasma half-life being less than 6 hours, which means that administration of the active ingredient has to be split into 2 or 3 administrations per day in order to ensure sufficient plasma levels. The dosage regimen most frequently required during treatments is three tablets per day. Multiple daily administrations bear the risk of being forgotten both by patients leading an active life and by elderly patients already taking a number of medications.

It is known to be important to maintain effective myocardial protection throughout the 24 hour period and especially in the early morning when the consequences of ischemia are most serious. To accomplish better aspects like enabling better coverage and maintain the efficacy, sustained release dosage forms provide a much better therapy as compared to the conventional forms with regards to the pharmacokinetics. The disadvantages of the known medicinal preparations in the form of tablets pressed with powdered synthetic polymers, and also enclosed in coats of such polymers, is that they can be improperly administered (especially by children who can chew them before swallowing) and hence produce undesirable side effects due to rapid uncontrolled absorption into the body.

WO03043610 relates to formulations and processes for the preparation of polymer coated trimetazidine microbeads for once a day dosing.

EP1108424 discloses matrix tablets for prolonged release of trimetazidine or its additive salts, the release being controlled by use of a cellulose polymer.

EP1195160 discloses sustained release pharmaceutical compositions comprising at least one of hydrocolloid forming material(s); hydrophobic polymers and another category of hydrophobic materials.

From the art, it has been observed there is a problem with the sustained release solid dosage forms comprising water soluble polymers such as class of cellulose derivatives in that they tend to adhere to the internal membrane of GI tract hampering the pulsatile release of the drug, and ultimately leading to minimum drug efficacy at the target tissues. There are other functional issues of sustained release formulations incorporating these mucoadhesive polymers such as batch to batch variation of the finished product (e.g. tablets).

US5837379 discloses extended release tablets containing osmotic tablets, which have an osmotically active drug core surrounded by a semi-permeable membrane with the core comprising two layers one with the active drug & the other being a push layer.

US5536507 relates to an enteric coated delayed release pharmaceutical composition which comprises the active material, pH sensitive polymer and optionally an osmotic agent.

US4783337 discloses an osmotic system comprising a wall made at least partly of a semipermeable material that surrounds a compartment.

Other techniques for making sustained release formulations, as disclosed in the above patents, depend on the pH sensitivity of the polymer involved or require presence of an osmopolymer which in turn requires additional monitoring of the release characteristics and may lead to above mentioned drawbacks. Hence, there is a need to provide sustained release pharmaceutical composition which are pH independent and which overcome the above drawbacks, by means of modified release of the active drug throughout its dosage which shows the intended therapeutic efficacy.

Object of the invention:

An object of the present invention is to provide a modified release pharmaceutical composition.

Another object of the present invention is to provide a pulsatile sustained release dosage form having therapeutic efficacy substantially equivalent to zero order release rate.

Yet another object of the present invention is to provide a modified release pharmaceutical composition processed as an osmotic delivery device that makes an active ingredient available to a patient in need of cardiac and related therapy.

Still another object of the present invention is to provide the process of manufacture for the modified release pharmaceutical composition.

Summary of the invention:

According to one aspect of the present invention there is provided a modified release pharmaceutical composition comprising one or more antianginals and/or other drugs for treatment in cardiac and related disorders by means of an osmotic delivery system.

According to another aspect of the present invention there is provided a modified release pharmaceutical composition having a high drug to osmostic agent (hereinafter referred to as "osmogent") ratio thereby achieving the desired therapeutic efficacy equivalent to zero order release rate.

According to another aspect of the invention there is provided a pharmaceutical composition comprising: a core comprising an antianginal agent, an osmotic agent, and, optionally, one or more pharmaceutically acceptable excipients; and a semipermeable membrane surrounding the core, wherein the semipermeable membrane includes at least one aperture therein through which the antianginal agent can be discharged from the pharmaceutical composition to a patient in need thereof; wherein the ratio of antianginal agent to osmotic agent in the core is from 1:1 to 1:10.

In an advantageous embodiment, the semipermeable membrane is substantially impermeable to the antianginal agent. Furthermore, the semipermeable membrane is permeable to an external fluid, such as water, whereby, when the pharmaceutical composition is placed in an

environment containing the external fluid (for example, the gastrointestinal tract of a patient in need of the active agent), fluid from the environment is drawn by osmosis into the core through the semipermeable membrane. The ingress of fluid into the core causes the contents of the core, in particular the active agent, to be pumped out of the core through the aperture.

