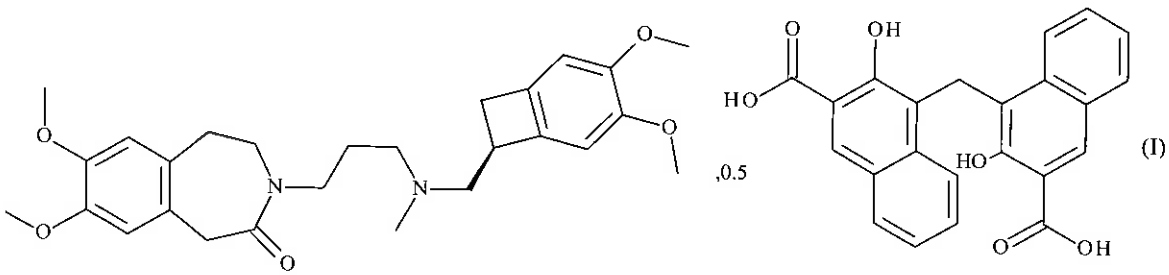
NEW IVABRADINE SALT AND ITS PREPARATION PROCESS

The present invention relates to a new salt of ivabradine, to a process for the preparation thereof, and to pharmaceutical compositions containing it.

Ivabradine, or 3-{3-[{[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}-(methyl)amino]propyl}-7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one, and its addition salts with a pharmaceutically acceptable acid, and more especially its hydrochloride, have very valuable pharmacological and therapeutic properties, especially bradycardic properties, which make these compounds useful in the treatment or prevention of the various clinical situations of myocardial ischaemia, such as angina pectoris, myocardial infarction and the associated rhythm disturbances, as well as in the various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in heart failure, both systolic and diastolic.

The preparation and therapeutic use of ivabradine and its addition salts with a pharmaceutically acceptable acid, and more especially its hydrochloride, have been described in European patent EP 0 534 859.

The present invention relates to ivabradine hemipamoate of formula (I):



(I)

and its hydrates, to a process for the preparation of said salt, and to pharmaceutical compositions containing it, in particular those which permit controlled release of the active ingredient over time.

Pamoic acid is also called 4,4'-methanediylbis(3-hydroxynaphthalene-2-carboxylic) acid.

The compound of formula (I) has an ivabradine/pamoic acid ratio of 1/0.5.

The compound of formula (I) is obtained by treating ivabradine hydrochloride with the disodium salt of pamoic acid or sodium pamoate in an aqueous medium.

Ivabradine hydrochloride and sodium pamoate are brought together in a proportion of from 1/0.5 to 1/0.6.

The compound of formula (I) so prepared is then extracted from the aqueous medium by means of an organic solvent, for example dichloromethane.

After it has been formed, the compound of formula (I) can advantageously be taken up in methanol in order to remove the residual organic solvent.

The present invention relates also to pharmaceutical compositions comprising as active ingredient ivabradine hemipamoate, in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or carriers.

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, dragées, sublingual tablets, gelatin capsules, capsules, suppositories, creams, ointments, dermal gels, injectable or drinkable preparations, aerosols, eye or nasal drops.

In addition to ivabradine hemipamoate, the pharmaceutical compositions according to the invention comprise one or more excipients or carriers such as diluents, lubricants, binders, disintegrators, absorbents, colourings, sweeteners.

Examples of excipients or carriers which may be mentioned include:

- *for the diluents*: lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycerin;
- *for the lubricants*: silica, talc, stearic acid and its magnesium and calcium salts, polyethylene glycol;

- *for the binders*: magnesium aluminium silicate, starch, maltodextrin, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and polyvinylpyrrolidone;
- *for the disintegrators*: agar, alginic acid and its sodium salt, effervescent mixtures.

The percentage of ivabradine hemipamoate in the pharmaceutical composition is preferably from 5 % to 50 % by weight.

The dosage used varies according to the sex, age and weight of the patient, the administration route, the nature of the disorder and of any associated treatments and ranges from 2.5 to 30 mg of ivabradine per 24 hours, and more preferably from 5 to 15 mg per day, and yet more preferably from 10 to 15 mg per day.

