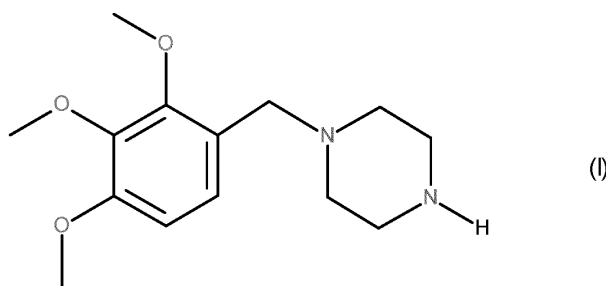


NOVEL TRIMETAZIDINE SOLID PHASES

The present invention relates to novel trimetazidine solid phases.

Trimetazidine, or 1-(2,3,4-trimethoxybenzyl)piperazine (formula (I)), is a compound which, by
5 maintaining the energy metabolism of a cell exposed to hypoxia or ischaemia, 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.



10 Trimetazidine, in its free base form, is a liquid at room temperature.

The trimetazidine dihydrochloride salt is disclosed in GB929252 and is currently used
therapeutically for the prophylactic treatment of angina pectoris crisis, in chorioretinal attacks
and for the treatment of vertigo of vascular origin (Ménière's vertigo, tinnitus).

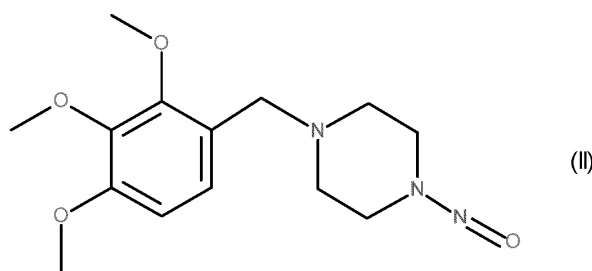
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The patent applications CN110105307, CN110183398 and CN110054599 respectively disclose
the synthesis of trimetazidine hemioxalate, oxalate and dioxalate salts, in order to overcome
flowability, poor tableting property and hygroscopicity issues of the trimetazidine
dihydrochloride salt.

20

Trimetazidine nitrosamine of formula (II) is an impurity which may be formed during the
process of synthesis of trimetazidine or trimetazidine salts or during the formulation process of
such salts, in presence of nitrites coming from water and/or excipients.

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The Applicant has now found that the novel trimetazidine solid phases of the present invention allow to reduce the formation of trimetazidine nitrosamine in presence of nitrites.

5 In a first embodiment, the present invention relates to trimetazidine solid dispersions.

As used herein, the term “trimetazidine solid dispersion” refers to a dispersion of trimetazidine in its free base, liquid form, in a non-acidic, pharmaceutically acceptable solid matrix compound.

10

Among the non-acidic pharmaceutically acceptable matrix compounds, there may be mentioned more especially non-acidic pharmaceutically acceptable polymers, preferably cellulose derivatives such as cellulose, pregelatinized starch, cellulose ethers such as hydroxypropylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, methylcellulose or

15

hydroxypropyl methylcellulose. The preferred non-acidic pharmaceutically acceptable matrix compounds are hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose and pregelatinized starch, more preferably hydroxypropylmethylcellulose (HPMC).

20

The weight ratio between trimetazidine and the non-acidic pharmaceutically acceptable matrix compound is preferably about 50/50 or below, more preferably between about 50/50 and about 10/90, for example between about 40/60 and about 20/80, more preferably about 20/80.

25

The trimetazidine solid dispersions may be prepared by addition of trimetazidine to the matrix compound in solution, followed by freeze-drying of the so-obtained mixture. The trimetazidine solid dispersions are obtained in the form of an amorphous powder.

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In another embodiment, the present invention relates to trimetazidine complexes with theophylline.

As used herein, the term “complex” refers to a solid made up of two chemical entities in a defined stoichiometric ratio, linked by weak interactions, typically hydrogen bonding or other non-covalent and non-ionic interactions. In the present invention, the two chemical entities are trimetazidine and theophylline.

The trimetazidine complexes with theophylline may be prepared by stirring trimetazidine and theophylline in a solvent, followed by a slow rise in temperature to the heating temperature, for example about 50°C, maintenance at said temperature for 2 hours, then return to room temperature, additional stirring and finally filtration and drying of the powder thus obtained.

