

PHARMACEUTICAL COMPOSITION FOR THE PROLONGED RELEASE OF TRIMETAZIDINE

5 The invention relates to a pharmaceutical form for the prolonged release of trimetazidine and also to the use thereof in the treatment of angina.

Trimetazidine, or 1-(2,3,4-trimethoxybenzyl)piperazine, is a compound which, by maintaining the energy metabolism of a cell exposed to hypoxia or ischaemia, avoids the collapse of the intracellular level of adenosine triphosphate (ATP). It
10 accordingly ensures functioning of the ion pumps and sodium-potassium trans-membrane flows and maintains cellular homeostasis.

Trimetazidine dihydrochloride is used therapeutically in the prophylactic treatment of angina pectoris attacks, in the course of chorioretinal disorders, and also for the
15 treatment of vertigo of vascular origin (Meniere's vertigo, tinnitus).

The use of trimetazidine therapeutically has been described, in the form of an immediate-release pharmaceutical composition administered three times per day, especially in the patent specification FR 2 490 963.

20 The patent specification EP 1 108 424 describes a prolonged-release form which makes it possible to cover the entire 24-hour period on the basis of administration twice per day. That prolonged-release form makes it possible to obtain plasma levels in humans which are greater than 70 µg/l after each administration and to maintain a plasma level which is greater than or equal to 40 µg/l before the
25 subsequent administration.

Reservoir-type pharmaceutical compositions for the prolonged release of trimetazidine which ensure release of the active ingredient over a period of 16 hours have been described in the patent specification EP 0 673 649. These reservoir-type forms for single daily administration have the advantage of reducing
30 blood level peaks whilst ensuring regular and constant plasma levels of trimetazidine.

In the therapeutic arsenal available to patients, forms for the prolonged release of trimetazidine are proving necessary in order to ensure compliance and optimum therapeutic protection for the patient. The prolonged-release forms according to the present invention make possible, on the one hand, gradual and sustained
5 release over 24 hours at a therapeutically efficacious plasma concentration of trimetazidine and, on the other hand, the availability of trimetazidine at a therapeutically efficacious plasma concentration a short time after administration. A therapeutically efficacious plasma concentration of trimetazidine is understood to be a plasma level greater than or equal to 40 µg/l, making possible efficacious
10 myocardial protection. Furthermore, a short time is understood to be a period of less than 4 hours, preferably a period of less than 3 hours.

The pharmaceutical composition according to the invention is applied by oral administration once per day and releases trimetazidine throughout the 24-hour period whilst providing a high level of security with respect to any "burst"-type or
15 discontinuous release.

The pharmaceutical composition according to the present invention is a composition for the prolonged release of trimetazidine in which the inner phase comprises trimetazidine and the outer layer comprises a retardant and
20 anti-agglomerant.

The nature and the thickness of the excipients in the outer layer make it possible to control the release of the trimetazidine active ingredient as a function of time. More particularly, the retardant present in the outer layer, i.e. a retardant for the
25 diffusion of the active ingredient, is involved in the process of prolonged release.

Among the retardants that may be used in the compositions according to the invention there may be mentioned, by way of non-limiting example, ethylcellulose (EC), ethylcellulose derivatives such as cellulose acetate, cellulose acetate
30 butyrate, cellulose acetate propionate, cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate and/or polymethacrylates. The retardants are placed in organic solution or in aqueous suspension in the course of their being

used in the process for manufacture of the pharmaceutical compositions according to the invention. Among the retardants there may be mentioned, more especially, ethylcellulose.

Among the anti-agglomerants according to the invention there may be mentioned
5 talc, silicas and derivatives thereof, magnesium stearate, stearic acid and/or sodium fumaryl stearate. Preference is given to the anti-agglomerant being talc.

Besides the retardant and the anti-agglomerant, the outer layer of the pharmaceutical composition according to the invention comprises a plasticiser.

10 Among the plasticisers which come into consideration according to the invention there may be mentioned acetyl tributyl citrate, glycerol triacetate, acetyl triethyl citrate, acetyl ethyl citrate, diethyl sebacate, dibutyl sebacate, ethyl phthalate, dibutyl phthalate, polyethylene glycol (PEG), glycerol and/or propylene glycol. Among the plasticisers there may be mentioned, more especially, acetyl tributyl
15 citrate.

