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(54) Title: CONTROLLED RELEASE PHARMACEUTICAL DOSAGE FORMS OF TRIMETAZIDINE

(57) Abstract: The present invention relates to new solid dosage forms for the controlled release of trimetazidine suitable for once-daily dosing, in which the dosage form exhibits a controlled in vitro release of trimetazidine in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours when measured using USP Apparatus I at 100 rpm, thereby decreasing the incidence and severity of burst release or dose dumping.

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CONTROLLED RELEASE PHARMACEUTICAL DOSAGE FORMS OF TRIMETAZIDINE

Field of the Invention

The present invention relates to new solid pharmaceutical dosage forms for the controlled release of trimetazidine suitable for once-daily dosing.

Background of the Invention

Trimetazidine [1-(2,3,4-trimethoxybenzyl piperazine] is a 3-ketoacyl-coenzyme A thiolase inhibitor with a cytoprotective effect, which by preserving the energy metabolisms of the cell exposed to the hypoxia or ischaemia, avoids the collapse of the intracellular rate of adenosine triphosphate (ATP). Thus it ensures the functioning of the ion pumps and the sodium-potassium transmembrane flux and maintains the cellular homeostasis.

Trimetazidine dihydrochloride is used therapeutically in the long-term treatment of angina pectoris. It is freely soluble in water and has two pKa values 4.32 and 8.95. Trimetazidine dihydrochloride is administered orally in doses of 40 to 60mg daily in divided doses as an immediate release preparation. It is quickly absorbed and eliminated by the organism with plasma half-life of around 6.0 +/- 1.4 hours and Tmax of around 1.8 +/- 0.7 hours. Since it has a shorter plasma half life, in practice 20mg preparation is given twice or thrice a day in order to ensure relatively constant plasma levels.

Servier had developed a modified-release dosage form containing 35mg for twice-daily administration, marketed under the brand name "VASTAREL MR". This dosage form was bioequivalent to the 20 mg conventional thrice-a-day formulation of trimetazidine hydrochloride. The modified-release formulation is based on a hydrophilic matrix that utilizes polymers which swell in contact with gastrointestinal fluids to form gels. This formulation has been covered by Servier in a European patent published as EP 1 108 424, which discloses a matrix tablet enabling prolonged release of trimetazidine comprised of cellulose derivative polymers. The formulation described releases more than 90% of the drug *in-vitro* within a period of 4 hours.

European patent EP 0 673 649 also assigned to Servier describes pharmaceutical compositions for the prolonged release of trimetazidine wherein prolonged release is

ensured by the reservoir system. The composition is prepared by compression of the active ingredient mixture and excipient, which are then coated with an insoluble polymer.

The prior art describes the use of hydrophilic polymers for controlling the release of trimetazidine from the controlled release pharmaceutical compositions. However, for water-soluble salts such as hydrochloride salt of trimetazidine, it may result in burst release or dose dumping.

The PCT application WO 03/043610 filed by Themis Laboratories, discloses a process for manufacturing microbeads, which enable "once a day" dosing for 60 mg dose of trimetazidine dihydrochloride per unit dose. The application further provides dissolution rates at different time periods which correspond to 24 hours therapeutic blood levels. Further, it discloses the dissolution rate to be not less than 65% w/w in 6 hours.

The European patent application EP 1 195 160 filed by USV, discloses a sustained release dosage form of trimetazidine that releases more than 90% of the drug in-vitro within a period of about 6 hours to about 8 hours. The dosage form employs hydrophobic substance and a hydrocolloid for sustaining the release.

A controlled in vitro release of trimetazidine is of most importance in the context of *in vivo* drug profiles. Drug absorption from a solid dosage form following oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two of these steps, in vitro dissolution may be relevant to the prediction of *in vivo* performance.

Therefore, taking into account the great therapeutic interest of trimetazidine, there exists a need in the state of the art for new pharmaceutical dosage forms for “once a day” dosing of trimetazidine, prepared by a simpler process that is cost-effective and yields a dosage form with pH independent release of trimetazidine for at least 16 hours without any lag period.

