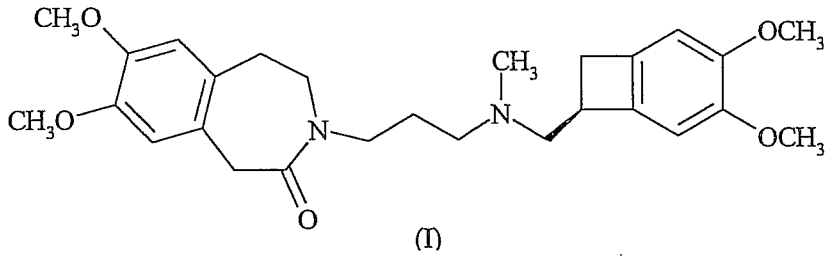
γ-Crystalline form of ivabradine hydrochloride, a process for its preparation and pharmaceutical compositions containing it

The present invention relates to the new γ-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 γ-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	4.2	1456	144	0.1004	20.762
2	6.9	125	99	0.8029	12.880
3	8.4	182	18	0.1004	10.503
4	10.7	240	32	0.1338	8.249
5	11.3	74	15	0.2007	7.858
6	12.0	644	64	0.1004	7.392
7	12.5	1476	219	0.1506	7.060
8	13.4	2691	400	0.1506	6.612
9	14.5	541	80	0.1506	6.119
10	14.8	104	17	0.1673	5.981
11	15.9	815	67	0.0836	5.559
12	16.3	501	74	0.1506	5.419
13	17.0	1168	154	0.1338	5.210
14	17.9	430	43	0.1004	4.962
15	19.0	667	121	0.184	4.672
16	19.8	527	104	0.2007	4.483

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
17	20.2	726	144	0.2007	4.392
18	20.5	282	28	0.1004	4.323
19	21.1	2255	260	0.1171	4.208
20	21.4	694	68	0.1004	4.147
21	21.6	744	86	0.1171	4.111
22	22.3	175	35	0.2007	3.987
23	23.5	310	61	0.2007	3.784
24	24.2	1635	270	0.1673	3.683
25	24.5	1335	220	0.1673	3.625
26	24.9	523	95	0.184	3.568
27	25.5	657	130	0.2007	3.485
28	26.0	933	154	0.1673	3.431
29	26.4	1549	230	0.1506	3.380
30	26.8	419	83	0.2007	3.323
31	27.3	350	69	0.2007	3.267
32	28.0	1108	146	0.1338	3.186
33	29.1	144	19	0.1338	3.066

The invention relates also to a process for the preparation of the γ-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 product is collected by filtration.

- 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 γ-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 : γ-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 water content of the crystals obtained, determined by coulometry, is 3.5 %, which corresponds to a monohydrate.

X-ray powder diffraction diagram :

The X-ray powder diffraction profile (diffraction angles) of the γ-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	4.2	1456	144	0.1004	20.762
2	6.9	125	99	0.8029	12.880
3	8.4	182	18	0.1004	10.503
4	10.7	240	32	0.1338	8.249
5	11.3	74	15	0.2007	7.858
6	12.0	644	64	0.1004	7.392
7	12.5	1476	219	0.1506	7.060
8	13.4	2691	400	0.1506	6.612
9	14.5	541	80	0.1506	6.119
10	14.8	104	17	0.1673	5.981
11	15.9	815	67	0.0836	5.559
12	16.3	501	74	0.1506	5.419
13	17.0	1168	154	0.1338	5.210
14	17.9	430	43	0.1004	4.962

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
15	19.0	667	121	0.184	4.672
16	19.8	527	104	0.2007	4.483
17	20.2	726	144	0.2007	4.392
18	20.5	282	28	0.1004	4.323
19	21.1	2255	260	0.1171	4.208
20	21.4	694	68	0.1004	4.147
21	21.6	744	86	0.1171	4.111
22	22.3	175	35	0.2007	3.987
23	23.5	310	61	0.2007	3.784
24	24.2	1635	270	0.1673	3.683
25	24.5	1335	220	0.1673	3.625
26	24.9	523	95	0.184	3.568
27	25.5	657	130	0.2007	3.485
28	26.0	933	154	0.1673	3.431
29	26.4	1549	230	0.1506	3.380
30	26.8	419	83	0.2007	3.323
31	27.3	350	69	0.2007	3.267
32	28.0	1108	146	0.1338	3.186
33	29.1	144	19	0.1338	3.066

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

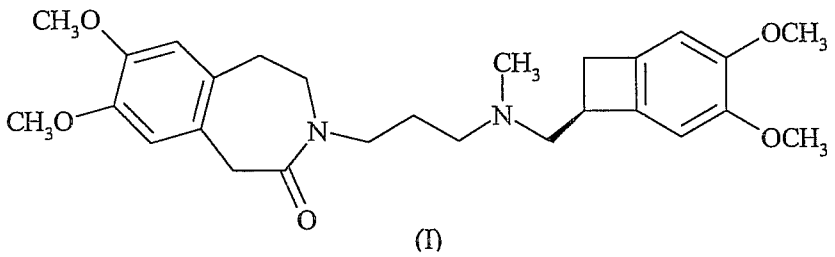
Mannitol ..... 63.91 g

PVP ..... 10 g

Magnesium stearate ..... 0.5 g

CLAIMS

1. γ-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):

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	4.2	1456	144	0.1004	20.762
2	6.9	125	99	0.8029	12.880
3	8.4	182	18	0.1004	10.503
4	10.7	240	32	0.1338	8.249
5	11.3	74	15	0.2007	7.858
6	12.0	644	64	0.1004	7.392
7	12.5	1476	219	0.1506	7.060
8	13.4	2691	400	0.1506	6.612
9	14.5	541	80	0.1506	6.119
10	14.8	104	17	0.1673	5.981
11	15.9	815	67	0.0836	5.559
12	16.3	501	74	0.1506	5.419

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
13	17.0	1168	154	0.1338	5.210
14	17.9	430	43	0.1004	4.962
15	19.0	667	121	0.184	4.672
16	19.8	527	104	0.2007	4.483
17	20.2	726	144	0.2007	4.392
18	20.5	282	28	0.1004	4.323
19	21.1	2255	260	0.1171	4.208
20	21.4	694	68	0.1004	4.147
21	21.6	744	86	0.1171	4.111
22	22.3	175	35	0.2007	3.987
23	23.5	310	61	0.2007	3.784
24	24.2	1635	270	0.1673	3.683
25	24.5	1335	220	0.1673	3.625
26	24.9	523	95	0.184	3.568
27	25.5	657	130	0.2007	3.485
28	26.0	933	154	0.1673	3.431
29	26.4	1549	230	0.1506	3.380
30	26.8	419	83	0.2007	3.323
31	27.3	350	69	0.2007	3.267
32	28.0	1108	146	0.1338	3.186
33	29.1	144	19	0.1338	3.066

2. Process for the preparation of the γ-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 product is collected by filtration.

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

6. Use of the γ-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.