The percentage of retardant in the pharmaceutical composition is strictly less than 9 % of the total weight of the inner phase. More especially, the percentage of retardant is between 5.5 % and 8 % inclusive of the total weight of the inner
20 phase.

The percentage of ethylcellulose in the pharmaceutical composition is strictly less than 9 % of the total weight of the inner phase. More especially, the percentage of ethylcellulose is between 5.5 % and 8 % inclusive of the total weight of the inner phase. More particularly, the percentage of ethylcellulose is 6.5 % of the total
25 weight of the inner phase.

The percentage of anti-agglomerant in the pharmaceutical composition is between 25 % and 200 % inclusive, preferably between 100 % and 200 % inclusive, of the weight of the retardant.

The percentage of talc as anti-agglomerant in the pharmaceutical composition is
30 preferably between 100 % and 200 % inclusive of the weight of the retardant.

The percentage of plasticiser in the pharmaceutical composition is between 5 % and 50 % inclusive, preferably between 5 % and 30 % inclusive, of the weight of the retardant.

5 The percentage of acetyl tributyl citrate as plasticiser in the pharmaceutical composition is preferably between 5 % and 30 % inclusive of the weight of the retardant.

The inner phase of the pharmaceutical compositions according to the present invention comprises the active ingredient trimetazidine and a binder.

10 Among the binders according to the invention there may be mentioned hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), maltodextrin, polyvinylpyrrolidone (PVP) and/or microcrystalline cellulose.

15 Among the binders there may be mentioned, more especially, hydroxypropyl methylcellulose, which is customarily used in the field of the formulation of medicaments. More especially, the selected hydroxypropyl methylcellulose is of low viscosity. Preferably, the hydroxypropyl methylcellulose used is PharmaccoatTM 606.

20 Preferably, the trimetazidine and the binder are deposited on a neutral core, the entirety thereof constituting the inner phase.

The cores or pellets used may be soluble or insoluble in water. These cores are spheres of sugar or spheres of sucrose/starch or of microcrystalline cellulose, smoothed and protected - or not - by a pharmaceutical excipient, preferably by
25 cellulose derivatives. The size of the cores varies from 100 to 1200 μm , preferably from 300 to 1000 μm and, even more preferably, from 710 to 850 μm ; where appropriate, the size may be modified if it proves necessary.

Preference is given to the trimetazidine in the compositions according to the
30 invention being in the form of the dihydrochloride of trimetazidine. The amount of trimetazidine dihydrochloride in the pharmaceutical composition is preferably 80 mg.

The percentage of binders in the pharmaceutical composition is between 1 % and 15 % inclusive of the total weight of the composition. The percentage of hydroxypropyl methylcellulose as binder in the pharmaceutical composition is
5 between 1 % and 15 % inclusive of the total weight of the composition.

The percentage of neutral cores in the pharmaceutical composition is between 15 % and 40 % inclusive of the total weight of the composition. The percentage of cores of the sucrose/starch type is between 15 % and 40 % inclusive of the total
10 weight of the composition.

The percentage of trimetazidine in the pharmaceutical composition is between 35 % and 70 % of the total weight of the composition.

15 Preferably, the outer layer of the pharmaceutical compositions according to the invention comprises from 5.5 % to 8 % of ethylcellulose relative to the total weight of the inner phase, from 5 % to 30 % of acetyl tributyl citrate relative to the weight of the retardant and from 100 % to 200 % of talc relative to the weight of the retardant.

20 Likewise preferably, the inner phase of the pharmaceutical compositions according to the invention comprises from 15 % to 40 % of neutral core, from 35 % to 70 % of trimetazidine and from 1 % to 15 % of hydroxypropyl methylcellulose relative to the total weight of the composition.

25 The amount of components of the pharmaceutical composition is 80 mg of trimetazidine dihydrochloride, 36.677 mg of neutral minigranules, 6.40 mg of hydroxypropyl methylcellulose, 1.2 mg of acetyl tributyl citrate, 8 mg of ethylcellulose and 12 mg of talc.

30 Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those that are suitable for oral administration, especially in capsule form.

The *in vitro* dissolution rate of the composition according to the invention, obtained according to the methodology of the European Pharmacopoeia, is from 8 % to 28 % of the trimetazidine released by 4 hours and from 37 % to 57 % of the trimetazidine released by 8 hours and more than 75 % of the trimetazidine released by 24 hours. These dissolution kinetics are selected so that the therapeutically efficacious plasma concentration of trimetazidine obtained *in vivo* is prolonged over 24 hours following administration of the pharmaceutical composition.

