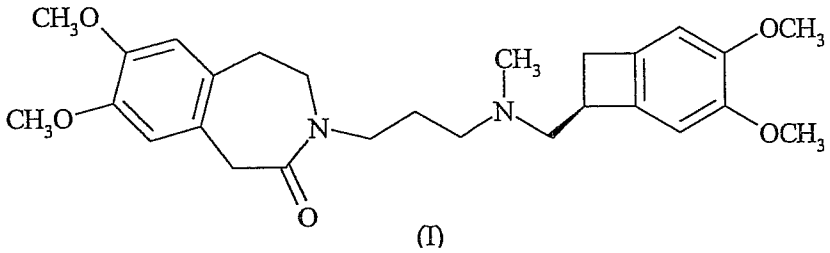
β-Crystalline form of ivabradine hydrochloride, a process for its preparation and pharmaceutical compositions containing it

The present invention relates to the β-crystalline form of ivabradine hydrochloride of formula (I), to a process for its preparation and to pharmaceutical compositions containing it.



(I)

Ivabradine, and addition salts thereof with a pharmaceutically acceptable acid, and more especially its hydrochloride, have very valuable pharmacological and therapeutic properties, especially bradycardic properties, making those compounds useful in the treatment or prevention of various clinical situations of myocardial ischaemia such as angina pectoris, myocardial infarct and associated rhythm disturbances, and also in various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in heart failure.

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

In view of the pharmaceutical value of this compound, it has been of prime importance to obtain it with excellent purity. It has also been important to be able to synthesise it by means of a process that can readily be converted to the industrial scale, especially in a form that allows rapid filtration and drying. Finally, that form had to be perfectly reproducible, easily formulated and sufficiently stable to allow its storage for long periods without particular requirements for temperature, light or oxygen level.

The patent specification EP 0 534 859 describes a synthesis process for ivabradine and its hydrochloride. However, that document does not specify the conditions for obtaining ivabradine in a form that exhibits those characteristics in a reproducible manner.

The Applicant has now found that a particular salt of ivabradine, the hydrochloride, can be obtained in a crystalline form that is well defined and that exhibits valuable characteristics of stability and processability.

More specifically, the present invention relates to the β-crystalline form of ivabradine hydrochloride, which is characterised by the following powder X-ray diffraction diagram measured using a PANalytical X'Pert Pro diffractometer together with an X'Celerator detector and expressed in terms of ray position (Bragg's angle 2 theta, expressed in degrees), ray height (expressed in counts), ray area (expressed in counts x degrees), ray width at half-height ("FWHM", expressed in degrees) and interplanar distance d (expressed in Å) :

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	6.8	130	86	0.6691	13.019
2	9.2	6141	507	0.0836	9.613
3	9.7	882	58	0.0669	9.083
4	10.0	875	72	0.0836	8.837
5	11.9	190	19	0.1004	7.433
6	12.2	500	58	0.1171	7.236
7	13.2	224	30	0.1338	6.694
8	13.8	633	52	0.0836	6.419
9	14.3	466	54	0.1171	6.209
10	14.8	926	76	0.0836	5.977
11	15.0	716	94	0.1338	5.887
12	15.7	531	79	0.1506	5.636
13	16.1	121	16	0.1338	5.502
14	16.9	1354	223	0.1673	5.254
15	18.4	5672	562	0.1004	4.824
16	18.8	1328	131	0.1004	4.716
17	19.7	1617	347	0.2175	4.508

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
18	20.4	296	34	0.1171	4.341
19	20.7	767	51	0.0669	4.286
20	21.3	1419	211	0.1506	4.178
21	21.6	2458	243	0.1004	4.114
22	22.6	1737	258	0.1506	3.937
23	23.0	1467	73	0.0502	3.865
24	23.7	486	128	0.2676	3.751
25	23.9	504	50	0.1004	3.718
26	25.3	4606	304	0.0669	3.513
27	25.7	791	91	0.1171	3.464
28	26.2	458	91	0.2007	3.406
29	26.6	221	44	0.2007	3.352
30	27.4	706	151	0.2175	3.251
31	27.7	208	27	0.1338	3.215
32	28.1	483	40	0.0836	3.176
33	28.8	242	24	0.1004	3.096
34	29.3	450	74	0.1673	3.049

The invention relates also to a process for the preparation of the β-crystalline form of ivabradine hydrochloride, which process is characterised in that a mixture of ivabradine hydrochloride and water or a mixture of ivabradine hydrochloride, isopropanol and water is heated until dissolution is complete and is then progressively cooled until crystallisation is complete, and the crystals formed are collected.

- In the crystallisation process according to the invention it is possible to use ivabradine hydrochloride obtained by any process, for example ivabradine hydrochloride obtained by the preparation process described in patent specification EP 0 534 859.

- The solution may advantageously be seeded during the cooling step.

The invention relates also to pharmaceutical compositions comprising as active ingredient the β-crystalline form of ivabradine hydrochloride together with one or more appropriate,

inert, non-toxic excipients. Among the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions.

The useful dosage can be varied according to the nature and severity of the disorder, the administration route and the age and weight of the patient. That dosage varies from 1 to 500 mg per day in one or more administrations.

The following Examples illustrate the invention.

The X-ray powder diffraction spectrum was measured under the following experimental conditions :

- PANalytical X'Pert Pro diffractometer, X'Celerator detector, temperature-regulated chamber,
- voltage 45 kV, intensity 40 mA,
- mounting θ-θ,
- nickel (Kβ) filter,
- incident-beam and diffracted-beam Soller slit : 0.04 rad,
- fixed angle of divergence slits : 1/8°,
- mask : 10 mm,
- antiscatter slit : 1/4°,
- measurement mode : continuous from 3° to 30°, in increments of 0.017°,
- measurement time per step : 19.7 s,
- total time : 4 min 32 s,
- measurement speed : 0.108°/s,
- measurement temperature : ambient.