According to yet another aspect of the present invention there is provided a process of manufacturing an osmotic delivery device comprising one or more antianginals and/or other drugs for treatment in cardiac and related disorders that avails said modified release following administration to a patient in need thereof.

According to another aspect of the invention there is provided a process for preparing a pharmaceutical composition, said process comprising: combining an antianginal agent with an osmotic agent, and, optionally, one or more pharmaceutically acceptable excipients, to form a core; coating the core with a semipermeable membrane; and forming at least one aperture in the core.

According to yet another aspect of the present invention there is provided a method of treating a patient with cardiac and related disorders in need thereof comprising administration of the said modified release pharmaceutical composition.

The invention is particularly suitable for use with trimetazidine and pharmaceutically acceptable salts thereof, especially the dihydrochloride.

Detailed description of the invention:

As discussed above, there is a need for development of modified release formulation containing one or more antianginal drugs. The present inventors have surprisingly found that a formulation can be manufactured as an osmotic delivery device having a high drug to osmogent ratio. Further it has been found that the desired zero order release rate is achieved without any substantial amount of osmopolymer and is fairly independent of pH and hydrodynamic conditions of the body. It was found that the amount of drug release rate increased with the increase in the amount of osmogent because of the increased water uptake, and hence increased driving force for drug release.

According to the present invention, the drug to osmogent ratio is the characteristic criteria for the desired modified release effect following administration of the formulation.

The term "modified release" used in the present context is defined as the formulation from which the delivery or release of the active at the target site differs from that of a conventional dosage form. The release rate is in other words controlled and it is possible to manipulate the release rate by e.g. changing the formulation parameters. The term "modified" is often used in the sense of prolonged, but the term is not restricted to an extended or prolonged effect; the term "modified" may as well cover the situation where the release rate is manipulated in such a manner that a quicker release than normally expected is obtained. Thus, in the present context, the terms "quick", "fast" and "enhanced" release as well as "controlled", "delayed", "sustained", "prolonged", "extended" and other synonyms well known to a person skilled in the art are covered by the term "modified".

Suitably, the pharmaceutical dosage form according to the present invention may be presented in a solid dosage form, conveniently in unit dosage form, and include dosage forms suitable for oral and/or buccal administration.

Solid dosage forms according to the present invention may preferably be administered in the form of tablets.

In the preferred embodiment, the present invention comprises an osmotic delivery system comprising a core structure incorporating one or more drugs and optionally one or more excipients & a semi permeable membrane. The membrane comprises one or more water soluble polymers (e.g. cellulosic polymers) or water insoluble or combination of both that are water permeable along with one or more solvents for dissolving the polymer. Further, the delivery system is provided with a passageway, an aperture or an orifice or a bore on the outer water permeable membrane that is desirably formed by laser drilling, erosion, or leaching, and which serves as drug delivery pathway. The system absorbs water by osmosis, driven by the difference in water activity within and outside the membrane. The contents of the core are thus displaced and delivered through the orifice by the pumping action of the

water continuously in flux. The core and membrane are formulated so that the delivery process is independent of external pH and stirring conditions.

According to the present invention, the osmotic delivery system comprise a core structure incorporating one or more drug selected from the class of antianginals, antiarrhythmics, antihypertensives, antihyperlipidemics, vasodilators, and other relative class of drugs; one or more osmotic agents and optionally one or more excipients wherein the ratio of drug to osmogent ranges from 1:1 to 1:10 by weight of the formulation.

In one embodiment, the present invention pertains to a modified release pharmaceutical formulation in the form of oral osmotic drug delivery system comprising one or more drugs and one or more osmogents, optionally with one or more pharmaceutical excipients wherein the ratio of drug to osmogent ranges from 1:1 to 1:10 by weight of the formulation, preferably in the range of 1:1 to 1:8 by weight of the formulation. The present invention may optionally comprise one or more surfactants, binders, lubricants, film coating or membrane coating solution which may comprise polymers, plasticizers, solvents.

The present invention is applicable to a range of compounds, including poorly soluble or highly soluble drugs i. e. that include water soluble to practically insoluble in water. The drug may be provided in the form of a pharmaceutically acceptable salt, solvate, ester, prodrug or derivative, enantiomer, tautomer, or polymorph.