In accordance with the process for manufacture of the pharmaceutical compositions according to the invention, cores are coated with successive layers of the active ingredient using a coating pan, with or without perforations, or fluidised-bed apparatus. The active ingredient in the form of a solution or suspension, which is aqueous or organic, is sprayed onto the cores and then dried.

The minigranules, prepared by one or other of the processes, are subsequently coated, either in a coating pan, with or without perforations, or in a fluidised-bed type apparatus. The minigranules are coated using a solution or suspension of the retardant which is involved in the diffusion of the active ingredient and thereby controls the release kinetics.

The coated minigranules are placed in capsules.

By way of example, the following manufacturing process may be mentioned:

Neutral cores composed of sucrose/starch are coated with successive layers of trimetazidine hydrochloride solution associated with hydroxypropyl methylcellulose in a fluidised-bed system.

Coating of the minigranules thereby prepared is carried out in a fluidised-bed apparatus using a suspension composed of ethylcellulose, acetyl tributyl citrate and talc.

The coated minigranules are filled into capsules in the presence of magnesium stearate.

The present invention relates also to use of the pharmaceutical compositions according to the invention in the prophylactic treatment of angina pectoris, in the course of chorioretinal disorders and also for the treatment of vertigo of vascular origin.

The Examples hereinbelow illustrate, but do not limit, the invention.

Example 1: Pharmaceutical composition for a capsule containing 80 mg of trimetazidine

The trimetazidine minigranules are coated with a film containing 6.5 % ethylcellulose.

Figure 1 illustrates the structure and formulation of the pharmaceutical composition described below.

Table 1:

Compounds	Amount (mg)
Active ingredient minigranules	
Trimetazidine dihydrochloride	80.00
Neutral minigranules	36.677
Hydroxypropyl methylcellulose	6.40
Coating (6.5 % EC)	
Acetyl tributyl citrate	1.20
Ethylcellulose	8.00
Talc	12.00
Capsule	
Coated minigranules	144.277
Magnesium stearate	0.434

Example 2: Macroscopic appearance of the minigranules

In the absence of anti-agglomerant in the outer phase of the pharmaceutical compositions there are found, on an industrial scale, irregular minigranules (Figure 2), numerous cracks in the minigranules' coating and even amalgamations between the minigranules. These coating defects cause major modifications to the *in vitro* dissolution kinetics, especially profiles of accelerated dissolution.

If the anti-agglomerant is in excess, then the minigranules obtained on an industrial scale have an irregular and flaky surface (Figure 2) due to the presence of excessive talc sticking to the surface of the minigranules. These minigranules have dissolution kinetics that are greatly accelerated and even immediate-release kinetics.

Example 3: Dissolution kinetics compared as a function of the percentage of ethylcellulose in the coating

Table 2:

Batch	E110055	E110118	E110120	E110121	E110124
EC % Coating ratio %	6.5 14.7	10 20.9	4.5 10.7	9 19.3	5 11.7
Composition					
Trimetazidine	80	80	80	80	80
Neutral cores	36.677	36.677	36.677	36.677	36.677
HMPC	6.4	6.4	6.4	6.4	6.4
Ethylcellulose	8	12.3	5.5	11.1	6.2
Acetyl tributyl citrate	1.2	1.8	0.8	1.7	0.9
Talc	12	18.5	8.3	16.7	9.3
Mg stearate	0.4	0.4	0.4	0.4	0.4
Total weight	144.711	156	138	152.9	139.8
Dissolution					
4 hrs	20.9	2.1	46.3	4.9	36.6
8 hrs	48.5	26.9	69.1	31.7	62.9

12 hrs	62.0	44.1	80	48.1	75.7
16 hrs	72.6	54.5	86.5	58.3	83.4
24 hrs	86.3	67.8	93.2	71.1	91.6

It is to be noted that the coating ratio was calculated as follows: weight of outer phase / total weight.

- 5 Furthermore, the above dissolution profiles were obtained starting from minigranules which had not been distributed into capsules. The dissolution profiles of batches on an industrial scale (minigranules encapsulated in capsules) are slowed down by 4, 3, 2 and 1 % at the 4, 8, 12 and 16 hour points, respectively, relative to the dissolution profiles described above (not filled).

