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(54) Title: STABLE CRYSTALLINE FORM X OF STRONTIUM RANELATE

(57) Abstract: The invention provides a stable crystalline form X of strontium ranelate, a method for the preparation thereof and its use for the preparation of a solid pharmaceutical composition of strontium ranelate designed for the preparation of a solution. The new form is characterized by high stability of the crystalline structure with regard to changes of air humidity and by excellent dissolution characteristics in water.



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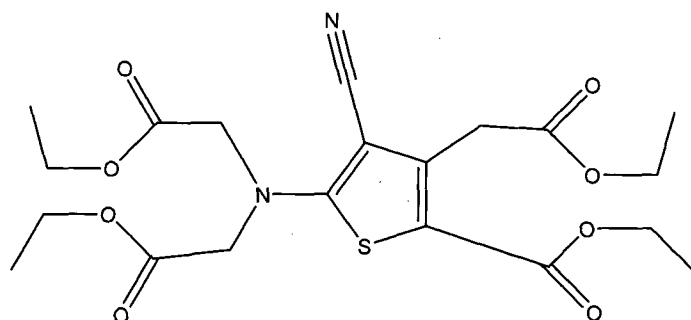
Stable crystalline form X of strontium ranelate

5 Technical Field

The present invention provides a stable crystalline form X of strontium ranelate, a method of its preparation and its use for the preparation of a solid pharmaceutical composition of strontium ranelate designed for the preparation of a solution. The new form is characterized with high stability of the crystalline structure with regard to changes of the air humidity and
10 with excellent dissolution properties in water.

Background Art

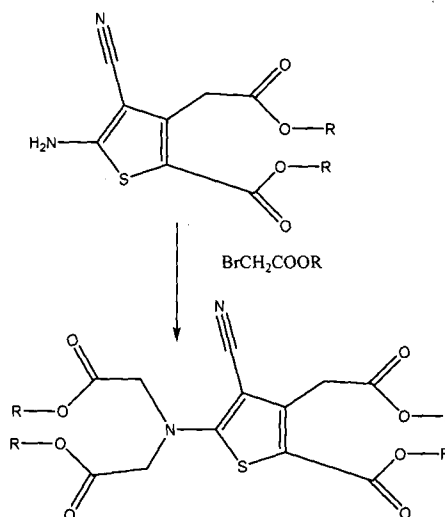
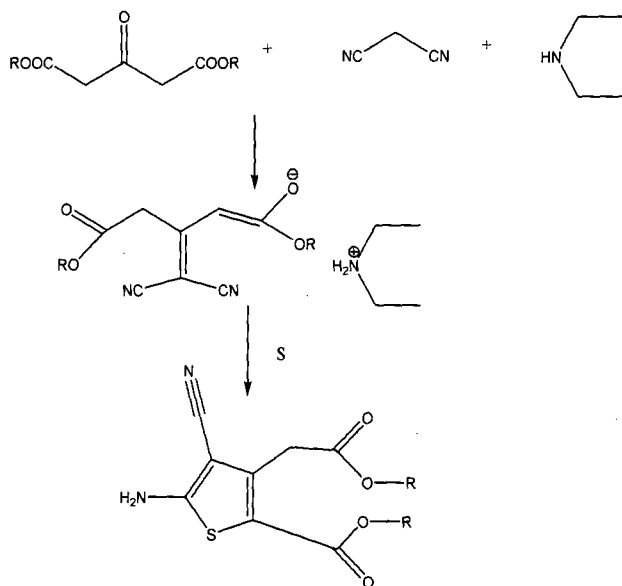
Strontium ranelate is an anti-osteoporotic agent that supports bone formation and at the same time reduces resorption of bone matter. Bone tissue is a dynamic matter. Osteoblasts and
15 osteoclasts are cells that influence dynamics of the bone matter. Osteoblasts support growth of the bone matter and strontium ranelate supports their formation. On the other hand, osteoclasts support resorption of the bone matter. Strontium ranelate stimulates calcium receptors to support the development of osteoblasts and inhibits the formation of osteoclasts. Strontium ranelate is an unusual representative of a drug where the cation (strontium) is responsible for
20 the pharmacological effect.



(1)

The tetraethyl ester of ranelic acid (1) has already been described, including synthesis (M. Wierzbicki et al: Bull.Soc.Chim.France 1786 (1975), based on K. Gewald et al: Chem Ber. 99, 94 (1966)).

