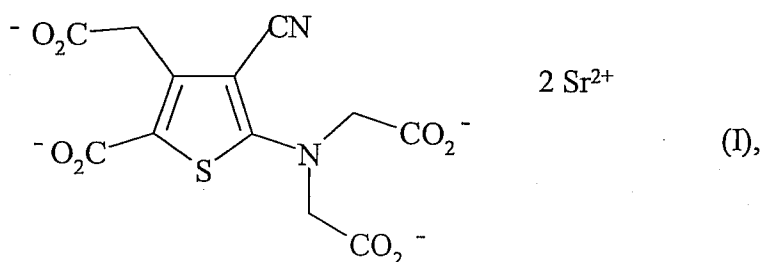


Alpha crystalline form of strontium ranelate, a process for its preparation, and pharmaceutical compositions containing it

The present invention relates to the alpha crystalline form of strontium ranelate, to a process for its preparation and to pharmaceutical compositions containing it.

Strontium ranelate, represented by formula (I) :



5 or the distrontium salt of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid, and its hydrates have very valuable pharmacological and therapeutic properties, especially pronounced anti-osteoporotic properties, making these compounds useful in the treatment and prevention of bone diseases.

10 Strontium ranelate and its hydrates also have properties making them useful in the treatment and prevention of arthrosis.

The preparation and therapeutic use of strontium ranelate and its tetrahydrate, heptahydrate and octahydrate have been described in the European Patent Specification EP 0 415 850.

The use of strontium ranelate in the prevention and treatment of arthrosis has been described in the European Patent Specification EP 0 813 869.

15 The Applicant has now found that strontium ranelate can be obtained in a well-defined crystalline form which is perfectly reproducible and which, by virtue of that fact, has valuable characteristics in terms of filtration and ease of formulation.

20 More specifically, the present invention relates to the alpha crystalline form of strontium ranelate, characterised by a water content of from 22 to 24 % and 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) :

5

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	7.6	4527	448	0.1004	11.649
2	8.0	1438	142	0.1004	11.069
3	8.3	3522	349	0.1004	10.642
4	8.6	11347	1123	0.1004	10.272
5	8.9	7332	726	0.1004	9.889
6	11.0	1047	104	0.1004	8.072
7	11.3	1655	164	0.1004	7.840
8	12.0	2186	216	0.1004	7.355
9	13.2	2887	381	0.1338	6.703
10	13.5	1705	169	0.1004	6.557
11	14.1	154	30	0.2007	6.275
12	14.7	803	79	0.1004	6.035
13	14.9	1346	178	0.1338	5.942
14	15.8	1556	154	0.1004	5.613
15	16.0	3339	441	0.1338	5.527
16	16.7	1845	183	0.1004	5.308
17	17.3	2835	281	0.1004	5.127
18	17.6	1252	124	0.1004	5.049
19	18.0	2183	216	0.1004	4.939
20	19.2	2303	228	0.1004	4.622
21	19.8	1298	128	0.1004	4.475
22	20.3	788	78	0.1004	4.373
23	20.6	1039	103	0.1004	4.317
24	21.1	882	116	0.1338	4.211
25	21.7	390	38	0.1004	4.103
26	22.3	1919	253	0.1338	3.990
27	22.7	1805	179	0.1004	3.923
28	23.0	4043	467	0.1171	3.861
29	23.5	650	86	0.1338	3.792
30	24.0	8677	1002	0.1171	3.711
31	24.7	229	30	0.1338	3.600
32	25.1	1246	164	0.1338	3.543
33	25.6	1659	219	0.1338	3.473
34	25.9	1773	175	0.1004	3.442
35	26.3	695	69	0.1004	3.385
36	26.6	401	46	0.1171	3.355
37	27.0	2800	370	0.1338	3.300
38	27.6	1415	140	0.1004	3.230

Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
39	28.0	3250	429	0.1338	3.186
40	28.4	1513	250	0.1673	3.144
41	29.1	1456	144	0.1004	3.068
42	29.6	1943	192	0.1004	3.022
43	30.1	3637	540	0.1506	2.967
44	30.5	707	117	0.1673	2.929
45	30.9	596	59	0.1004	2.897
46	31.8	577	76	0.1338	2.816
47	32.0	1080	107	0.1004	2.796
48	32.5	512	51	0.1004	2.756
49	32.9	1268	167	0.1338	2.726
50	33.4	1180	117	0.1004	2.685

The invention relates also to a process for the preparation of the alpha crystalline form of strontium ranelate, characterised in that a solution of strontium ranelate or a hydrate thereof in water is heated to reflux and then cooled until crystallisation is complete, and the product is collected by filtration.