Among the solvents which may be used for the preparation of the trimetazidine complex with theophylline, there may be mentioned acetonitrile, methanol, ethanol, toluene, tetrahydrofuran, ethyl acetate, methyl *tert*-butyl ether, water or n-heptane.

The present invention also relates to pharmaceutical compositions comprising the trimetazidine complex with theophylline or trimetazidine solid dispersions of the present invention, in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or carriers.

The useful dosage varies according to the age and weight of the patient, the administration route, the nature and severity of the disorder and any associated treatments, and ranges from 15 mg to 200 mg per day in one or more administrations.

Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, nasal, rectal, perlingual, ocular or respiratory administration, and especially tablets or dragées, sublingual tablets, gelatin capsules, capsules, minigranules, suppositories, creams, ointments, dermal gels, injectable or drinkable preparations, aerosols, and eye or nasal drops.

The pharmaceutical compositions may be in the form of immediate release or prolonged release compositions.

According to one aspect of the present invention, the pharmaceutical composition is a tablet for
5 immediate release oral administration.

According to another aspect of the present invention, the pharmaceutical composition is a matrix tablet for prolonged release oral administration.

According to another aspect of the present invention, the pharmaceutical composition is in the form of coated minigranules in capsules, for oral, once-a-day administration.

10

In addition to the trimetazidine solid phase of the present invention, the tablets according to the invention comprise one or more excipients or carriers, such as diluents, retardants, lubricants, binders, disintegrators, absorbents, plasticizers, colourants and sweeteners.

There may be mentioned as examples of excipients or carriers:

- 15 ♦ *for the diluents*: lactose, dextrose, sucrose, mannitol, sorbitol, glycerol, calcium hydrogen phosphate dihydrate, calcium carbonate, cellulose, cellulose ethers such as hydroxypropylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, methylcellulose or hydroxypropyl methylcellulose,
- ♦ *for the controlled-release agent*: ethylcellulose, ethylcellulose derivatives such as cellulose
20 acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate and/or polymethacrylates,
- ♦ *for the lubricants*: silica, talc, stearic acid and its magnesium and calcium salts, polyethylene glycol, glycerol behenate or sodium benzoate,
- ♦ *for the binders*: aluminium and magnesium silicate, starch, gelatin, tragacanth,
25 methylcellulose, sodium carboxymethylcellulose and polyvinylpyrrolidone,
- ♦ *for the plasticizers*: acetyl tributyl citrate, glycerol triacetate, acetyl triethyl citrate, acetyl ethyl citrate, diethyl sebacate, dibutyl sebacate, ethyl phthalate, dibutyl phthalate, polyethylene glycol, glycerol and/or propylene glycol,
- ♦ *for the disintegrants*: agar, alginic acid and its sodium salt, effervescent mixtures.

30

The percentage of active ingredient of formula (I) in the tablet is preferably between 5% and 50% by weight.

According to one aspect of the present invention, the trimetazidine solid phase according to the present invention is administered in association with one or more additional active ingredients. The administration in association may be in the form of a simultaneous or successive co-administration of two or more separate pharmaceutical compositions each containing one of the
5 active ingredients (free association), or in the form of the administration of a fixed-dose combination including two or more active ingredients combined in a single dosage form.

Among the additional active ingredients, there may be mentioned more especially betablockers.
10 According to one aspect of the present invention, the trimetazidine solid phase of the present invention is administered in association with a betablocker in the form of a fixed-dose combination.

Among the betablockers, there may be mentioned more especially metoprolol and bisoprolol. According to a preferred aspect of the present invention, the fixed-dose combination of the
15 trimetazidine solid phase and bisoprolol is a capsule containing the trimetazidine solid phase minigranules in an amount which is equivalent to 80 mg trimetazidine dihydrochloride minigranules, and 5 or 10 mg bisoprolol hemifumarate pellets.

According to another preferred aspect of the present invention, the fixed-dose combination of
20 the trimetazidine solid phase and metoprolol is a capsule containing the trimetazidine solid phase minigranules in an amount which is equivalent to 80 mg trimetazidine dihydrochloride minigranules, and 47.5 or 95 mg metoprolol succinate pellets.