EXAMPLE 1 : β-Crystalline form of ivabradine hydrochloride

720 ml of purified water are preheated to 50°C, and then 250 g of ivabradine hydrochloride obtained according to the process described in the patent specification EP 0 534 859 are added in portions, with stirring, and the mixture is heated at 74°C until dissolution is complete. The resulting clear solution is heated for 2 more hours at 74°C and is then progressively cooled, first to 40°C, and then to ambient temperature. The solution is subsequently stored at ambient temperature for 2 days, and then the solid suspension is spread out in a thin layer on a crystallisation plate. The excess water is driven off under a gentle current of nitrogen.

The water content of the resulting product, determined by coulometry, is 12.4 %, which corresponds to a tetrahydrate.

X-ray powder diffraction diagram :

The X-ray powder diffraction profile (diffraction angles) of the β-form of ivabradine hydrochloride is given by the significant rays collated in the following table :

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	6.8	130	86	0.6691	13.019
2	9.2	6141	507	0.0836	9.613
3	9.7	882	58	0.0669	9.083
4	10.0	875	72	0.0836	8.837
5	11.9	190	19	0.1004	7.433
6	12.2	500	58	0.1171	7.236
7	13.2	224	30	0.1338	6.694
8	13.8	633	52	0.0836	6.419
9	14.3	466	54	0.1171	6.209
10	14.8	926	76	0.0836	5.977
11	15.0	716	94	0.1338	5.887

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
12	15.7	531	79	0.1506	5.636
13	16.1	121	16	0.1338	5.502
14	16.9	1354	223	0.1673	5.254
15	18.4	5672	562	0.1004	4.824
16	18.8	1328	131	0.1004	4.716
17	19.7	1617	347	0.2175	4.508
18	20.4	296	34	0.1171	4.341
19	20.7	767	51	0.0669	4.286
20	21.3	1419	211	0.1506	4.178
21	21.6	2458	243	0.1004	4.114
22	22.6	1737	258	0.1506	3.937
23	23.0	1467	73	0.0502	3.865
24	23.7	486	128	0.2676	3.751
25	23.9	504	50	0.1004	3.718
26	25.3	4606	304	0.0669	3.513
27	25.7	791	91	0.1171	3.464
28	26.2	458	91	0.2007	3.406
29	26.6	221	44	0.2007	3.352
30	27.4	706	151	0.2175	3.251
31	27.7	208	27	0.1338	3.215
32	28.1	483	40	0.0836	3.176
33	28.8	242	24	0.1004	3.096
34	29.3	450	74	0.1673	3.049

EXAMPLE 2 : Pharmaceutical composition

Formula for the preparation of 1000 tablets each containing 5 mg of ivabradine base:

Compound of Example 1 ..... 5.39 g

Maize starch ..... 20 g

Anhydrous colloidal silica ..... 0.2 g

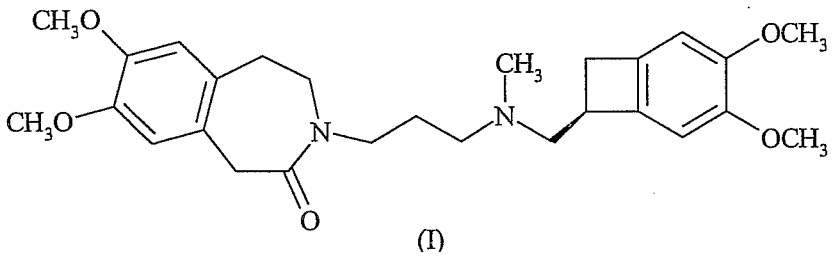
Mannitol ..... 63.91 g

PVP ..... 10 g

Magnesium stearate ..... 0.5 g

CLAIMS

1. β-Crystalline form of ivabradine hydrochloride of formula (I) :



. HCl,

(I)

characterised by the following powder X-ray diffraction diagram measured using a PANalytical X'Pert Pro diffractometer together with an X'Celerator detector and expressed in terms of ray position (Bragg's angle 2 theta, expressed in degrees), ray height (expressed in counts), ray area (expressed in counts x degrees), ray width at half-height ("FWHM", expressed in degrees) and interplanar distance d (expressed in Å):

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32	28.1	483	40	0.0836	3.176
33	28.8	242	24	0.1004	3.096
34	29.3	450	74	0.1673	3.049

2. Process for the preparation of the β-crystalline form of ivabradine hydrochloride, characterised in that a mixture of ivabradine hydrochloride and water or a mixture of ivabradine hydrochloride, isopropanol and water is heated until dissolution is complete and is then progressively cooled until crystallisation is complete, and the crystals formed are collected.

3. Process according to claim 2, characterised in that the solution of ivabradine hydrochloride is seeded during the cooling step.

4. Pharmaceutical composition comprising as active ingredient the β-crystalline form of ivabradine hydrochloride according to claim 1, in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.

5. Use of the β-crystalline form of ivabradine hydrochloride according to claim 1 in the manufacture of medicaments which are of use as bradycardics.

6. Use of the β-crystalline form of ivabradine hydrochloride according to claim 1 in the manufacture of medicaments which are of use in the treatment or prevention of various clinical situations of myocardial ischaemia such as angina pectoris, myocardial infarct and associated rhythm disturbances, and also in various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in heart failure.