Matrix tablet enabling the prolonged release of trimetazidine after administration by the oral route

The present invention relates to a matrix tablet enabling the prolonged release of trimetazidine, or an addition salt thereof with a pharmaceutically acceptable acid, after administration by the oral route.

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

Trimetazidine dihydrochloride 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).

Trimetazidine dihydrochloride has, until now, been administered by the oral route at doses of from 40 to 60 mg/day, in the form of tablets containing 20 mg of active ingredient or a drinkable solution containing 20 mg of active ingredient per ml. Those two forms are immediate-release forms. Patent FR 2 490 963 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.

Because of the rapid absorption and the 6-hour half-life, such immediate-release forms result in low levels in the blood by the time of the next administration. 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 ischaemia are most serious. Because complete coverage of the day is not achieved with the immediate-release form, the Applicant has developed a prolonged-release form enabling perfect 24-hour coverage, ensuring a sufficient level in the blood between two administrations whilst retaining a large

plasma peak after each administration so as to maintain the efficacy of the trimetazidine, maintaining the energy metabolism of a cell exposed to hypoxia or ischaemia and avoiding the lowering of the intracellular level of ATP.

It also allows peripheral vasodilator effects to be avoided, while stabilising blood flow rates and tensional effects.

The new formulation according to the invention accordingly allows the positive characteristics of the formulation described in patent FR 2 490 963 to be retained while enabling better coverage of the day, which leads to better compliance and permanent protection.

The present invention relates more especially to a matrix tablet which enables the prolonged release of trimetazidine, or a pharmaceutically acceptable salt thereof, after administration by the oral route and which is composed of a hydrophilic matrix characterised in that the prolonged release is controlled by the use of a cellulose derivative polymer.

This matrix tablet, administrable preferably twice a day, enables prolonged active ingredient release to be obtained whilst retaining a large plasma peak on each administration. It allows plasma levels greater than 70 µg/l to be obtained in humans after each administration and a plasma level greater than or equal to 40 µg/l to be maintained until the next administration, which was not the case with the tablet described in patent FR 2 490 963 when administered 3 times per day.

Among the cellulose derivatives used in the matrix according to the invention, there may be mentioned, more especially, cellulose ethers such as hydroxypropylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, methylcellulose and hydroxypropyl methylcellulose.

The cellulose derivative is preferably hydroxypropyl methylcellulose. The percentage of cellulose derivative polymer is from 25 to 50 % of the total mass of the tablet.

Hydroxypropyl methylcelluloses that have a viscosity of from 100 cP to 100 000 cP may be used. The preferred viscosity is 4 000 cP.

Various excipients are added to the hydrophilic matrix, for example binders, diluents, lubricants and flow agents. Among the binders, polyvidone is preferably used. The percentage of polyvidone is from 3 to 12 % of the total mass of the tablet. Among the diluents, calcium hydrogen phosphate dihydrate is preferably used, which provides better fluidity and better compressibility than other diluents such as lactose monohydrate. The percentage of calcium hydrogen phosphate is from 25 to 75 % of the total mass of the tablet.

Among the lubricants, there may be mentioned, without implying any limitation, magnesium stearate, stearic acid, glycerol behenate and sodium benzoate. The preferred lubricant is magnesium stearate. Finally, colloidal silica is preferably used as flow agent.

The trimetazidine used in the matrix tablets according to the invention is preferably in the dihydrochloride form.

The percentage of trimetazidine dihydrochloride is from 15 to 30 % of the total mass of the tablet, preferably from 15 to 18 %.

The person skilled in the art will generally consider the release kinetics of matrix tablets to be dependent on the nature and amount of the basic component of the matrix - in this case, namely, the cellulose derivative.

It now appears, surprisingly, that the release kinetics of the matrix tablet according to the invention are influenced neither by the amount nor by the grade of the cellulose derivative used.

Various formulations produced using, on the one hand, hydroxypropyl methylcelluloses of different viscosities and, on the other hand, variable amounts of the same grade of

hydroxypropyl methylcellulose have exhibited equivalent release kinetics, which implies that there exists a specific synergy between the cellulose derivative and the trimetazidine.

The present invention relates also to a process for the preparation of the matrix tablet. The matrix tablet may be prepared by wet granulation followed by compression, by dry granulation followed by compression, or by direct compression. The preparation process is preferably wet granulation followed by compression.

The wet granulation is performed by mixing the trimetazidine, the polyvidone and the diluent, and then wetting that mixture. That first step enables a hydrophilic environment to be created around the active ingredient, which is beneficial for its dissolution, and also enables a unit dose that is as uniform as possible to be obtained.

In a second step, the previously obtained granulate is mixed with the cellulose derivative. The lubricant and the flow agent are then added to the mixture. The third step is compression of the lubricated mixture previously obtained.