Likewise, J.Chem.Tech. Biotechnol 47, 39 (1990) describes a procedure of synthesis according to Scheme 1 starting from 3-ketoglutaric acid ethyl ester in ethanol, using diethylamine as a base; this source declares that the synthesis does not provide a higher yield than 84%.



10 Scheme 1

Scheme 2

Further on, there is Adir's patent (EP 0 415 850) (1991), which describes preparation of ranelic acid and its salt with strontium(II) ions and the use of the product for the treatment of osteoporosis.

EP 0 415 850 describes alkaline hydrolysis of (1) in an aqueous-ethanolic environment with sodium hydroxide.

According to the former preparation method of strontium ranelate the thus prepared solution of the ranelic acid sodium salt is neutralized with hydrochloric acid and the product is diluted with acetone. The precipitated sodium chloride is filtered off and, after evaporation of acetone, the product is converted into the acid in an ion exchanger in the acidic cycle. After evaporation of water the crude acid is crystallized from diethyl ether and then from acetone or

tetrahydrofuran. With acetone it forms a solvate with 11% of acetone and with tetrahydrofuran a solvate with 26% of THF. The resulting purified acid is dissolved in water and subjected to distillation to remove the residual organic solvent, followed by neutralization of the resulting solution with strontium hydroxide, filtering and leaving to crystallize for 24 - 48 hours. It is possible to isolate, by filtration, a ranelic acid distrontium salt octahydrate, which was characterized in EP 0 415 850 by the wave number of the absorption band of the CN group at 2206 cm^{-1} in the infrared (IR) spectrum. By drying in nitrogen or a stream of dry air the product can be dried to a heptahydrate (IR characterization: CN group band at 2210 cm^{-1}). Drying at $55\text{ }^{\circ}\text{C}$ or at a reduced pressure can provide a tetrahydrate (IR characterization: CN group bands at 2200 cm^{-1} and 2200 cm^{-1}).

The latter method described in the patent allows obtaining the product by removing by distillation at a reduced pressure, after alkaline hydrolysis, ethanol and most of the water and precipitating the oily sodium salt with ethanol and filtering it off. The same is dissolved in water and then converted to the strontium(II) salt by addition of two equivalents of an aqueous solution of strontium chloride and the resulting strontium ranelate is aspirated. Again, an octahydrate is obtained.

Another method of hydrolysis of the ranelic acid ester is described in the patent application WO 2007/020527, where a lithium salt of ranelic acid is isolated after hydrolysis of the ester with lithium hydroxide. After isolation, this salt is re-dissolved and converted to the strontium salt by means of a solution of strontium chloride. Again, an octahydrate of strontium ranelate is isolated.

Polymorphism of strontium ranelate

The patent EP 0 415 850 describes strontium ranelate in three hydrate forms – in the forms of an octahydrate, heptahydrate and tetrahydrate. The octahydrate is the most stable one and heptahydrate and tetrahydrate can be prepared by drying. The patent also mentions that ranelic acid forms solvates with tetrahydrofuran and acetone and the solvates as such crystallize from these solvents.

A recent patent EP 1 642 897 describes the preparation and spectral data of X-ray Powder Diffraction (XRPD) of a very stable form of strontium ranelate, which is well filterable. This “alpha form” is prepared by heating of strontium ranelate prepared in accordance with EP 0 415 850 in water to the boiling point and leaving it to cool down to $20\text{ }^{\circ}\text{C}$. However, the

water content mentioned in the patent (22 - 24 %) indicates that this is a crystalline form with a variable water content that may be prepared as both octa- and nonahydrate since the stoichiometric water content corresponding to the above mentioned percentages is in the range of 8.1 - 9 molecules of water per one molecule of strontium(II) ranelate. This alpha form is used by Servier in their original product Protelos. An XPRD record of the alpha form is shown in Fig. 1 in the Annex.

Another data of a strontium ranelate hydrate of 2006 are contained in the Chinese patent CN 2006-10014798, which describes the preparation and X-ray diffraction of strontium ranelate heptahydrate with a water content of 19-20.4 %. Its XRPD is shown in Figure 2 in the Annex.