The invention in another embodiment pertains to a method for delivering a drug at a constant rate with a pulsatile release, which method comprises the steps of: (A) administering orally an osmotic device shaped, sized and structured in the form of a tablet into the gastro intestinal tract of a patient, the osmotic tablet comprising: (a) a wall formed of a semipermeable material that is permeable to the passage of an exterior fluid and substantially impermeable to the passage of drug; (b) a compartment surrounded by the wall and containing a dosage unit amount of drug and an effective amount of osmotic agent which osmotic agent is a means for providing a pulsed delivery of drug; and (c) a passageway for the release of the drug; (B) imbibing exterior fluid through the semipermeable wall into the compartment at a rate determined by the permeability of the semipermeable wall and the

osmotic pressure gradient across the semipermeable wall to form a solution comprising the drug that is hydrodynamically and osmotically delivered from the system; and (C) delivering the drug in a therapeutically effective amount at a substantially constant rate accompanied by a pulsed delivery of drug in an effective amount larger than the constant rate through the passageway to the gastro intestinal tract of the patient to produce the desired beneficial effect of the constant rate and the pulsed rate of drug delivery over the prolonged period of time.

The passageway is preferably a laser drilled passageway. Preferably the passageway is a single hole.

The drugs that may be incorporated, according to the present invention, include one or more of anti-anginals such as nitrate drugs (such as amyl nitrite, nitroglycerin, and isosorbide), β-adrenaline receptor blocking drugs (such as propranolol, pindolol, indenolol, carteolol, bunitrolol, atenolol, acebutolol, metoprolol, timolol, nipradilol, penbutolol, nadolol, tilisolol, carvedilol, bisoprolol, betaxolol, celiprolol, bopindolol, bevantolol, labetalol, alprenolol, amosulalol, arotinolol, befunolol, bucumolol, bufetolol, buferalol, buprandolol, butylidine, butofilolol, carazolol, cetamolol, cloranolol, dilevalol, epanolol, levobunolol, mepindolol, metipranolol, moprolol, nadoxolol, nevibolol, oxprenolol, practol, pronetalol, sotalol, sufinalol, talindolol, tertalol, toliprolol, and xybenolol), calcium channel blocking drugs (such as aranidipine, efonidipine, nicardipine, bamidipine, benidipine, manidipine, cilnidipine, nisoldipine, nitrendipine, nifedipine, nilvadipine, felodipine, amlodipine, diltiazem, bepridil, clentiazem, phendiline, galopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, cilnidipine, elgodipine, isradipine, lacidipine, lercanidipine, nimodipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, and perhexiline), trimetazidine, dipyridamole, etafenone, dilazep, trapidil, nicorandil, enoxaparin, and aspirin.

The anti-anginal agent may be present in the range of 10 to 30 % by weight of the formulation.

Examples of antihyperlipidemic drugs include one or more of atorvastatin, simvastatin, pravastatin sodium, fluvastatin sodium, clinofibrate, clofibrate, simfibrate, fenofibrate, bezafibrate, colestimide, and colestyramine.

Examples of antihypertensive drugs include one or more of angiotensin converting enzyme inhibitors (such as captopril, alacepril, lisinopril, imidapril, quinapril, temocapril, delapril, benazepril, cilazapril, trandolapril, enalapril, ceronapril, fosinopril, imadapril, mobertpril, perindopril, ramipril, spirapril, and randolapril), angiotensin II antagonists (such as losartan, candesartan, valsartan, eprosartan, and irbesartan).

Examples of antiarrhythmic drugs include one or more of ajmaline, pirmenol, procainamide, cibenzoline, disopyramide, quinidine, aprindine, mexiletine, lidocaine, phenytoin, pilsicainide, propafenone, flecainide, atenolol, acebutolol, sotalol, propranolol, metoprolol, pindolol, amiodarone, nifekalant, diltiazem, bepridil, and verapamil.

Examples of vasodilators include one or more of bencyclane, cinnarizine, citicoline, cyclandelate, cyclonicate, ebumamonine, phenoxezyl, flunarizine, ibudilast, ifenprodil, lomerizine, naphlole, nikamate, nosergoline, nimodipine, papaverine, pentifylline, nofedoline, vincamin, vinpocetine, vichizyl, pentoxifylline.

Through the specification, mention of the term "drug" or "compound" or "active" *per se* shall encompass not only the drug names but also their corresponding pharmaceutically acceptable salts, solvates, esters, prodrugs or derivatives, enantiomers, tautomers, polymorphs thereof.