- 5 • In the preparation process according to the invention it is possible to use strontium ranelate or a hydrate thereof obtained by any process, for example strontium ranelate octahydrate obtained by the preparation process described in the Patent Specification EP 0 415 850.
- 10 • An advantage of obtaining the said crystalline form is to allow especially rapid and efficient filtration and also the preparation of pharmaceutical formulations of consistent and reproducible composition, which is especially advantageous when the formulations are intended for oral administration.
- 15 • The form thereby obtained is sufficiently stable to allow its storage for an extended period without particular conditions in terms of temperature, light, humidity or oxygen levels.

The invention relates also to pharmaceutical compositions comprising as active ingredient the alpha crystalline form of strontium ranelate 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, granules, sublingual tablets, capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions and chewing gums.

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 0.2 to 10 g 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,
- voltage 45 kV, intensity 40 mA,
- mounting θ - θ ,
- $K\beta$ (Ni) filter,
- incident-beam and diffracted-beam Soller slit : 0.04 rad,
- divergence slits : automatic, irradiated length: 10 mm,
- mask : 10 mm,
- antiscatter slit : $1/2^\circ$,
- measurement mode : continuous from 3° to 34° , in increments of 0.017° ,
- measurement time per step : 31.1 s,
- total time : 8 min 07 s,
- measurement speed : $0.068^\circ/\text{s}$,
- spinner : turning at 1 revolution/s,
- measurement temperature : ambient.

EXAMPLE 1 : Alpha crystalline form of strontium ranelate

200 g of strontium ranelate octahydrate obtained according to the process described in Patent Specification EP 0 415 850 are mixed with 2 litres of water and heated to reflux.

The mixture is then cooled to 20°C.

5 The solid obtained is collected by filtration.

The water content of the product obtained, determined by loss on drying, is from 22 to 24 %, which corresponds to from 8.1 to 9 molecules of water per molecule of strontium ranelate.

X-ray powder diffraction diagram :

10 The X-ray powder diffraction profile (diffraction angles) of the alpha form of strontium ranelate 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	7.6	4527	448	0.1004	11.649
2	8.0	1438	142	0.1004	11.069
3	8.3	3522	349	0.1004	10.642
4	8.6	11347	1123	0.1004	10.272
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17	17.3	2835	281	0.1004	5.127
18	17.6	1252	124	0.1004	5.049
19	18.0	2183	216	0.1004	4.939
20	19.2	2303	228	0.1004	4.622
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Ray no.	Angle 2 theta (degrees)	Height (counts)	Area (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
22	20.3	788	78	0.1004	4.373
23	20.6	1039	103	0.1004	4.317
24	21.1	882	116	0.1338	4.211
25	21.7	390	38	0.1004	4.103
26	22.3	1919	253	0.1338	3.990
27	22.7	1805	179	0.1004	3.923
28	23.0	4043	467	0.1171	3.861
29	23.5	650	86	0.1338	3.792
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32	25.1	1246	164	0.1338	3.543
33	25.6	1659	219	0.1338	3.473
34	25.9	1773	175	0.1004	3.442
35	26.3	695	69	0.1004	3.385
36	26.6	401	46	0.1171	3.355
37	27.0	2800	370	0.1338	3.300
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39	28.0	3250	429	0.1338	3.186
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46	31.8	577	76	0.1338	2.816
47	32.0	1080	107	0.1004	2.796
48	32.5	512	51	0.1004	2.756
49	32.9	1268	167	0.1338	2.726
50	33.4	1180	117	0.1004	2.685

EXAMPLE 2 : Pharmaceutical composition

Formula for the preparation of 1000 tablets each containing 0.5 g of active ingredient:

Compound of Example 1 658 g

Sodium carboxymethyl starch 25.5 g

5 Microcrystalline cellulose..... 119.4 g

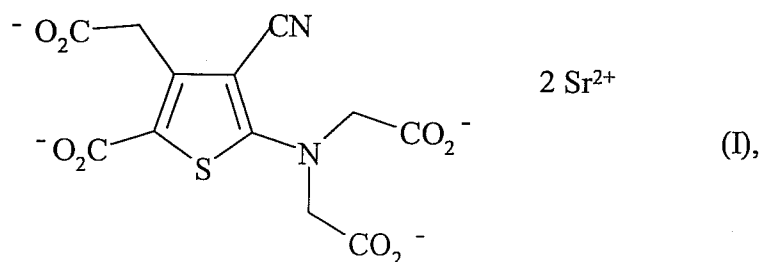
Povidone 38 g

Anhydrous colloidal silica 1.5 g

Magnesium stearate 7.6 g

CLAIMS

1. Alpha crystalline form of strontium ranelate of formula (I) :



characterised by a water content of from 22 to 24 % and 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)	Surface (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
1	7.6	4527	448	0.1004	11.649
2	8.0	1438	142	0.1004	11.069
3	8.3	3522	349	0.1004	10.642
4	8.6	11347	1123	0.1004	10.272
5	8.9	7332	726	0.1004	9.889
6	11.0	1047	104	0.1004	8.072
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9	13.2	2887	381	0.1338	6.703
10	13.5	1705	169	0.1004	6.557
11	14.1	154	30	0.2007	6.275
12	14.7	803	79	0.1004	6.035
13	14.9	1346	178	0.1338	5.942
14	15.8	1556	154	0.1004	5.613
15	16.0	3339	441	0.1338	5.527
16	16.7	1845	183	0.1004	5.308

Ray no.	Angle 2 theta (degrees)	Height (counts)	Surface (counts x degrees)	FWHM (degrees)	Interplanar distance (Å)
17	17.3	2835	281	0.1004	5.127
18	17.6	1252	124	0.1004	5.049
19	18.0	2183	216	0.1004	4.939
20	19.2	2303	228	0.1004	4.622
21	19.8	1298	128	0.1004	4.475
22	20.3	788	78	0.1004	4.373
23	20.6	1039	103	0.1004	4.317
24	21.1	882	116	0.1338	4.211
25	21.7	390	38	0.1004	4.103
26	22.3	1919	253	0.1338	3.990
27	22.7	1805	179	0.1004	3.923
28	23.0	4043	467	0.1171	3.861
29	23.5	650	86	0.1338	3.792
30	24.0	8677	1002	0.1171	3.711
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32	25.1	1246	164	0.1338	3.543
33	25.6	1659	219	0.1338	3.473
34	25.9	1773	175	0.1004	3.442
35	26.3	695	69	0.1004	3.385
36	26.6	401	46	0.1171	3.355
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39	28.0	3250	429	0.1338	3.186
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45	30.9	596	59	0.1004	2.897
46	31.8	577	76	0.1338	2.816
47	32.0	1080	107	0.1004	2.796
48	32.5	512	51	0.1004	2.756
49	32.9	1268	167	0.1338	2.726
50	33.4	1180	117	0.1004	2.685

2. Process for the preparation of the alpha crystalline form of strontium ranelate according to claim 1, characterised in that a solution of strontium ranelate or a hydrate thereof in water is heated to reflux and then cooled until crystallisation is complete, and the product is collected by filtration.

3. Pharmaceutical composition comprising as active ingredient the alpha crystalline form of strontium ranelate according to claim 1 in combination with one or more pharmaceutically acceptable, inert and non-toxic carriers.
4. Use of the alpha crystalline form of strontium ranelate according to claim 1 in the manufacture of medicaments for use in the treatment or prevention of osteoporosis.
5. Use of the alpha crystalline form of strontium ranelate according to claim 1 in the manufacture of medicaments for use in the treatment or prevention of arthrosis.
6. The alpha crystalline form of strontium ranelate according to claim 1 substantially as herein described with reference to Example 1.
7. The process according to claim 2 substantially as herein described with reference to Example 1.
8. The pharmaceutical composition according to claim 3 substantially as herein described with reference to Example 2.
9. Use of the alpha crystalline form of strontium ranelate according to claim 6 in the manufacture of medicaments for use in the treatment or prevention of osteoporosis.
10. Use of the alpha crystalline form of strontium ranelate according to claim 6 in the manufacture of medicaments for use in the treatment or prevention of arthrosis.