The present invention provides new solid pharmaceutical dosage forms for the controlled release of trimetazidine suitable for once-daily dosing, in which the dosage form exhibits a controlled in vitro release of trimetazidine in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours when measured using USP Apparatus I at 100 rpm,

thereby decreasing the incidence and severity of burst release or dose dumping. The pharmaceutical dosage form of the present invention uses a cost effective and rapid operation process.

Although water-insoluble polymers have been employed as a coating polymer in reservoir systems, these systems produced a release profile where trimetazidine hydrochloride is not available for immediate absorption and pharmacological action. Other factors such as complexity of process, need for specialized equipment, incomplete release, etc. may also limit its use.

The present invention utilizes a simpler process of employing water-insoluble polymers as the matrix forming polymer. However, the water insoluble polymers, due to their nature, may result in a slower release, particularly in the beginning, leading to a lag phase. This is mainly due to less intake of aqueous medium. To avoid this, a water swellable polymer may be incorporated in the matrix which results in increased early wetting.

Summary of the Invention

In one general aspect there is provided a controlled release monolithic matrix dosage form comprising:

(a) therapeutically effective amount of trimetazidine or its pharmaceutically acceptable salts,

(b) one or more rate controlling polymers selected from the group consisting of a water-insoluble polymer , water-swellable polymer, and mixture thereof, and

(c) one or more pharmaceutically acceptable excipients,

wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

Controlled release dosage forms of trimetazidine suitable for once-daily dosing, contain less than about 100mg of trimetazidine.

Particularly the dosage forms contain about 50 mg to about 80 mg of trimetazidine. Particularly, controlled release dosage forms of trimetazidine suitable for once-daily dosing contain about 70 mg of trimetazidine.

Controlled release dosage forms of the present invention comprise about 5 to 50% by weight of trimetazidine based upon the total weight of the dosage form.

Examples of water-insoluble rate controlling polymers include but are not limited to, one or more of ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, co-polymers of acrylate or methacrylate having a low quaternary ammonium content, poly vinyl acetate, or mixtures thereof. Particularly the water-insoluble polymers are ethyl cellulose, acrylic acid polymers or a combination of the two. The water-insoluble polymers comprise about 5 to about 90% by weight of the dosage form. Particularly the water-insoluble polymers may comprise about 20 to about 60% by weight of the dosage form.

Examples of water swellable rate controlling polymers include but are not limited to, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose, hydroxyethylcellulose, methylcellulose, starch, gums, alginates, acrylic acid derivatives, gelatin and polyethylene oxide.

Particularly the water swellable rate controlling polymer is xanthan gum.

The water swellable polymers may comprise about 5 to about 90% by weight of the dosage form. Particularly the water swellable polymers may comprise about 7% to about 60% by weight of the dosage form.

To further control the release in the early phase and to obtain a near zero-order release profile, the highly water soluble drug trimetazidine or one of its salts is dispersed in a hydrophobic material.

In another aspect there is provided a controlled release monolithic matrix dosage form of trimetazidine comprising:

(a) therapeutically effective amount of trimetazidine or its pharmaceutically acceptable salts,

(b) at least one hydrophobic material, and

(c) one or more rate controlling polymers selected from the group consisting of a water-insoluble polymer , water-swellable polymer, and mixture thereof,

wherein trimetazidine is dispersed uniformly in the hydrophobic material, and wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

Examples of hydrophobic material include but are not limited to, one or more of fatty acids, long chain fatty alcohols, waxes, vegetable oil and glycerides of C_6-C_{18} fatty acids or mineral oil or mixtures thereof.

Particularly, the hydrophobic material comprises carnauba wax, stearic acid or mixtures thereof.

The hydrophobic materials may comprise about 5 to about 90% by weight of the dosage form. Particularly the hydrophobic materials may comprise about 20 to about 60% by weight of the dosage form.

