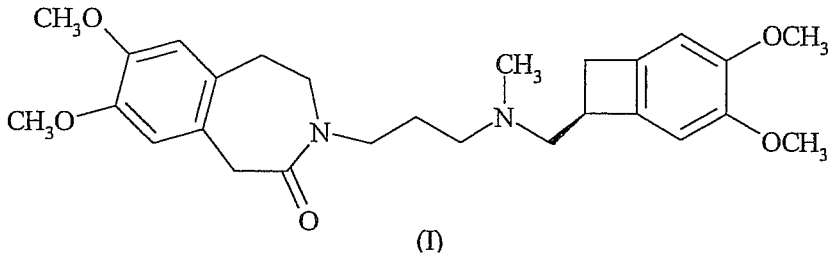
γd-Crystalline form of ivabradine hydrochloride, a process for its preparation and pharmaceutical compositions containing it

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



. HCl

(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 γd-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	4.3	1077	124	0.1171	20.633
2	6.9	132	70	0.5353	12.787
3	8.4	269	35	0.1338	10.482
4	10.6	322	26	0.0836	8.310
5	11.9	733	97	0.1338	7.414
6	12.5	1406	278	0.2007	7.069
7	13.4	2975	442	0.1506	6.619
8	14.4	825	122	0.1506	6.134
9	15.8	1036	205	0.2007	5.598
10	16.3	540	107	0.2007	5.450
11	16.9	1007	183	0.184	5.233
12	17.8	499	58	0.1171	4.978
13	18.9	1062	140	0.1338	4.686
14	19.8	570	85	0.1506	4.485
15	20.2	549	63	0.1171	4.399
16	20.9	2565	635	0.2509	4.241

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
17	21.6	531	105	0.2007	4.104
18	22.3	213	35	0.1673	3.981
19	23.4	278	27	0.1004	3.807
20	24.1	1404	185	0.1338	3.694
21	24.4	1526	176	0.1171	3.650
22	24.8	676	100	0.1506	3.591
23	25.4	702	139	0.2007	3.504
24	26.2	1737	401	0.2342	3.403
25	26.8	258	51	0.2007	3.331
26	27.2	182	24	0.1338	3.282
27	27.9	838	249	0.3011	3.193
28	29.1	152	20	0.1338	3.071

The invention relates also to a process for the preparation of the γd-crystalline form of ivabradine hydrochloride, which process is characterised in that a mixture of ivabradine hydrochloride and 2-ethoxyethanol, a mixture of ivabradine hydrochloride, 2-ethoxyethanol and water, or a mixture of ivabradine hydrochloride, ethanol and water is heated until dissolution is complete and is then cooled until crystallisation is complete, and the crystals obtained are collected by filtration and dehydrated.

- 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 γd-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 : γd-Crystalline form of ivabradine hydrochloride

40 ml of 2-ethoxyethanol are preheated to 80°C, and then 8.4 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 80°C until dissolution is complete. After returning to ambient temperature, the solution is stored for

8 days, and then the crystals formed are collected by filtration and rinsed with cyclohexane.

The product thereby obtained is dehydrated by progressively heating at a rate of 5°C/min up to a temperature of 80°C.

X-ray powder diffraction diagram :

The X-ray powder diffraction profile (diffraction angles) of the γd-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	4.3	1077	124	0.1171	20.633
2	6.9	132	70	0.5353	12.787
3	8.4	269	35	0.1338	10.482
4	10.6	322	26	0.0836	8.310
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14	19.8	570	85	0.1506	4.485
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17	21.6	531	105	0.2007	4.104
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26	27.2	182	24	0.1338	3.282
27	27.9	838	249	0.3011	3.193
28	29.1	152	20	0.1338	3.071

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

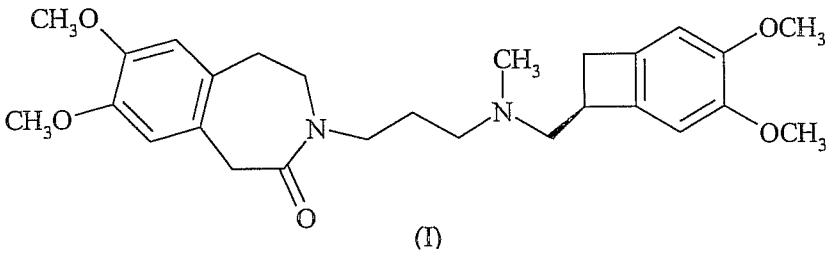
Mannitol ..... 63.91 g

PVP ..... 10 g

Magnesium stearate ..... 0.5 g

CLAIMS

1. γd-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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Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
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26	27.2	182	24	0.1338	3.282
27	27.9	838	249	0.3011	3.193
28	29.1	152	20	0.1338	3.071

2. Process for the preparation of the γd-crystalline form of ivabradine hydrochloride according to claim 1, characterised in that a mixture of ivabradine hydrochloride and 2-ethoxyethanol, a mixture of ivabradine hydrochloride, 2-ethoxyethanol and water, or a mixture of ivabradine hydrochloride, ethanol and water is heated until dissolution is complete and is then cooled until crystallisation is complete, and the crystals obtained are collected by filtration and dehydrated.

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

6. Use of the γd-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.

7. A γd-Crystalline form of ivabradine hydrochloride according to claim 1 substantially as herein described with reference to any example thereof.

8. A process according to claim 2 substantially as herein described with reference to any example thereof.

9. A pharmaceutical composition according to claim 4 substantially as herein described with reference to any example thereof.

10. A use according to claim 5 or claim 6 substantially as herein described with reference to any example thereof.