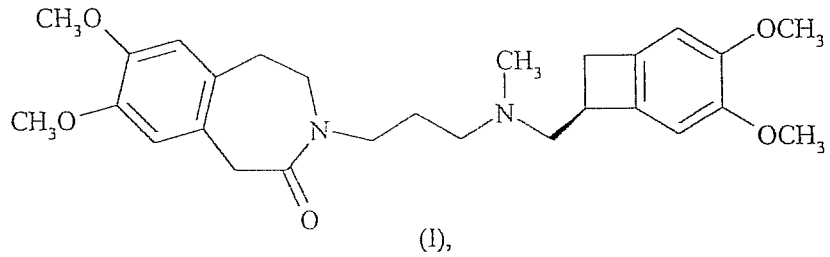
δ-CRYSTALLINE FORM OF IVABRADINE HYDROCHLORIDE, A PROCESS FOR ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

The present invention relates to the δ-crystalline form of ivabradine hydrochloride of formula (I)



(I),

to a process for its preparation and to pharmaceutical compositions containing it.

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 well defined crystalline form that exhibits valuable characteristics for stability and processability.

More specifically, the present invention relates to the δ-crystalline form of ivabradine hydrochloride, 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 line position (Bragg's angle 2 theta, expressed in degrees), line height (expressed in counts), line area (expressed in counts x degrees), line width at half-height ("FWHM", expressed in degrees) and interplanar distance d (expressed in Å):

Line no.	Angle 2 theta (degrees)	Height (counts)	Area(counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	4.1	1115	110	0.1004	21.753
2	6.8	183	145	0.8029	12.907
3	8.4	755	75	0.1004	10.531
4	10.9	1104	128	0.1171	8.087
5	12.2	195	19	0.1004	7.268
6	14.3	569	75	0.1338	6.214
7	14.7	1847	274	0.1506	6.013
8	15.3	1734	315	0.184	5.802
9	16.3	1164	154	0.1338	5.442
10	16.8	3420	734	0.2175	5.269
11	17.5	790	78	0.1004	5.069
12	17.9	3389	503	0.1506	4.960
13	19.2	2467	407	0.1673	4.635

Line no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
14	19.8	145	29	0.2007	4.477
15	20.4	313	52	0.1673	4.362
16	21.2	928	169	0.184	4.198
17	21.7	2093	414	0.2007	4.099
18	22.2	3850	635	0.1673	4.007
19	22.5	576	76	0.1338	3.948
20	23.1	1588	236	0.1506	3.855
21	24.8	1665	247	0.1506	3.594
22	25.2	1212	120	0.1004	3.534
23	25.6	1507	249	0.1673	3.477
24	26.7	2042	303	0.1506	3.342
25	27.6	2281	414	0.184	3.229
26	28.4	485	96	0.2007	3.138
27	29.6	599	99	0.1673	3.014

The invention relates also to a process for the preparation of the δ-crystalline form of ivabradine hydrochloride, which process is characterised in that acetonitrile or a mixture of acetonitrile and water is preheated, ivabradine hydrochloride is added, the solution obtained is allowed to cool at room temperature, held at room temperature 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 acetonitrile or mixture of acetonitrile and water is preferably preheated to a temperature between 60°C and reflux, more preferably between 65 and 75°C.

- The dilution is preferably more than 15 ml/g, more preferably between 50 and 100 ml/g.

The invention relates also to pharmaceutical compositions comprising as active ingredient the δ-crystalline form of ivabradine hydrochloride together with one or more appropriate, inert and 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, capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations and 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. The dosage varies from 1 to 500 mg per day in one or more administrations.

The Examples that follow 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,
- automatic divergence slits : irradiated length of 10 mm,
- mask : 10 mm,
- antiscatter slit : 1/2°,
- 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 : δ-crystalline form of ivabradine hydrochloride

160 ml of acetonitrile are preheated to 70°C and then 2 g of ivabradine hydrochloride obtained according to the process described in patent specification EP 0 534 859 are added, in portions, with stirring until dissolution is complete. The solution is then stored at ambient temperature for 2 days. The crystals are removed by filtration *in vacuo* and are spread out onto a crystallisation plate.

The water content of the product obtained, determined by coulometry, is 2.8 %.

Powder X-ray diffraction diagram :

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

Line no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	4.1	1115	110	0.1004	21.753
2	6.8	183	145	0.8029	12.907
3	8.4	755	75	0.1004	10.531
4	10.9	1104	128	0.1171	8.087
5	12.2	195	19	0.1004	7.268
6	14.3	569	75	0.1338	6.214
7	14.7	1847	274	0.1506	6.013
8	15.3	1734	315	0.184	5.802
9	16.3	1164	154	0.1338	5.442
10	16.8	3420	734	0.2175	5.269
11	17.5	790	78	0.1004	5.069
12	17.9	3389	503	0.1506	4.960
13	19.2	2467	407	0.1673	4.635

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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

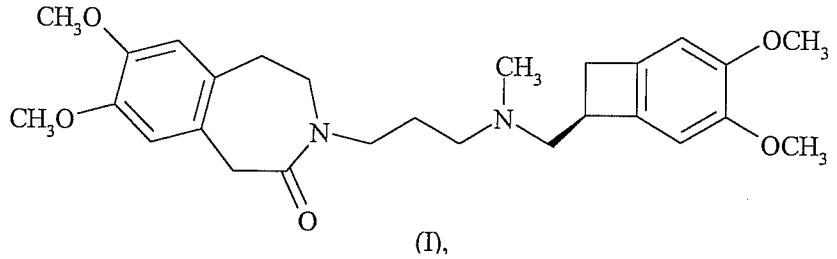
Mannitol ..... 63.91 g

PVP ..... 10 g

Magnesium stearate ..... 0.5 g

CLAIMS

1. δ-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 line position (Bragg's angle 2 theta, expressed in degrees), line height (expressed in counts), line area (expressed in counts x degrees), line width at half-height ("FWHM", expressed in degrees) and interplanar distance d (expressed in Å):

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25	27.6	2281	414	0.184	3.229
26	28.4	485	96	0.2007	3.138
27	29.6	599	99	0.1673	3.014

2. Process for the preparation of the δ-crystalline form of ivabradine hydrochloride according to claim 1, characterised in that acetonitrile or a mixture of acetonitrile and water is preheated, ivabradine hydrochloride is added, the solution obtained is allowed to cool at room temperature, held at room temperature 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 δ-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 δ-crystalline form of ivabradine hydrochloride according to claim 1 in the manufacture of medicaments which are of use as bradycardics.

6. Use of the δ-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.