In another aspect there is provided a process for preparing a controlled release monolithic matrix dosage form of trimetazidine comprising the steps of:

(a) blending/mixing trimetazidine and one or more rate controlling polymers with one or more pharmaceutically acceptable excipients, and

(b) compressing the blend of step (a) into tablets;

wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

In another aspect there is provided a process for preparing a controlled release monolithic matrix dosage form of trimetazidine comprising the steps of:

(a) granulating trimetazidine, atleast one pharmaceutically acceptable excipient and one or more rate controlling polymers,

(b) blending/mixing the material of step (a) with one or more pharmaceutically acceptable excipients, and

(c) compressing the blend of step (b) into tablets;

wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

In one of the embodiments, the granulation is carried out by wet granulating the active and the pharmaceutically acceptable excipients with a solution or dispersion of rate controlling polymer.

In another embodiment, a part of the rate controlling polymer is added along with the active. Alernatively, the granulation is carried out by dry blending the active, the pharmaceutically acceptable excipients and the rate controlling polymers and compacting to form granules.

In another aspect there is provided a process for preparing a controlled release monolithic matrix dosage form of trimetazidine comprising the steps of:

(a) dispersing trimetazidine in at least one hydrophobic material;

(b) milling the material of step (a);

(c) mixing/blending the material of step (b) with a rate controlling polymer and other excipients;

(d) compressing the blend of step (c) into tablets;

wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

In another aspect there is provided a process for preparing a controlled release monolithic matrix dosage form of trimetazidine comprising the steps of:

(a) dispersing trimetazidine in atleast one hydrophobic material;

(b) milling the material of step (a);

(c) granulating the material of step (b) with a rate controlling polymer and other excipients;

(d) compressing the blend of step (c) into tablets;

wherein the dosage form exhibits *in vitro* release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

The active is dispersed in at least one hydrophobic material with the help of solvents or by melting the hydrophobic material slightly above its melting point and dispersing the active in it.

In one of the embodiments, the granulation is carried out by wet granulating the active and the pharmaceutically acceptable excipients with a solution or dispersion of rate controlling polymer.

In another embodiment, a part of the rate controlling polymer is added along with the active. Alernatively, the granulation is carried out by dry blending the active, the pharmaceutically acceptable excipients and the rate controlling polymers and compacting to form granules.

Example of solvents used for granulation comprise methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water or mixtures thereof.

The hydrophobic materials were melted at temperatures ranging from about 40°C to about 120° C. Particularly, the hydrophobic materials were melted at a temperature range of about 60° C to about 80° C.

The controlled release dosage forms comprise one or more pharmaceutically acceptable excipients selected from one or more of binders, fillers, lubricants, glidants, coloring agents and flavoring agents.

In another embodiment, the dosage form is optionally coated with one or more layers comprising film forming agents and/or pharmaceutically acceptable excipients.

In another aspect there is provided a method of prophylactic treatment of angina pectoris comprising administering a controlled release monolithic matrix dosage form of trimetazidine, wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

The controlled release monolithic matrix dosage form of trimetazidine may be administered in combination with other cardio therapeutic agents.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and claims.

Detailed Description of the Invention

The present invention relates to controlled release dosage forms of trimetazidine suitable for once-daily dosing, containing less than about 100mg of trimetazidine.

Preferably the dosage forms contain about 50 mg to about 80 mg of trimetazidine. Particularly, controlled release dosage forms of trimetazidine suitable for once-daily dosing contain about 70mg of trimetazidine.

Trimetazidine used herein should be understood as the base or any of its pharmaceutically acceptable salt thereof. Particularly, the salt is dihydrochloride. Controlled release dosage forms of the present invention comprise about 5 to 50% by weight of trimetazidine.

The term "controlled-release", as used herein, includes any type of controlled-release including prolonged release, sustained release, modified release and extended release.

The pharmaceutical dosage forms of the present invention can be administered orally in the form of tablets or capsules filled with pellets, beads, granules, multiparticulates, tablets or powder.

The present invention employs water insoluble polymeric matrix to control the release of highly water soluble trimetazidine. A water swellable polymer is also added to the matrix to allow the aqueous medium to penetrate the dosage form and provide a tortuous path for uniform drug release. The active is released uniformly over a period of 12 to 24 hours in a substantially linear or zero order release.