The percentage of diluents in the pharmaceutical composition is preferably from 40 % to 80 % by weight.

The percentage of lubricants in the pharmaceutical composition is preferably from 0.2 % to 10 % by weight.

The percentage of binders in the pharmaceutical composition is preferably from 5 % to 50 % by weight.

The applicant has found that the use of ivabradine hemipamoate made it possible to prepare a pharmaceutical composition with controlled release of the active ingredient, while overcoming the problems generated by the conventional methods.

Numerous pharmaceutical compositions intended for the controlled release of pharmaceutical active ingredients have been proposed and produced, for their administration by the oral, buccal, sublingual, ocular, rectal, vaginal and/or parenteral route. The objectives of these new compositions were substantially as follows:

- to reduce the frequency of administration of the medicaments,
- to obtain relatively constant levels of active ingredient in the medium or at the intended biological site,

- to obtain release profiles which correlate with the pharmacological activity of the medicaments.

The principle that is most commonly used to control the release is to incorporate the active ingredient or ingredients with excipients, mostly of polymeric nature, in matrices.

Irrespective of the matrix compositions that are envisaged, the obtainment thereof encounters specific manufacturing problems such as:

- complex manufacturing process in a plurality of steps,
- stability of the active ingredient during the manufacturing process and with respect to the excipients used,
- modulation of the speed of release of the active ingredient or ingredients is difficult, often variable over time and dependent, for example, on the particle size of the batches of polymers with the compression methods,
- manufacturing process allowing a pharmaceutical form to be obtained that is substantially suitable for only one administration route,
- reproducibility of the batches owing to the multiplication of the steps.

The use of ivabradine hemipamoate makes it possible to obtain a controlled release profile of the active ingredient without employing the complex galenic formulation techniques described in the prior art.

Accordingly, the applicant has shown that the use of ivabradine hemipamoate in the pharmaceutical composition of the invention permits controlled release of ivabradine even when the galenic formulation used corresponds to that employed with ivabradine hydrochloride for the immediate release of the active ingredient.

While all the ivabradine hydrochloride is released in 15 minutes *in vitro*, the *in vitro* dissolution test described in the present application has shown that only 80 % of the ivabradine hemipamoate had been released after approximately 6 hours.

The examples which follow illustrate the invention.

EXAMPLE 1: Preparation of ivabradine hemipamoate

The elemental analysis was performed on a Carlo Erba 1108 device.
The results are corrected by the water content of the product, which is 1.82 % (measured by coulometry).

4.1 g of ivabradine hydrochloride (8.12 mmol) are dissolved in 200 mL of water, and 2.0 g of sodium pamoate (4.63 mmol) are dissolved in 200 mL of water.

The sodium pamoate solution is added to the ivabradine hydrochloride solution with vigorous stirring. The hemipamoate salt is formed immediately by precipitation. Stirring is maintained for about 30 minutes, and then ivabradine hemipamoate is extracted once with 200 mL of dichloromethane and then a second time with 100 mL of dichloromethane. The organic fractions are combined and rinsed with 100 mL of water. The organic phase is dried with magnesium sulfate, yielding a clear yellow-coloured solution.
The organic phase is evaporated to dryness at 40°C *in vacuo* in a rotary evaporator. A yellow powder is obtained.
The yellow powder is dried at 40°C *in vacuo* (10 mbar) for 16 hours and then taken up in 200 mL of methanol.
The solution is evaporated to dryness at 40°C *in vacuo* in a rotary evaporator. A yellow powder is again obtained.
The yellow powder is dried at 40°C *in vacuo* (10 mbar) for 20 hours.
The ^{1}H NMR spectrum shows a residual methanol content of 0.8 %.
Subsequent drying of the powder at 80°C *in vacuo* (10 mbar) for 24 hours yields 3.53 g of a product having a residual methanol content of less than 0.1 %.
Yield = 66.5 %

Elemental analysis:

Element	% theoretical	% corrected mean
C	69.77	69.40
H	6.69	6.60
N	4.23	4.25
O	19.31	

Method for correcting the results:

Example for C: 69.14*100/(100-1.82) = 69.40 %

Example for H: 6.68*100/(100-1.82) – 2*1.82/18 = 6.60 % because (the hydrogen atoms of water must be taken into account (2/18))

EXAMPLE 2: Pharmaceutical composition

Preparation formula for tablets containing a dose of 5 mg of ivabradine in 100 mg

Ivabradine hemipamoate	7.07 mg
Lactose monohydrate	62.23 mg
Maize starch	20 mg
Maltodextrin (Lycatab® DSH)	10 mg
Magnesium stearate	0.5 mg
Anhydrous colloidal silica (Aerosil 200)	0.2 mg

EXAMPLE 3: Dissolution test

Operating conditions for dissolution

Paddle dissolution apparatus described in the European pharmacopoeia (*2.9.3*)

Dissolution medium: 0.01 N hydrochloric acid (pH ~ 2.1) degassed

Temperature of the medium: 37°C ± 0.5°C

Volume of the medium: 500 mL ± 5 mL

Speed of rotation of the blades: 50 rpm ± 2 rpm

Standard sampling time: 0, 15, 30 and 45 min

Added sampling times: 1, 2, 4, 6, 8, 12 and 16 h

Volume removed: 1 mL

Replacement of the volume removed: no

Number of units tested: 6

Number of units per flask: 1

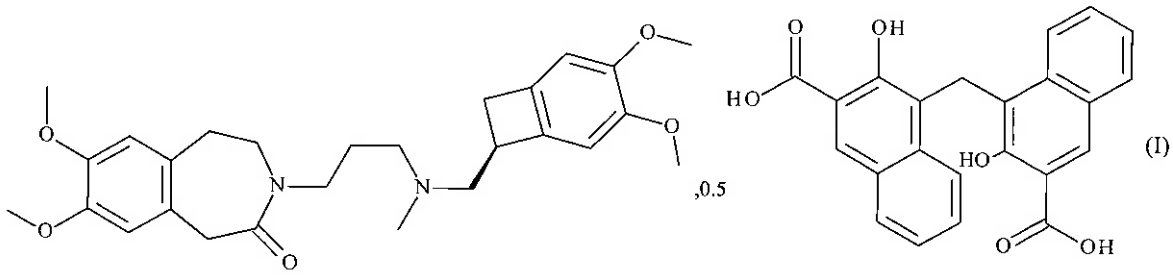
Table 1 – Dissolution results

	% of active ingredient released								
Time (hour)	B1	B2	B3	B4	B5	B6	Mean	Standard deviation	Derivative
0	0	0	0	0	0	0	0	0	0
0.25	12	11	12	13	12	11	12	0.84	0.79
0.5	18	17	18	20	17	16	18	1.15	0.4
0.75	21	22	22	24	21	20	22	1.5	0.26
1	24	25	26	28	23	23	25	1.8	0.2
2	38	40	40	43	38	34	39	2.87	0.23
4	64	70	71	70	72	66	69	3	0.25
6	81	89	88	85	91	84	86	3.58	0.15
8	89	99	96	94	101	93	95	4.34	0.07
12	96	109	102	103	110	101	104	5.16	0.03
16	98	114	104	106	114	105	107	6.27	0.01

Figure 1 is a graphical illustration of the data presented in the table above.

CLAIMS

1. Ivabradine hemipamoate of formula (I):



(I)