The tablets thus formed are then, if desired, coated according to a conventional coating technique.

The following Examples illustrate the invention but do not limit it in any way. The matrix tablets described in the Examples were prepared in the following manner :

- ***Step A*** : Mixture of trimetazidine, polyvidone and calcium hydrogen phosphate dihydrate, then wetting of the mixture using a sufficient amount of purified water, granulation and then drying of the granulate.

- ***Step B*** : Mixture of the granulate obtained in Step A with hydroxypropyl methylcellulose.

- ***Step C*** : Lubrication of the mixture obtained in Step B with magnesium stearate and colloidal silica.

- ***Step D*** : Compression of the lubricated mixture obtained in Step C on a rotary tablet machine so as to obtain tablets having a hardness of about from 40 to 160 N, measured by breaking across a diameter.

EXAMPLE 1 : Formulations of different matrix tablets containing various amounts of trimetazidine

Table 1 : Unitary formulae for 3 types of tablet

Compound	Amount (mg)		
	F_1	F_2	F_3
Trimetazidine dihydrochloride	60	30	35
Hydroxypropyl methylcellulose	112	74	74
Polyvidone	13.3	8.7	8.7
Calcium hydrogen phosphate dihydrate	92	85.9	80.9
Magnesium stearate	2.2	1	1
Anhydrous colloidal silica	0.5	0.4	0.4
Total mass of the tablet	***280***	***200***	***200***

EXAMPLE 2 :

Example 2 shows that different amounts of hydroxypropyl methylcellulose do not have an influence on the dissolution kinetics of the tablet.

Table 2 : Unitary formulae / variable amounts of HPMC

Compound	Amount (mg)	
	F_4	F_5
Trimetazidine dihydrochloride	35	35
Hydroxypropyl methylcellulose	54	94
Polyvidone	10.1	7.3
Calcium hydrogen phosphate dihydrate	99.5	62.3
Magnesium stearate	1	1
Anhydrous colloidal silica	0.4	0.4
Total mass of the tablet	***200***	***200***

Table 3 shows the percentages of compound released as a function of time for the formulations F_4 and F_5.

Table 3 : Release kinetics

Time (h)	Percentage of compound released (%)	
	F_4	F_5
1	41	38
2	59	59
3	80	77
4	97	96

EXAMPLE 3 :

Example 3 shows that different grades of hydroxypropyl methylcellulose do not have an influence on the dissolution kinetics of the tablet.

Table 4 : Formulations / variable grades of HPMC

Compound	Amount (mg)		
	F_3	F_6	F_7
Trimetazidine dihydrochloride	35	35	35
Hydroxypropyl methylcellulose 4000 cP	74	-	-
Hydroxypropyl methylcellulose 100 cP	-	-	74
Hydroxypropyl methylcellulose 100 000 cP	-	74	-
Polyvidone	8.7	8.7	8.7
Calcium hydrogen phosphate dihydrate	80.9	80.9	80.9
Magnesium stearate	1	1	1
Anhydrous colloidal silica	0.4	0.4	0.4

Table 5 shows the percentages of compound released as a function of time for the formulations F_3, F_6 and F_7.

Table 5 : Release kinetics

Time (h)	Percentage of compound released (%)		
	F_3	F_6	F_7
1	43	41	40
2	62	59	60
3	86	83	83
4	105	102	100

EXAMPLE 4 : Plasma kinetics study

The plasma kinetics were studied after administration of the matrix tablet of formulation F_3 described in Example 1 to 12 healthy volunteers.

Administration was carried out for 4 days at the rate of two tablets per day.

The plasma kinetics of the tablet of formula F_3 were compared to those of an immediate-release (IR) tablet administered for 4 days at the rate of three tablets per day.