Examples of water-insoluble rate controlling polymers include but are not limited to, one or more of ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, co-polymers of acrylate or methacrylate having a low quaternary ammonium content, poly vinyl acetate, or mixtures thereof. Particularly the water-insoluble polymers are ethyl cellulose, acrylic acid polymers or a combination of the two. The water-insoluble polymers comprise about 5 to about 90% by weight of the dosage form. Particularly the water-insoluble polymers may comprise about 20 to about 60% by weight of the dosage form.

Examples of water swellable rate controlling polymers include but are not limited to, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose, hydroxyethylcellulose, methylcellulose, starch, gums, alginates, acrylic acid derivatives, gelatin and polyethylene oxide. The water swellable polymers may

comprise about 5 to about 90% by weight of the dosage form. Particularly the water swellable polymers may comprise about 7% to about 60% by weight of the dosage form.

The release of trimetazidine from the dosage form is further controlled in the early phase and a near zero-order release profile is obtained when the drug is dispersed in a hydrophobic material.

Examples of hydrophobic material include but are not limited to, one or more of fatty acids, long chain fatty alcohols, waxes, vegetable oil and glycerides of C_6-C_{18} fatty acids or mineral oil or mixtures thereof. The hydrophobic materials may comprise about 5 to about 90% by weight of the dosage form. Particularly the hydrophobic materials may comprise about 20 to about 60% by weight of the dosage form.

The controlled release dosage forms may further comprise one or more pharmaceutically acceptable excipients.

The pharmaceutically acceptable excipients are those known to the skilled in the art and may be selected from binders, fillers, lubricants, glidants, coloring agents and flavoring agents.

Examples of binders include, but are not limited to, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pregelatinized starch, agar, tragacanth, sodium alginate and propylene glycol.

Examples of fillers or diluents include, but are not limited to, corn starch, lactose, white sugar, sucrose, sugar compressible, sugar confectioners, glucose, sorbitol, calcium carbonate, calcium dihydrogen phosphate dihydrates, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose, fructose, kaolin, lactitol, mannitol, starch and starch pregelatinized.

Particularly, the fillers comprise microcrystalline cellulose, calcium dihydrogen phosphate dihydrate or a mixture of both.

Examples of lubricants and glidants include, but are not limited to, colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated

castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax and white beeswax.

The coloring agents and flavoring agents of the present invention may be selected from any FDA approved colors and flavors for oral use.

The ingredients discussed above may be formed into dosage forms by conventional techniques, for example either by direct compression, or first compacting some of the ingredients, milling the compacts, blending with the remaining ingredients and then compressing as appropriate.

The controlled release monolithic matrix dosage forms may also be prepared using wet granulation techniques. The process may include granulation of trimetazidine and the rate controlling polymers with a solvent or granulation of trimetazidine with a solution of the polymer. The process may further include drying the granules prior to compressing into tablets.

The controlled release dosage forms of the present invention can optionally be coated with one or more layers comprising film forming agents and/or pharmaceutically acceptable excipients.

Coating may be performed by applying one or more film forming polymers with or without other pharmaceutically inert excipients. This may be done as a solution or suspensions using any conventional coating technique known in the prior art, such as spray coating in a conventional coating pan or fluidized bed processor, or dip coating.

Suitable film forming polymers include one or more of ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, cellulose acetate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, waxes, methacrylic acid polymers such as Eudragit® RL and RS, and mixtures thereof. The coating can also be performed using any commercially available ready to coat preparations such as Opadry-AMB, Opadry-White, Opadry-Clear, etc.

Suitable solvents used for making a solution/suspension of film forming polymer include one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and mixtures thereof.

Use of a controlled release monolithic matrix dosage form of trimetazidine in the prophylactic treatment of angina pectoris is provided, wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

The controlled release monolithic matrix dosage form of trimetazidine may be administered in combination with other cardio therapeutic agents.