According to the present invention, the osmotically effective compounds or solutes are a substantial motive force for the osmotic system and they exhibit an osmotic pressure gradient against an external fluid across the membrane. The solutes are conveniently used by dispensing or homogenously or heterogeneously mixing a solute or a mixture of solutes with the active agent, composition, product or the like. In operation, these solutes osmotically attract fluid into the tablet to produce a solution of the solute and the active drug which further releases the drug by means of laser drilled hole in the tablet. The osmotic agents which may be used comprises a pharmaceutically acceptable alkali metal salt or alkaline

earth metal salt, in particular pharmaceutically acceptable sodium, potassium, lithium, magnesium and calcium salts, such as sodium chloride, magnesium sulfate, magnesium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, calcium bicarbonate, sodium sulfate, calcium sulfate, potassium acid phosphate, calcium lactate, magnesium succinate. Other suitable osmotic agents include tartaric acid, and soluble pharmaceutically acceptable carbohydrates such as raffinose, glucose, sorbitol, mannitol, mixtures thereof and the like. The osmogent may be present in the range of 40 to 95 % by weight of the formulation. Preferably, the osmotic agent, according to the present invention, is sodium chloride.

The formulation, according to the present invention, may comprise a binder or binder solution which may be an alcoholic, aqueous or hydroalcoholic solution. According to a preferred embodiment suitable binders include starch and its derivatives, maltodextrins, cellulose derivatives that are not limited to hydroxypropylmethylcellulose (HPMC) , hydroxypropylcellulose (HPC) and the like; polyvinylpyrrolidones that are not limited to PVP K 25, PVP K 30 and the like. One or more pharmaceutically acceptable solvents that may be incorporated include hydrophilic alcohols that are not limited to ethanol, methanol, n-butanol, n-hexanol and the like. In a preferred embodiment, the present invention may incorporate a binder solution in the range of 1 to 10 % by weight of the formulation.

According to the present invention, the pharmaceutical formulation may also comprise suitable lubricants. Preferably, the lubricants may comprise stearates and stearic acid derivatives such as magnesium stearate, zinc stearate, calcium stearate, sodium stearyl fumarate. The lubricants may be present in the range of 0.25 to 3% by weight of the formulation.

Optionally, the formulation may further comprise one or more surfactants which include but are not limited to Sorbitan fatty acid esters (Spans) like Span 20, Span 40, Span 60, Span 80; Polyoxyethylene sorbitan fatty acid esters (Tweens) like tween 20, tween 40, tween 60, tween 80, and/or mixtures thereof.

Further, according to the invention, the pharmaceutical formulation comprises semipermeable film coating or membrane coating i. e. a coating material that is permeable to an external fluid such as water and the like while essentially impermeable to the drug and the related. Typically, coating materials may include one or more polymers, plasticizers, solvents and optionally other excipients. Suitable polymers that may be used comprise cellulose derivatives like unplasticized cellulose acetate, plasticized cellulose acetate, reinforced cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate, cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethaminoacetate, cellulose acetate ethyl carbonate, cellulose acetate chloroacetate, cellulose acetate ethyl oxalate, cellulose acetate methyl sulfonate, cellulose acetate butyl sulfonate and cellulose acetate propionate. Preferably, the membrane (in particular the polymer) may be present in a range of 2 to 10 % by weight of the formulation.

The semipermeable film coating or membrane coating may further comprise low viscosity methyl cellulose derivatives like HPMC grade 3 CPS, HPMC grade 5 CPS, HPMC grade 6 CPS up to HPMC grade 15CPS low viscosity derivatives. Preferably, one or more of these derivatives may be present in a range of 10 to 50 % by weight of the polymer.

The coating solution may further, optionally, comprise plasticizers which include, but are not limited to poly ethylene glycol (PEG) derivatives like PEG200, PEG400, PEG600, PEG 1000, PEG 2000, PEG3000, PEG 4000, PEG 6000, etc. The plasticizer may be present in a range of 1 to 15 % by weight of the polymer.

The coating solution may further comprise suitable solvents selected from one or more aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents, and mixtures thereof. Preferably, the solvent is acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methylpropyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, acetone

and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, ethylene dichloride, methanol, or a combination thereof.

According to the present invention, the modified release pharmaceutical composition may be manufactured by means known to person skilled in the art. Accordingly, the said modified release pharmaceutical composition may be processed by techniques such as but not limited to dry or wet granulation, melt granulation, extrusion (e.g. melt extrusion), spheronization, melt congeal technique, spray drying.