A formulation of bisoprolol hemifumarate pellets is already disclosed in Example 4a of
25 WO2016/071631.

Figure 1 is the ^1H NMR spectrum of the trimetazidine theophylline $\frac{1}{2}$ complex obtained in Example 1.

Figure 2 is the XRPD pattern of the trimetazidine theophylline $\frac{1}{2}$ complex obtained in Example
30 1.

Figure 3 depicts the DSC and TG graphs of the trimetazidine theophylline $\frac{1}{2}$ complex obtained in Example 1.

ABBREVIATIONS

	DSC	Differential Scanning Calorimetry
5	eq.	molar equivalent
	HPMC	HydroxyPropylMethylCellulose
	NMR	Nuclear Magnetic Resonance
	TG	Thermal gravimetry
	TMZ	Trimetazidine
10	XRPD	X-Ray Powder Diffraction

EXPERIMENTAL PART

The XRPD pattern was recorded from $3.5^{\circ}2\theta$ to $35^{\circ}2\theta$ using an X-ray diffractometer operating
15 in the transmission mode with CuK α radiation ($\lambda = 1.5418\text{\AA}$) at 45 kV and 40 mA and with a
0.013 $^{\circ}2\theta$ step size for 10 minutes.

Only the peaks with a relative intensity higher than 10% have been mentioned in the XRPD
table.

The relative intensity may vary in case of preferential orientation.

20

The chemical shifts, in ppm, are given with respect to tetramethylsilane (TMS), using partially
deuterated dimethylsulfoxide or partially deuterated methanol as internal standard.

In solution in partially deuterated dimethylsulfoxide, the resonance at 2.5 ppm on the 1D ^1H
NMR spectrum is due to partially deuterated dimethylsulfoxide.

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The DSC profile was obtained after equilibration step at 0°C followed by heating step up to
130 $^{\circ}\text{C}$ at 10 $^{\circ}\text{C}/\text{min}$. The TG profile was obtained by heating from 25 $^{\circ}\text{C}$ up to 130 $^{\circ}\text{C}$ at
10 $^{\circ}\text{C}/\text{min}$.

30 **EXAMPLE 1 : Trimetazidine theophylline $\frac{1}{2}$ complex**

10.16g of trimetazidine was placed in 200mL of n-Heptane and then 6.98g of theophylline was
added in the solution. The mixture was placed under stirring for 25 minutes at ambient

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temperature, heated up to 50°C at 1°C/min followed by isothermal step at 50°C for 2 hours and finally cooled down to 20°C at 0.1°C/min followed by isothermal step for 12 hours. The suspension was filtered, and the powder was dried at 40°C under vacuum overnight. The obtained powder corresponds to an anhydrous crystalline powder with the ½ stoichiometry (Trimetazidine/Theophylline) and a melting point at approximately 95°C.

¹H NMR: 9,61 ppm (1H, b), 7,97 ppm (2H, s); 6,95 and 6,75 ppm (2H, d, J₁₂₋₁₃= 8,50 Hz); 3,77 and 3,73 ppm (9H, s); 3,44 ppm (6H, s); 3,34 ppm (2H, s); 3,24 ppm (6H, s); 2,71 ppm (4H, bt); 2,30 ppm (4H, bt)

b = broad, s = singulet, t = triplet

10

The corresponding ¹H NMR spectrum is in Figure 1.

XRPD table:

No.	Pos. [°2θ]	Rel. Int. [%]
1	3.7985	79.99
2	7.6297	24.49
3	9.4593	12.4
4	10.3205	72.85
5	11.4641	100
6	11.9711	37.67
7	12.3671	45.51
8	12.6611	40.04
9	13.0052	44.87
10	14.6497	31.73
11	18.3028	13.3
12	19.001	15.62
13	19.5134	22.53
14	20.2697	13.89
15	20.7522	30.86
16	21.7879	14.25
17	23.4148	10.86
18	24.686	11.2
19	25.1912	60.44
20	25.649	54.62
21	27.2195	11.55
22	28.3875	13.6
23	28.513	14.3

15

The corresponding XRPD pattern is in Figure 2.

The DSC/TG graphs are in Figure 3.