EXAMPLES

Examples 1, 2 & 3: Controlled release monolithic matrix dosage forms of trimetazidine dihydrochloride

Ingredients	**Percent w/w (total weight) of the dosage form**		
	Example 1	**Example 2**	**Example 3**
Trimetazidine dihydrochloride	10.9	11.1	11.3
Microcrystalline cellulose (High viscosity)	15.6	15.8	16.1
Xanthan gum	15.6	15.8	16.1
Ethylcellulose (High viscosity)	46.7	47.4	48.2
Ethylcellulose (Low viscosity)	1.6	1.6	1.6
Microcrystalline cellulose (Low viscosity)	3.1	3.2	3.2
Carbopol	4.7	3.2	1.6
Colloidal silicone dioxide	0.6	0.6	0.6
Magnesium stearate	1.2	1.3	1.3

Process:

1. Trimetazidine dihydrochloride, microcrystalline cellulose (High viscosity), xanthan gum & ethylcellulose (High viscosity) were mixed and granulated with ethylcellulose (Low viscosity).
2. Granules of step-1 were blended with microcrystalline cellulose (Low viscosity), carbopol, colloidal silicon dioxide and magnesium stearate.
3. Blend of step-2 was compressed into tablets.

The controlled release (CR) dosage forms prepared according to Examples 1, 2 and 3 were subjected to in vitro drug release test which utilizes the United States Pharmacopeia (USP) Apparatus 1 (rotating basket) at 100 rpm with 500 ml of phosphate buffer at pH 6.8 and 37° C. The results of the in vitro release test are given in Table 1.

Table 1: Drug Release of Trimetazidine CR dosage forms prepared as per Examples 1, 2 and 3 in Phosphate buffer pH 6.8, 500 ml, USP 1 at 100 rpm.

Time in Hours	Percent (%) Drug Released		
	Example 1	Example 2	Example 3
1	35	33	34
2	34	37	36
3	48	46	49
4	48	57	53
6	57	62	63
8	70	72	72
12	83	88	83
16	92	91	90
20	101	91	91

Example 4: Controlled release monolithic matrix dosage form of trimetazidine dihydrochloride

Ingredients	**Percent (%) w/w (total weight of the dosage form)**
Trimetazidine dihydrochloride	7.75
Carnauba wax	33.25
Stearic acid	0.55
Ethyl cellulose	32.12
Xanthan gum	11.08
Microcrystalline cellulose	13.29
Colloidal silicon dioxide	0.98
Magnesium stearate	0.98

Process:

1. Trimetazidine hydrochloride was dispersed in a molten mass of carnauba wax and stearic acid.
2. Dispersion of step 1 was stirred till it cooled.
3. Material of step 2 was milled and blended with ethyl cellulose; xanthan gum; microcrystalline cellulose; colloidal silicon dioxide and magnesium stearate.
4. Blend of step 3 was compressed into tablets.

Example 5: Controlled release monolithic matrix dosage form of trimetazidine dihydrochloride

Ingredients	Percent (%) w/w (total weight of the dosage form)
Core	
Trimetazidine dihydrochloride	7.98
Carnauba wax	34.22
Stearic acid	0.57
Ethyl cellulose	22.52
Xanthan gum	11.26
Microcrystalline cellulose	13.96
Calcium dihydrogen phosphate dihydrate	4.65
Colloidal silicon dioxide	0.95
Magnesium stearate	0.95
Coating	
Hydroxypropyl methylcellulose E - 5	2.94
Titanium dioxide	
Polyethylene glycol 400	
Purified water	

Process:

1. Trimetazidine hydrochloride was dispersed in a molten mass of carnauba wax and stearic acid.
2. Dispersion of step 1 was stirred till it cooled.

1. Material of step 2 was milled and blended with ethyl cellulose; xanthan gum; microcrystalline cellulose; calcium dihydrogen phosphate dihydrate; colloidal silicon dioxide and magnesium stearate.
2. Material of step 3 was compressed into tablets.
3. Tablets of step 4 were coated with the coating composition.

The controlled release (CR) dosage form prepared according to Example 5 were subjected to in vitro drug release test which utilizes the United States Pharmacopeia (USP) Apparatus 1 (rotating basket) at 100 rpm with 500 ml of phosphate buffer at pH 6.8 and 37° C. The results of the in vitro drug release test are given in Table 2.

Table 2: In Vitro Release of Trimetazidine CR dosage form prepared as per Example 5 in Phosphate buffer pH 6.8, 500 ml, USP 1 at 100 rpm.