In a preferred embodiment, the present invention provides a process for preparing a pharmaceutical composition, said process comprising: combining an antianginal agent with an osmotic agent, and, optionally, one or more pharmaceutically acceptable excipients, to form a core; coating the core with a semipermeable membrane; and forming at least one aperture in the core.

Alternatively, the process of preparing the pharmaceutical composition comprises forming the core by granulating the antianginal agent and the osmotic agent in a binder solution; drying the granules; blending the granules with a lubricant; and compressing the blended granules into a tablet.

The present invention also provides methods of using an oral osmotic delivery system to provide controlled and/or sustained delivery of a drug. For example, the present invention provides a method of delivering a drug to a subject comprising administering to the subject an osmotic drug delivery system as described above.

The present invention further provides a method of treating a cardiac disorder comprising administering a therapeutically effective amount of a pharmaceutical composition according to any preceding claim to a patient in need thereof.

According to the present invention, the oral osmotic delivery system may optionally include additional drug layers, osmotic layers, and/or internal piston layers. When provided, the additional drug layer(s) may be included in order to achieve a particular release profile of the

drug being administered, for example, by including more than one layer of the same drug, where the drug layers have different formulations (e.g., each drug layer includes a different hydrophilic polymer). Such additional drug layers may also be used to provide for co-administration of additional compounds useful in treating a particular disease or condition. When additional osmotic layer(s) are provided, these may be useful for achieving a particular release profile. This may be accomplished, for example, by utilizing osmotic layer(s) that have different swelling characteristics. The optional additional piston layer may be provided to assist in displacing the drug layer from the dosage form.

Reference is now made to Fig. 1, which is a schematic cross sectional view of a pharmaceutical composition according to the invention.

The pharmaceutical composition is generally designated 10, and comprises a semipermeable membrane 12, which surrounds a core 14. The core 14 contains an active agent, such as trimetazidine, along with an osmotic agent, such as sodium chloride.

The semipermeable membrane 12 includes at least one aperture 16 through which the active agent may be discharged from the core in the direction of the arrow A.

The semipermeable membrane 12 is permeable to an exterior fluid (e.g. gastrointestinal fluid, especially water) but is substantially impermeable to the active agent. When the pharmaceutical composition 10 is placed in an aqueous environment (for example, the gastrointestinal tract of a patient in need of the active agent), water from the environment is drawn by osmosis into the core 14 through the semipermeable membrane 12 as indicated by the arrow B. The ingress of water into the core 14 causes the contents of the core 14, in particular the active agent, to be pumped out of the core 14 through the aperture 16.

The following example is for the purpose of illustration of the invention only and is not intended in any way to limit the scope of the present invention

Sr. No.	INGREDIENTS	Quantity (mg/tablet)
	Dry Mix	
1.	Trimetazidine dihydrochloride	35.00
2.	Sodium Chloride	138.50
	Binder	
3.	Povidone (PVP K-30)	5.00
4.	Purified water	q. s.
	Lubricant	
5.	Magnesium stearate	1.50
	Coating	
6.	Cellulose Acetate (CA-398-10)	5.60
7.	Hypromellose (HPMC 6cps)	2.40
8.	Dichloromethane	q. s.
9.	Ethanol	q. s.
	Total	**188.00**

Process:

(1) Dry mix of pre-sifted quantities of trimetazidine dihydrochloride and sodium chloride was prepared.

(2) A binder solution was prepared by dissolving povidone in purified water under continuous stirring to get a clear solution.

(3) The dry mix obtained in (1) was granulated using the binder solution to obtain a wet mass which was dried and sifted.

(4) The granules obtained in (3) were blended with magnesium stearate and compressed into tablets.

(5) A coating solution was prepared by dissolving hypromellose in a mixture of ethanol and dichloromethane followed by addition of cellulose acetate and mixed thoroughly.

(6) The tablets obtained in (4) were coated with the above coating solution and finally laser drilled.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by the preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and such modifications and variations are considered to be falling within the scope of the invention.

It is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "a propellant" includes a single propellant as well as two or more different propellants, and the like.

CLAIMS:

1. A pharmaceutical composition comprising: a core comprising an antianginal agent, an osmotic agent, and, optionally, one or more pharmaceutically acceptable excipients; and a semipermeable membrane surrounding the core, wherein the semipermeable membrane includes at least one aperture therein through which the antianginal agent can be discharged from the pharmaceutical composition to a patient in need thereof; wherein the ratio of antianginal agent to osmotic agent in the core is from 1:1 to 1:10.