EXAMPLE 2 : Trimetazidine solid dispersions

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Example 2a. Trimetazidine/non-acidic polymer 20/80 solid dispersions

TMZ/HPMC 20/80:

2.4g of HPMC were slowly added in 350mL of water and after complete dissolution, 0.64g of
10 trimetazidine was added in the solution. The mixture was freeze dried under vacuum at 0.05
mbar and at the end, an amorphous powder was obtained.

Other examples of TMZ/non-acidic polymer 20/80 solid dispersions, including
TMZ/hydroxyethylcellulose 20/80, TMZ/methylcellulose 20/80 and TMZ/pregelatinized
15 starch 20/80 solid dispersions are prepared with the same operating conditions as above,
replacing HPMC with hydroxyethylcellulose, methylcellulose or pregelatinized starch,
respectively.

Example 2b. Trimetazidine/non-acidic polymer solid dispersions with other ratios

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TMZ/HPMC 50/50:

2.0g of HPMC were slowly added in 350mL of water and after complete dissolution, 2.0g of
trimetazidine was added in the solution. The mixture was freeze dried under vacuum at 0.05
mbar and at the end, an amorphous powder was obtained.

25

Other examples of trimetazidine solid dispersions, including TMZ/HPMC 40/60 and
TMZ/HPMC 30/70 solid dispersions, are prepared with the same operating conditions as above
by adapting the trimetazidine and HPMC amounts.

EXAMPLE 3: Comparative experiment: trimetazidine nitrosamine formation

In order to model the formation of trimetazidine nitrosamine at the solid state, trimetazidine solid phases (salts, complex, solid dispersions) products containing excipients with high nitrite content were prepared. The sodium nitrite mimics the presence of nitrites in drug product.

Preparation of excipients with high nitrite content:

- The first step consists to prepare 100mL of a sodium nitrite solution at 1mg/mL.
- a) Pregelatinized starch with high nitrite content:
4g of pregelatinized starch were placed in 500 mL of water and after complete dissolution, 3mL of the sodium nitrite solution were added. The solution was placed at -40°C for freezing and then freeze-drying process was performed to obtain a powder.
 - b) Hydroxyethylcellulose with high nitrite content:
2.8g of hydroxyethylcellulose were placed in 500 mL of water and after complete dissolution, 2.1mL of the sodium nitrite solution were added. The solution was placed at -40°C for freezing and then freeze-drying process was performed to obtain a powder.
 - c) HPMC with high nitrite content:
4.8g of HPMC were placed in 500 mL of water and after complete dissolution, 3.6mL of the sodium nitrite solution were added. The solution was placed at -40°C for freezing and then freeze-drying process was performed to obtain a powder.

Preparation of physical mixtures between trimetazidine salts or cocrystal and high nitrite content excipients:

Physical mixtures between salts or cocrystal and high nitrite content excipients were prepared in a 25mL glass vial by mixing of the two powders with a spatula.

Trimetazidine solid phase	Trimetazidine (mg)	High nitrite content excipient (mg)
Theophylline cocrystal	235	400
Dichloride salt	127	400

Monochloride salt	114	400
Dioxalate salt	168	400
Oxalate salt	134	400
Hemioxalate salt	117	400

Preparation of trimetazidine solid dispersions with high nitrite content:

- 5 a) TMZ/pregelatinized starch 20/80 solid dispersions with high nitrite content:
400mg of pregelatinized starch were placed in 500 mL of water and after complete dissolution, 100mg of trimetazidine base and 0.3mL of the sodium nitrite solution were added. The solution was placed at -40°C for freezing and then freeze-drying process was performed to obtain a powder.
- 10 b) TMZ /hydroxyethylcellulose 20/80 solid dispersions with high nitrite content:
400mg of hydroxyethylcellulose were placed in 500 mL of water and after complete dissolution, 100mg of trimetazidine base and 0.3mL of the sodium nitrite solution were added. The solution was placed at -40°C for freezing and then freeze-drying process was performed to obtain a powder.
- 15 c) TMZ/HPMC 20/80 solid dispersions with high nitrite content:
400mg of HPMC were placed in 500 mL of water and after complete dissolution, 100mg of trimetazidine base and 0.3mL of the sodium nitrite solution were added. The solution was placed at -40°C for freezing and then freeze-drying process was performed to obtain a powder.