Time in Hours	Percent (%) Trimetazidine Released
1	20
2	31
3	39
4	46
6	57
8	66
12	78
16	86
20	92

In vivo Bioequivalence Study

In vivo performance of a single dose of trimetazidine controlled release dosage forms as per present invention administered once daily (OD) were evaluated with respect to three doses of VASTAREL 20 mg tablets (Immediate release product of trimetazidine) administered thrice daily and two doses of VASTAREL MR 35 mg tablets (Modified release product of trimetazidine) administered twice daily under fasting and fed conditions

in healthy male volunteers. Pharmacokinetic parameters C_{max} (Peak serum concentration); AUC_t (Area under the plasma concentration vs. time curve); and AUC_{inf} (Area under the plasma concentration vs. time curve upto infinity) were calculated from the data obtained. The results of the study are given in Tables 3 and 4.

Table 3: Pharmacokinetic data for controlled release (CR) monolithic matrix dosage forms prepared as per present invention. Once daily vs. three doses of VASTAREL 20 mg tablets (containing trimetazidine 20 mg) administered thrice daily

Condition	pK Parameter (log transformed)	C_{max}	AUC_t	AUC_{inf}
Fasting Condition	Ratio (%)	96.82	96.57	96.89
	90% Confidence Interval	(84.19-111.35)	(86.95-107.27)	(87.71-107.02)
Fed Condition	Ratio (%)	101.44	97.16	96.83
	90% Confidence Interval	(94.14-109.31)	(89.78-105.14)	(89.59-104.64)

Table 4: Pharmacokinetic data for controlled release monolithic matrix dosage forms prepared as per present invention. Once daily vs. two doses of VASTAREL MR 35 mg tablets (containing trimetazidine 35 mg) administered twice daily

Condition	pK Parameter (log transformed)	C_{max}	AUC_t	AUC_{inf}
Fasting Condition	Ratio (%)	81.32	83.57	83.87
	90% Confidence Interval	(75.70-87.35)	(78.45-89.03)	(79.40-88.59)
Fed Condition	Ratio (%)	99.22	86.25	86.00
	90% Confidence Interval	(87.00-97.75)	(81.11-91.73)	(80.89-91.44)

While there has been shown and described what are the preferred embodiments of the invention, one skilled in the pharmaceutical formulation art will appreciate that various modifications in the dosage forms and process can be made without departing from the scope of the invention as it is defined by the appended claims.

CLAIMS:

1. A controlled release monolithic matrix dosage form comprising:

(a) therapeutically effective amount of trimetazidine or its pharmaceutically acceptable salts,

(b) one or more rate controlling polymers selected from the group consisting of a water-insoluble polymer , water-swellable polymer, and mixture thereof, and

(c) one or more pharmaceutically acceptable excipients,

wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

2. The dosage form of claim 1, further comprising trimetazidine or its pharmaceutically acceptable salt dispersed in at least one hydrophobic material.

3. A controlled release monolithic matrix dosage form of trimetazidine comprising:

(a) therapeutically effective amount of trimetazidine or its pharmaceutically acceptable salts,

(b) atleast one hydrophobic material, and

(c) one or more rate controlling polymers selected from the group consisting of a water-insoluble polymer , water-swellable polymer and mixture thereof,

wherein trimetazidine is dispersed uniformly in the hydrophobic material, and wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

4. The dosage form according to claims 1-3, wherein the in vitro release is measured by a drug release test which utilizes the United States Pharmacopoeia (USP) Apparatus 1 (rotating basket) at 100 rpm with 500 ml of phosphate buffer at pH 6.8 and 37° C.

5. The dosage form according to claims 1-3, wherein the water-insoluble polymer comprises ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, co-polymers of acrylate or methacrylate having a low quaternary ammonium content, poly vinyl acetate, or mixtures thereof and wherein the water-insoluble polymer comprises about 20 to about 60% by weight of the dosage form.

6. The dosage form according to claims 1-3, wherein the water swellable polymer comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose, hydroxyethylcellulose, methylcellulose, starch, gums, alginates, acrylic acid derivatives, gelatin and polyethylene oxide or mixtures thereof.

7. The dosage form according to claim 6, wherein the water swellable polymer is xanthan gum.

8. The dosage form according to claim 6, wherein the water swellable polymer comprises about 7% to about 60% by weight of the dosage form.