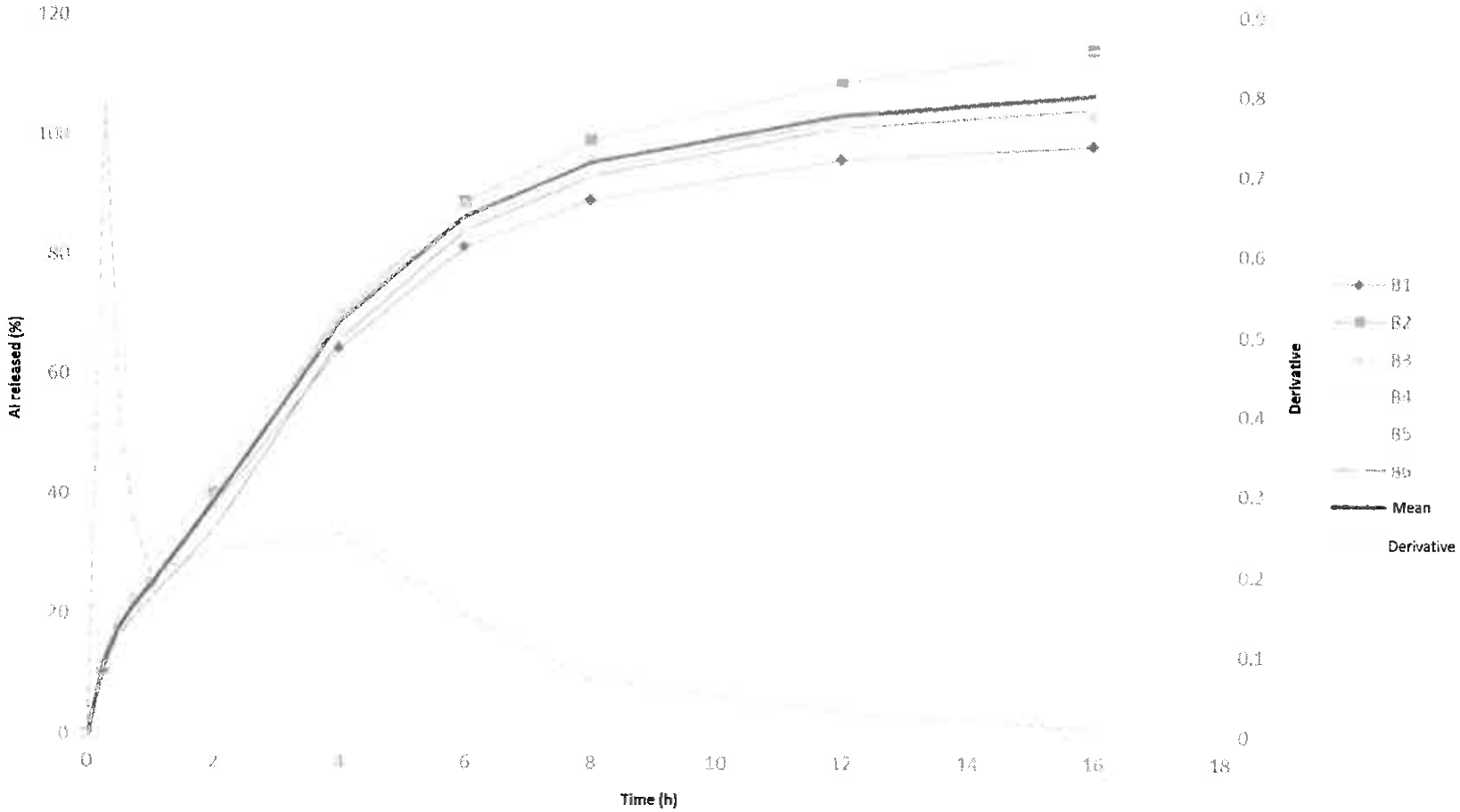
and its hydrates.

2. Process for the preparation of ivabradine hemipamoate, characterised in that ivabradine hydrochloride is brought together with sodium pamoate in an aqueous medium in a proportion ivabradine hydrochloride/sodium pamoate of from 1/0.5 to 1/0.6.

3. Pharmaceutical composition comprising as active ingredient ivabradine hemipamoate, in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or carriers.

4. Pharmaceutical composition according to claim 3 for use in the treatment or prevention of the various clinical situations of myocardial ischaemia such as angina pectoris, myocardial infarction and the associated rhythm disturbances, as well as in the various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in systolic or diastolic heart failure.

Figure 1


120
100
80
60
40
20
0
AI released (%)
0.9
0.8
0.7
0.6
0.5
0.4
0.2
0.2
0.1
0
Derivative
0
2
4
6
8
10
12
14
16
18
Time (h)
B1
B2
B3
B4
B5
B6
Mean
Derivative