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The *in vitro* dissolution kinetics of the pharmaceutical compositions E110118 (EC 10 %), E110120 (EC 4.5 %), E110121 (EC 9 %), and E110124 (EC 5 %) (Figure 4) were compared to the *in vitro* release kinetics of the reference pharmaceutical composition E110055 (EC 6.5 %). The dissolution profiles are compared with the aid of the similarity factor (f_2).

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The dissolution kinetics of the compositions E110118 (EC 10 %) and E110121 (EC 9 %), on the one hand, and E110120 (EC 4.5 %) and E110124 (EC 5 %), on the other hand, are not similar to the dissolution kinetics of the reference pharmaceutical composition E110055 (EC 6.5 %). Consequently, the percentage of retardant in the pharmaceutical composition is, on the one hand, strictly less than 9 % and, on the other hand, strictly greater than 5 %.

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Two dissolution profiles are considered to be similar when the value (f_2) is greater than or equal to 50. Calculation of the similarity factor (f_2) is advised by the directives of the EMA and the FDA in order to compare two dissolution profiles and to make it possible to decide if said dissolution profiles are the same.

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The similarity factor (f_2) has the following formula:

$$f_2 = 50 \cdot \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} [\bar{R}(t) - \bar{T}(t)]^2}{n}}} \right]$$

wherein f_2 is the similarity factor, n is the number of normalised points, $R(t)$ is the percentage mean of active ingredient dissolved from the reference pharmaceutical composition E110055 and $T(t)$ is the percentage mean of active ingredient dissolved from a pharmaceutical composition E110118 (EC 10 %), E110120 (EC 4.5 %), E110121 (EC 9 %), and E110124 (EC 5 %). The normalised points are at least at $t = 8$ hours, $t = 12$ hours and $t = 16$ hours.

The evaluated minigranules filled into capsules have different formulations; these formulations vary especially as a function of the amount of ethylcellulose and anti-agglomerant.

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The observed *in vitro* dissolution profiles of the pharmaceutical compositions E110118 (EC 10 %), E110120 (EC 4.5 %), E110121 (EC 9 %), and E110124 (EC 5 %) (Figure 3) were modelled by applying Weibull's law to each of them (Figure 4). Weibull's law constitutes an especially valuable approximation which makes it possible to predict continuous *in vitro* dissolution profiles from observed *in vitro* dissolution profiles.

A *vitro-vivo* correlation equal to 1 was put forward as the hypothesis; consequently the profiles of the fractions absorbed *in vivo* (Figure 4) correspond exactly to the modelled *in vitro* dissolution profiles. A convolution step was then carried out in order to predict the pharmacokinetic profiles of the various pharmaceutical compositions. The convolution step (function $C_p(t)$) is defined as follows:

$$C_p(t) = I(t) * P(t)$$

wherein $I(t)$ is an input function and $P(t)$ is a disposition function.

The input function represents the fractions absorbed *in vivo* as a function of time and the disposition function is a polyexponential equation of the pharmacokinetics of a pharmaceutical composition for the prolonged release of trimetazidine obtained in the study SKH-6790-005-FRA. The predicted mean pharmacokinetic profiles are shown in Figure 5.

Starting from said plasma profiles obtained by convolution, the pharmacokinetic parameters AUC and C_{max} were calculated where AUC represents the exposure to the medicament and C_{max} the maximum concentration.

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Table 3:

	AUC (ng.h/mL)	Cmax (ng/mL)
E110124	1620	83.6
E110120	1678	85.6
E110055	1776	67.8
E110121	1501	57.0
E110118	1418	54.2

5 The AUC of the pharmaceutical composition E110055 (EC 6.5 %) is the highest of the pharmaceutical compositions evaluated above and the exposure of the patient to the trimetazidine is significantly improved.

Furthermore, the pharmacokinetic profiles make it possible to measure the efficacious myocardial protection time of the treated patient, or the time during which said patient is covered by a therapeutically efficacious plasma concentration (40 µg/l). This therapeutic protection time is at least 22 hours for the composition
 10 E110155 (EC 6.5 %) whereas it is only 16 hours for the composition E110118 (EC 10 %). The therapeutic protection time is improved even when the percentage of retardant, which is responsible for the prolonged release in the therapeutic composition, is reduced from 10 % to 6.5 %.