9. The dosage form according to claim 3, wherein the hydrophobic material comprises fatty acids, long chain fatty alcohols, waxes, vegetable oil and glycerides of C_6-C_{18} fatty acids, mineral oil, or mixtures thereof.

10. The dosage form according to claim 9, wherein the hydrophobic material comprises carnauba wax, stearic acid, or mixtures thereof.

11. The dosage form according to claim 9, wherein the hydrophobic material comprises about 20 to about 60% by weight of the dosage form.

12. The dosage form according to claims 1-3, further comprising pharmaceutically acceptable excipients selected from one or more of fillers, binders, lubricants, glidants, coloring agents and flavoring agents.

13. A process for preparing a controlled release monolithic matrix dosage form of trimetazidine according to claim 1 comprising the steps of:

(a) blending/mixing trimetazidine and one or more rate controlling polymers with one or more pharmaceutically acceptable excipients, and

(b) compressing the blend of step (a) into tablets;

wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

14. A process for preparing a controlled release monolithic matrix dosage form of trimetazidine according to claim 1 comprising the steps of:

(a) granulating trimetazidine, atleast one pharmaceutically acceptable excipient and one or more rate controlling polymers,

(b) blending/mixing the material of step (a) with one or more pharmaceutically acceptable excipients, and

(c) compressing the blend of step (b) into tablets;

wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

15. A process for preparing a controlled release monolithic matrix dosage form of trimetazidine according to claim 3 comprising the steps of:

(a) dispersing trimetazidine in atleast one hydrophobic material;

(b) milling the material of step (a);

(c) mixing/blending the material of step (b) with a rate controlling polymer and other excipients;

(d) compressing the blend of step (c) into tablets;

wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

16. A process for preparing a controlled release monolithic matrix dosage form of trimetazidine according to claim 3 comprising the steps of:

(a) dispersing trimetazidine in atleast one hydrophobic material;

(b) milling the material of step (a);

(c) granulating the material of step (b) with a rate controlling polymer and other excipients;

(d) compressing the blend of step (c) into tablets;

wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

17. A process of preparing a controlled release monolithic matrix dosage form of trimetazidine according to claims 15 and 16, wherein trimetazidine is dispersed in a molten mass of the hydrophobic material.

18. The dosage form according to the preceding claims, wherein the dosage form is further coated with one or more layers comprising film forming agents and/or pharmaceutically acceptable excipients.

19. Use of a controlled release monolithic matrix dosage form of trimetazidine in the prophylactic treatment of angina pectoris, wherein the dosage form exhibits in vitro release of trimetazidine or its pharmaceutically acceptable salt in phosphate buffer at pH 6.8 of not less than about 75% after 16 hours.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/053679

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/22 A61K31/495 A61P9/10

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU 780 011 B2 (SERVIER LAB) 24 February 2005 (2005-02-24) cited in the application page 1, line 22 - page 2, line 26 page 4, line 3 - line 15 examples 1-3 tables 1-5 claims 1-4,13-16 ----- -/--	1,2,4,6, 8,12,13, 18,19

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 May 2009	03/06/2009

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/053679

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 195 160 A (USV LTD [IN]) 10 April 2002 (2002-04-10) cited in the application paragraph [0001] paragraph [0008] paragraph [0014] - paragraph [0019] paragraph [0023] - paragraph [0026] examples 1-7 figures 1,2 claims 1-16	1-4,6-19
X	WO 2006/123073 A (MG PHARMA [FR]; BESSE JEROME [FR]) 23 November 2006 (2006-11-23) page 4, line 22 - page 5, line 12 page 6, line 12 - line 18 page 13, line 30 - page 14, line 9 examples 1,3,4 figures 1,2 tables 1,4 claims 1,3,4,12-14,17,18,23,25-31	1,4,6,8, 12-14, 18,19
X	WO 02/051417 A (SERVIER LAB [FR]; WUTHRICH PATRICK [FR]; ROLLAND HERVE [FR]; BRIAULT G) 4 July 2002 (2002-07-04) page 2, line 21 - page 3, line 12 page 6, line 19 - page 9, line 2 page 10, line 19 - line 23 examples 1,2 table 1 figures 1,2 claims 1-7,14,15	1,4-8, 12,13, 18,19
X	DATABASE WPI Week 198644 Thomson Scientific, London, GB; AN 1986-289031 XP002529250 -& JP 06 025055 B (NIPPON CHEMIPHAR CO) 6 April 1994 (1994-04-06) abstract	1-6,8,9, 11-14, 18,19