TMZ/excipient ratio	TMZ solid dispersion (mg)
TMZ/HPMC 20/80	250
TMZ/Hydroxyethylcellulose 20/80	250
TMZ/Pregelatinized starch 20/80	250

- 20 The trimetazidine solid dispersions with high nitrite content and physical mixtures between trimetazidine salts or cocrystal and high nitrite content excipients were placed at 40°C/75%RH in open glass vial for 2 weeks.

Results: trimetazidine nitrosamine dosage.

The sodium nitrite added in excipients allows in theory to form approximately 10 000ppm of trimetazidine nitrosamine if the formation was total.

- 5 The trimetazidine nitrosamine dosage was performed by LC/MS. The method allows to precisely quantify trimetazidine nitrosamine up to 300 ppm. Above the values are out of the linearity of the method and the values can just be used for tendency and not to quantify the percentage of trimetazidine nitrosamine formation. They were classified as follow:
- A: trimetazidine nitrosamine content between 300 and 500 ppm
 - 10 - B: trimetazidine nitrosamine content between 500 and 1000 ppm
 - C: trimetazidine nitrosamine content between 1000 and 2000 ppm
 - D: trimetazidine nitrosamine content between 2000 and 3000 ppm
 - E: trimetazidine nitrosamine content >3000 ppm
- 15 a) Products containing high nitrite content pregelatinized starch:

TMZ solid phase	Trimetazidine nitrosamine initial content	Trimetazidine nitrosamine content after 2 weeks at 40°C/75%RH in open glass vial
Theophylline cocrystal	6.6	A
Dichloride salt	0.2	E
Monochloride salt	0.8	C
Dioxalate salt	0.5	D
Oxalate salt	0.6	C
Hemioxalate salt	0.2	C
TMZ/Pregelatinized starch 20/80 solid dispersion	0.2	A

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b) Products containing high nitrite content hydroxyethylcellulose:

TMZ phase	Trimetazidine nitrosamine initial content	Trimetazidine nitrosamine content after 2 weeks at 40°C/75%RH in open glass vial
Theophylline cocrystal	6.6	144 ppm
Dichloride salt	0.2	E
Monochloride salt	0.8	D
Dioxalate salt	0.5	D
Oxalate salt	0.6	D
Hemioxalate salt	0.2	C
TMZ/ Hydroxyethylcellulose 20/80 solid dispersion	0.2	121 ppm

c) Products containing high nitrite content HPMC:

TMZ phase	Trimetazidine nitrosamine initial content	Trimetazidine nitrosamine content after 2 weeks at 40°C/75%RH in open glass vial
Theophylline cocrystal	6.6	111 ppm
Dichloride salt	0.2	D
Monochloride salt	0.8	C
Dioxalate salt	0.5	A
Oxalate salt	0.6	A
Hemioxalate salt	0.2	209 ppm
TMZ/HPMC 20/80 solid dispersion	0.2	121 ppm

5

The above results show that the trimetazidine solid phases of the present invention allow to reduce the formation of trimetazidine nitrosamine in presence of nitrites, compared to the trimetazidine salts of the prior art.

EXAMPLE 4 : Immediate release formulation - corresponding to a formulation containing 20 mg trimetazidine dihydrochloride

- Trimetazidine solid phase.....36.94 or 78.50 mg (see the table below)
- 5 Maize starch 26 mg
- Mannitol 34 mg
- Polyvidone..... 4 mg
- Magnesium stearate..... 1 mg
- Talc..... 5 mg

10

Equivalence table

Compound	Trimetazidine solid phase	M (g/mol)	Amount of trimetazidine solid phase in the IR tablet formulation (mg)
Example 1	1/2 complex with theophylline	626.67	36.94
Example 2a	TMZ/non-acidic polymer 20/80 solid dispersion	/	78.50

- Other immediate release formulations, containing TMZ/non-acidic matrix compound solid dispersions with other ratios, are prepared by adjusting the amount of the trimetazidine solid dispersion.
- 15

EXAMPLE 5 : MR matrix tablet - corresponding to the matrix MR tablet containing 35 mg trimetazidine dihydrochloride