CLAIMS

1. Pharmaceutical composition for prolonged release of trimetazidine, wherein:

- an inner phase comprises trimetazidine;
- 5 - an outer layer comprises a retardant and an anti-agglomerant.

2. Composition according to claim 1, characterised in that the retardant is selected from ethylcellulose, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate phthalate, hydroxypropyl methylcellulose acetate
10 succinate and/or polymethacrylates.

3. Composition according to claim 1, characterised in that the anti-agglomerant is selected from talc, colloidal silicon dioxide, magnesium stearate, stearic acid and/or sodium fumaryl stearate.
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4. Composition according to claim 1, characterised in that the outer layer comprises a plasticiser.

5. Composition according to claim 4, characterised in that the plasticiser is
20 selected from acetyl tributyl citrate, glycerol triacetate, acetyl triethyl citrate, acetyl ethyl citrate, diethyl sebacate, dibutyl sebacate, ethyl and dibutyl phthalate, polyethylene glycol, glycerol and/or propylene glycol.

6. Composition according to claim 1, characterised in that the percentage of
25 retardant is strictly less than 9 % of the total weight of the inner phase.

7. Composition according to claim 1, characterised in that the percentage of
retardant is between 5.5 % and 8 % inclusive of the total weight of the inner
30 phase.

8. Composition according to claim 1, characterised in that the percentage of anti-agglomerant is between 25 % and 200 % inclusive of the weight of the retardant.

5 9. Composition according to claim 4, characterised in that the percentage of plasticiser is between 5 % and 50 % inclusive of the weight of the retardant.

10. Composition according to claim 1, characterised in that the inner phase comprises a binder.

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11. Composition according to claim 10, characterised in that the binder is selected from hydroxypropyl methylcellulose, hydroxypropylcellulose, maltodextrin, polyvinylpyrrolidone and/or microcrystalline cellulose.

15 12. Composition according to claim 1, characterised in that the trimetazidine is coated onto a core.

13. Composition according to claim 12, characterised in that the core is composed of sucrose, sucrose and starch, or microcrystalline cellulose.

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14. Composition according to claim 1, characterised in that the trimetazidine is in the form of the dihydrochloride.

25 15. Composition according to claim 1, characterised in that it contains 80 mg of trimetazidine dihydrochloride.

16. Composition according to claim 1, characterised in that the outer layer comprises:

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- from 5.5 % to 30 % of acetyl tributyl citrate relative to the weight of the retardant;
- from 5 % to 8 % of ethylcellulose relative to the total weight of the inner phase;

- from 100 % to 200 % of talc relative to the weight of the retardant.

17. Composition according to claim 12, characterised in that the inner phase comprises:

- 5 - from 15 % to 40 % of neutral core relative to the total weight of the composition;
- from 35 % to 70 % of trimetazidine relative to the total weight of the composition;
- from 1 % to 15 % of hydroxypropyl methylcellulose relative to the total
10 weight of the composition.

18. Composition according to claim 1, characterised in that it contains 80 mg of trimetazidine dihydrochloride, 36.677 mg of neutral minigranules, 6.40 mg of hydroxypropyl methylcellulose, 1.2 mg of acetyl tributyl citrate, 8 mg of
15 ethylcellulose and 12 mg of talc.

19. Pharmaceutical composition according to any one of claims 1 to 18, characterised in that the level of *in vitro* dissolution of the composition is from 8 % to 28 % of the trimetazidine released by 4 hours and from 37 % to 57 % of the
20 trimetazidine released by 8 hours and more than 75 % of the trimetazidine released by 24 hours and is selected so that the therapeutically efficacious plasma concentration of trimetazidine obtained *in vivo* is prolonged over 24 hours following administration of the pharmaceutical composition.

25 20. Process for manufacture of a composition according to any one of claims 1 to 19, characterised in that it comprises the following steps:

- a) coating neutral cores with trimetazidine and a binder;
- b) coating the minigranules obtained in a) with a retardant, a plasticiser and an anti-agglomerant;
- 30 c) filling of the coated minigranules obtained in b) and lubricated.

21. Pharmaceutical composition according to any one of claims 1 to 19 for use in the prophylactic treatment of angina pectoris, in the course of chorioretinal disorders and also for the treatment of vertigo of vascular origin.