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/053679

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KRISHNAIAH Y S R ET AL: "Three-layer guar gum matrix tablet formulations for oral controlled delivery of highly soluble trimetazidine dihydrochloride" JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 81, no. 1-2, 17 May 2002 (2002-05-17), pages 45-56, XP004351102 ISSN: 0168-3659 abstract tables 1,2,4,5 page 47, right-hand column, line 3 - page 48, left-hand column, line 13 page 48, right-hand column, line 35 - page 49, left-hand column, line 11 page 51, left-hand column, line 10 - page 53, right-hand column, line 4 figures 1-3	1,4,6,8, 12-14, 18,19
X	AU 684 893 B2 (ADIR) 8 January 1998 (1998-01-08) cited in the application page 1, line 1 - line 2 page 2, line 30 - page 3, line 5 page 3, line 25 - page 4, line 12 examples 1-6 claims 1-7,10,11	1,4,5, 12,18,19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2008/053679

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
AU 780011 B2	24-02-2005	AR 026968 A1	05-03-2003
		AT 296622 T	15-06-2005
		AU 7228500 A	21-06-2001
		BG 106927 A	30-05-2003
		BR 0005915 A	02-10-2001
		CN 1302663 A	11-07-2001
		CY 2347 A	04-06-2004
		CZ 20022082 A3	11-09-2002
		DE 60020501 D1	07-07-2005
		DE 60020501 T2	27-04-2006
		EP 1108424 A1	20-06-2001
		ES 2240033 T3	16-10-2005
		ES 2176106 A1	16-11-2002
		WO 0143747 A1	21-06-2001
		FR 2802424 A1	22-06-2001
		GR 1003658 B2	05-09-2001
		HK 1036937 A1	06-05-2005
		HU 0004966 A2	29-06-2002
		IE 20001017 A1	03-04-2002
		IT RM20000667 A1	14-06-2002
		JP 2001172181 A	26-06-2001
		JP 2007314578 A	06-12-2007
		KR 20010062478 A	07-07-2001
		LU 90700 A2	03-12-2007
		MX PA00012462 A	04-06-2002
		NZ 508912 A	26-04-2002
		OA 12121 A	20-10-2003
		PL 344564 A1	18-06-2001
		PT 1108424 E	31-08-2005
		PT 102542 A	29-06-2001
		SK 8632002 A3	08-10-2002
		UA 80087 C2	27-08-2007
		ZA 200007548 A	19-06-2001
EP 1195160 A	10-04-2002	NONE	
WO 2006123073 A	23-11-2006	EP 1881831 A1	30-01-2008
		FR 2885807 A1	24-11-2006
WO 02051417 A	04-07-2002	AR 031970 A1	08-10-2003
		AR 032049 A1	22-10-2003
		FR 2818549 A1	28-06-2002
JP 6025055 B	06-04-1994	JP 1897899 C	23-01-1995
		JP 61212517 A	20-09-1986
AU 684893 B2	08-01-1998	AT 216583 T	15-05-2002
		AU 1502995 A	05-10-1995
		CA 2145248 A1	25-09-1995
		CN 1124140 A	12-06-1996
		DE 69526467 D1	29-05-2002
		DE 69526467 T2	05-12-2002
		DK 673649 T3	05-08-2002
		EP 0673649 A1	27-09-1995
		ES 2176296 T3	01-12-2002
		FI 951357 A	25-09-1995
		FR 2717687 A1	29-09-1995
		JP 3017040 B2	06-03-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2008/053679

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
AU 684893 B2		JP 7258086 A	09-10-1995
		NO 951110 A	25-09-1995
		NZ 270791 A	26-07-1996
		PT 673649 E	30-08-2002
		ZA 9502418 A	18-12-1995