- 20 Trimetazidine solid phase.....64.65 or 137.40 mg (see the table below)
- Hydroxypropyl methylcellulose..... 74.0 mg
- Povidone..... 8.7 mg
- Calcium hydrogen phosphate dihydrate..... 80.9 mg
- Magnesium stearate..... 1.0 mg
- 25 Anhydrous colloidal silica..... 0.4 mg

Equivalence table

Compound	Trimetazidine solid phase	M (g/mol)	Amount of trimetazidine solid phase in the MR matrix tablet formulation (mg)
Example 1	1/2 complex with theophylline	626.67	64.65
Example 2a	TMZ/non-acidic polymer 20/80 solid dispersion	/	137.40

Other MR matrix tablets, containing TMZ/non-acidic matrix compound solid dispersions with
5 other ratios, are prepared by adjusting the amount of the trimetazidine solid dispersion.

EXAMPLE 6 : OD formulation - corresponding to the OD formulation containing 80 mg trimetazidine dihydrochloride

- 10 Trimetazidine solid phase 147.77 or 266.85 mg (see the table below)
Neutral sucrose/maize starch minigranules..... 36.67 mg
Hydroxypropyl methylcellulose..... 6.40 mg
Acetyl tributyl citrate 1.20 mg
Ethylcellulose 8.00 mg
15 Talc..... 12.00 mg
Magnesium stearate..... 0.43 mg

Equivalence table

Compound	Trimetazidine solid phase	M (g/mol)	Amount of trimetazidine solid phase in the OD formulation (mg)
Example 1	1/2 complex with theophylline	626.67	147.77

Compound	Trimetazidine solid phase	M (g/mol)	Amount of trimetazidine solid phase in the OD formulation (mg)
Example 2a	TMZ/non-acidic polymer 20/80 solid dispersion	/	266.85

Other OD formulations, containing TMZ/non-acidic matrix compound solid dispersions with other ratios, are prepared by adjusting the amount of the trimetazidine solid dispersion.

5 **EXAMPLE 7: OD formulation- combination with bisoprolol hemifumarate**

The trimetazidine solid phase minigranules obtained in Example 6 and bisoprolol hemifumarate pellets containing 5 mg bisoprolol hemifumarate are mixed together and encapsulated.

10 **EXAMPLE 8: OD formulation- combination with metoprolol succinate**

The trimetazidine solid phase minigranules obtained in Example 6 and metoprolol succinate pellets containing either 47.5 mg, or 95 mg metoprolol succinate are mixed together and encapsulated.

CLAIMS

1- A trimetazidine solid phase, selected from trimetazidine solid dispersions in a non-acidic pharmaceutically acceptable matrix compound, and trimetazidine complexes with theophylline,
5 wherein a trimetazidine solid dispersion is a dispersion of trimetazidine in its free base, liquid form, in a non-acidic, pharmaceutically acceptable solid matrix compound.

2- A trimetazidine solid dispersion according to claim 1, wherein the non-acidic pharmaceutically acceptable matrix compound is a polymer, preferably pregelatinized starch or
10 a cellulose derivative, more preferably hydroxypropylmethylcellulose or hydroxyethyl cellulose.

3- A trimetazidine solid dispersion according to any one of claims 1 or 2, wherein the weight ratio between trimetazidine and the non-acidic pharmaceutically acceptable matrix compound
15 is preferably about 50/50 or below, more preferably between about 50/50 and about 10/90, for example between about 40/60 and about 20/80, more preferably about 20/80.

4-A pharmaceutical composition comprising a trimetazidine solid phase according to any one of claims 1 to 3, in combination with one or more inert, non-toxic, pharmaceutically
20 acceptable excipients or carriers.

5-A pharmaceutical composition according to claim 4, which is in the form of an immediate-release oral tablet, in the form of a prolonged release oral matrix tablet or in the form of coated minigranules in capsules for oral, once-a-day administration.

25

6-A pharmaceutical composition according to any one of claims 4 or 5, further comprising a betablocker.

7-A pharmaceutical composition according to claim 6, wherein the betablocker is metoprolol
30 or bisoprolol.

8- A trimetazidine solid phase according to any one of claims 1 to 3, or a pharmaceutical composition according to any one of claims 4 to 7, for use in the prophylactic treatment of

angina pectoris, in the course of chorioretinal disorders or for the treatment of vertigo of vascular origin.