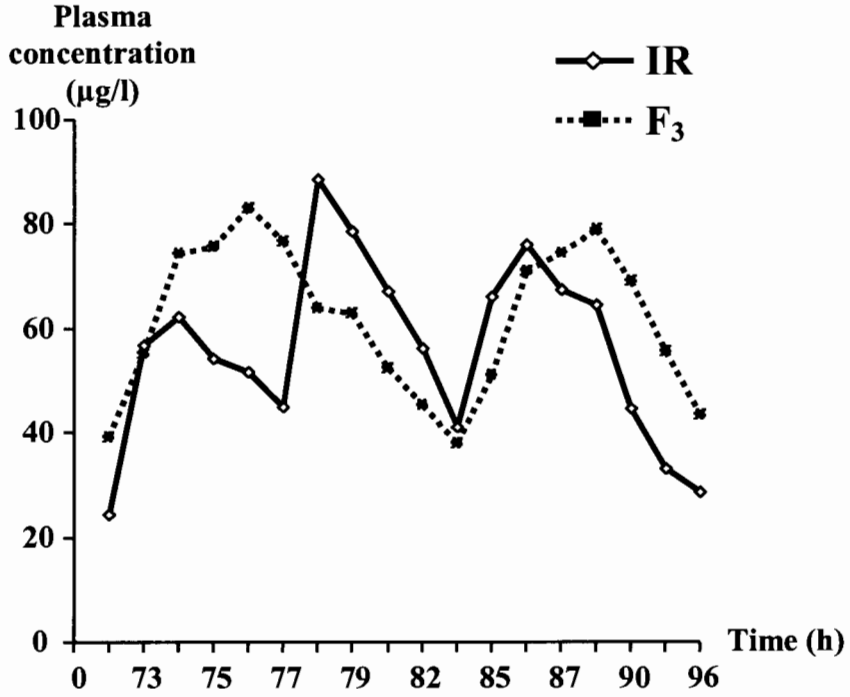
The unitary formulation of the immediate-release (IR) tablet is as follows :

Trimetazidine dihydrochloride	20 mg
Maize starch	26 mg
Mannitol	34 mg
Polyvidone	4 mg
Magnesium stearate	1 mg
Talc	5 mg

The average plasma concentration is given in Figure 1.

Figure 1 : Plasma kinetics of trimetazidine

Average plasma concentrations of trimetazidine (in µg/l) after oral administration of the F_3 form and an IR form to 12 healthy volunteers



This curve clearly shows that the F_3 form enables prolonged release of trimetazidine to be obtained while retaining a large plasma peak on each administration.

The plasma level observed after each administration is close to 90 µg/l and hardly different from that obtained with the IR form. At the end of 24 hours the plasma level is greater than 40 µg/l whereas, with the immediate-release formulation, it is only about 25 µg/l.

CLAIMS

1- Matrix tablet for the prolonged release of trimetazidine or a pharmaceutically acceptable salt thereof, characterised in that the prolonged release is controlled by the use of a cellulose derivative polymer.

2- Matrix tablet according to claim 1, characterised in that the cellulose derivative polymer is a hydroxypropyl methylcellulose.

3- Matrix tablet according to either claim 1 or claim 2, characterised in that the percentage of cellulose derivative is from 25 to 50 % of the total mass of the tablet.

4- Matrix tablet according to claim 1, characterised in that it also comprises a binder, a diluent, a lubricant and a flow agent.

5- Matrix tablet according to claim 4, characterised in that the binder is polyvidone.

6- Matrix tablet according to claim 5, characterised in that the percentage of polyvidone is from 3 to 12 % of the total mass of the tablet.

7- Matrix tablet according to any one of claims 4, 5 or 6, characterised in that the diluent is calcium hydrogen phosphate dihydrate.

8- Matrix tablet according to claim 7, characterised in that the percentage of calcium hydrogen phosphate dihydrate is from 25 to 75 % of the total mass of the tablet.

9- Matrix tablet according to any one of claims 4, 5, 6, 7 or 8, characterised in that the lubricant is magnesium stearate and the flow agent is anhydrous colloidal silica.

10- Matrix tablet according to claim 1, characterised in that the trimetazidine is in the dihydrochloride form.

11- Matrix tablet according to claim 10, characterised in that the percentage of trimetazidine dihydrochloride is from 15 to 30 % of the total mass of the tablet.

12- Matrix tablet according to either claim 10 or claim 11, characterised in that the percentage of trimetazidine dihydrochloride is 17.5 % of the total mass of the tablet.

13- Matrix tablet according to any one of claims 1 to 12, characterised in that it contains 35 mg of trimetazidine dihydrochloride, 74 mg of hydroxypropyl methylcellulose, 8.7 mg of polyvidone, 80.9 mg of calcium hydrogen phosphate dihydrate, 1 mg of magnesium stearate and 0.4 mg of anhydrous colloidal silica.

14- Matrix tablet according to claim 13, characterised in that it is administered twice per day.

15- Matrix tablet according to claim 1, characterised in that it enables plasma levels greater than 70 µg/l to be obtained in humans after each administration and a plasma level greater than or equal to 40 µg/l to be maintained until the next administration.

16- Process for the preparation of a matrix tablet according to any one of claims 1 to 13, characterised in that :
- wet granulation is carried out by mixing trimetazidine, polyvidone and the diluent and then wetting that mixture,
- the granulate thus obtained is mixed with the cellulose derivative,
- the lubricant and the flow agent are then added,
- the previous mixture is then compressed.

17- Matrix tablet according to any one of claims 1 to 15 for use in the prophylactic treatment of angina pectoris, in chorioretinal attacks and in the treatment of vertigo of vascular origin.