2. A pharmaceutical composition according to claim 1, wherein the ratio of antianginal agent to osmotic agent in the core is from 1:1 to 1:8.

3. A pharmaceutical composition according to claim 1 or 2, wherein the antianginal agent is a nitrate drug; a beta adrenaline receptor blocker; a calcium channel blocker; trimetazidine; dipyridamole; etafenone; dilazep; trapidil; nicorandil; enoxaparin; aspirin; or a combination thereof.

4. A pharmaceutical composition according to claim 1, 2 or 3, wherein the antianginal agent is trimetazidine or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition according to any preceding claim, wherein the osmotic agent comprises a pharmaceutically acceptable salt of an alkali metal or an alkaline earth metal; tartaric acid; or a soluble pharmaceutically acceptable carbohydrate.

6. A pharmaceutical composition according to any preceding claim, wherein the osmotic agent is sodium chloride.

7. A pharmaceutical composition according to any preceding claim, wherein the osmotic agent is present in an amount from 40 to 95 % by weight of the composition.

8. A pharmaceutical composition according to any preceding claim, wherein the semipermeable membrane comprises a polymer.

9. A pharmaceutical composition according to any preceding claim, wherein the semipermeable membrane comprises a cellulose derivative.

10. A pharmaceutical composition according to any preceding claim, wherein the semipermeable membrane is present in an amount from 2 to 10 % by weight of the composition.

11. A pharmaceutical composition according to any preceding claim, wherein the pharmaceutically acceptable excipient comprises a binder and/or a lubricant.

12. A process for preparing a pharmaceutical composition as defined in any preceding claim, said process comprising: combining an antianginal agent with an osmotic agent, and, optionally, one or more pharmaceutically acceptable excipients, to form a core; coating the core with a semipermeable membrane; and forming at least one aperture in the core.

13. A process according to claim 12, wherein the or each aperture is formed by laser drilling.

14. A process according to claim 12 or 13, wherein the core is formed by granulating the antianginal agent and the osmotic agent in a binder solution; drying the granules; blending the granules with a lubricant; and compressing the blended granules into a tablet.

15. A method of treating a cardiac disorder comprising administering a therapeutically effective amount of a pharmaceutical composition according to any preceding claim to a patient in need thereof.

16. A pharmaceutical composition substantially as herein described with reference to and as shown in the accompanying drawing.

17. A pharmaceutical composition substantially as described in the example.

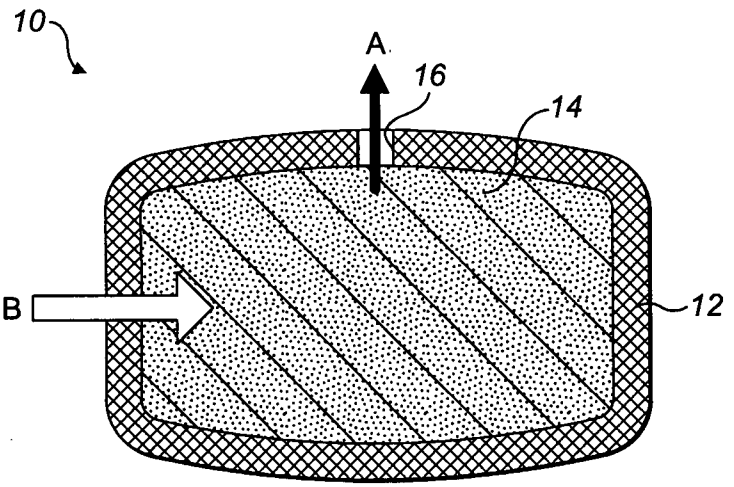


FIG. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/001962

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/28 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 10 2005 031577 A1 (BAYER HEALTHCARE AG [DE]) 11 January 2007 (2007-01-11) example 1.1	1-3,5,6, 8-17
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Y	examples 1-6	1-17
X	WO 01/51035 A (PHOENIX U S A INC LAB [US]; FAOUR JOAQUINA [AR]) 19 July 2001 (2001-07-19) example 2	1-3,5,6, 8-17

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
19 October 2009	27/10/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sindel, Ulrike

INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	US 2003/185888 A1 (WONG PATRICK S L [US] ET AL) 2 October 2003 (2003-10-02) paragraph [0025] examples 1-6	1-17

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