Other facts of the polymorphism of strontium ranelate are contained in the patent WO 2010/034806, which describes anhydrous strontium ranelate and forms having lower water contents than the previously known strontium ranelate hydrates. These are hydrates having water contents in the range of 1.5 - 5.5 %. Three crystalline modifications, I (hemihydrate), II (monohydrate) and III (sesquihydrate) are characterized therein with XRPD diffraction patterns. All these forms were prepared by drying of the alpha form, heptahydrate or tetrahydrate.

Disclosure of Invention

The invention provides a new crystalline form X of strontium (II) ranelate characterized by peaks in the X-ray powder diffraction pattern (XRPD) at the following values of the reflection angle: 8.5; 8.6; 8.8; 12.0; 13.1; 16.3; 17.4; 22.8 and 24.9° $2\theta \pm 0,1^\circ 2\theta$ and the following chemical shifts of the ^{13}C carbon in a solid phase nuclear magnetic resonance spectrum (ss NMR): 180.9; 178.8; 176.3; 165.4; 137.9; 121.0; 86.2; 59.2; 38.0 ppm. The invention also provides a method of preparation of the new form X of strontium ranelate by treatment with aqueous solutions of salts of known forms of strontium ranelate such as the alpha form or the heptahydrate form. Still other objects of the invention include solid dosage forms of strontium ranelate designed for the preparation of an aqueous solution, especially an aqueous solution for oral administration.

Detailed description of the invention

Strontium ranelate is a compound incompletely soluble in water and common organic solvents. All the hitherto known crystalline forms of strontium ranelate dissolve to a limited extent and relatively slowly in water. The crystalline form X of strontium ranelate prepared in accordance with the invention is remarkably better soluble than the hitherto known forms. It contains 18.7 – 19.0 % of water, which corresponds to 6.5 mole of water per 1 mole of strontium ranelate, i.e. trideca-hemihydrate. This polymorph has a stable crystalline structure, which does not change by drying, unlike such forms as the heptahydrate and alpha form, which changes its crystalline structure by drying to the crystalline structure of the tetrahydrate or the structure of the forms described in WO 2010/034806. The crystalline form X only loses a part of its crystal water by drying and it is able to regain it in conditions of increased relative humidity without a change of its polymorphous structure, which is documented by its tests using the DVS method. XRPD, ss NMR, TGA and DVS records of the known forms of strontium ranelate differ from the records of form X obtained in the same way, which is documented in Figures 2-15.

Form X of strontium ranelate in accordance with the invention can be prepared by treating, with a solution of a salt of a strong or semi-strong base in water, a suspension of any hitherto known form (alpha, tetrahydrate or heptahydrate) of strontium ranelate in the said solution. The anion of the salt may derive from an organic or inorganic acid. The acid anion used should produce a salt with strontium having higher solubility than that of strontium ranelate. Among the acids whose anions can be used in salts assisting in conversion of the other forms of strontium ranelate into form X those which are considered acceptable for use in pharmaceutical products are preferred with regard to possible small residues of these salts in the final product. Organic acids forming the anion of the salt may thus include, e.g., saturated or unsaturated monohydric or polyhydric aliphatic or aromatic C2-C12 carboxylic acids, such as formic, acetic, propionic, acrylic, maleic, fumaric or phthalic acid, aliphatic or aromatic C2-C12 hydroxyacids, such as glycolic, lactic, malic, citric, salicylic, mandelic or 1-hydroxy-2-naphthoic acid, or aliphatic C2-C4 halogenated acids, such as chloroacetic, bromoacetic, dichloroacetic, trichloroacetic or trifluoroacetic acid. The anion of the salt may further derive from aliphatic or aromatic C1-C12 sulfonic acids, such as methanesulfonic, benzenesulfonic, toluenesulfonic or naphthalenesulfonic acid. Suitable inorganic anions include, e.g., a nitrate, chloride, bromide or iodide. The cation of the salt used may include any pharmaceutically

acceptable cation capable to form a strong or semi-strong base provided that the solubility of its salt with ranelic acid is higher than that of strontium ranelate. Accordingly, out of strong bases, for example, cations of alkali metals, strontium (II) cation or tetraalkylammonium, tetraalkylphosphonium or trialkylsulfonium cations are suitable. Alkyl groups of onium salts may be selected independently of each other from the group containing linear C1-C6 alkyls, branched C3-C6 alkyls, C3-C6 cycloalkyls and benzyl. It is preferable if the total carbon atoms number in the alkyl groups of a tetraalkylonium (tetraalkylammonium or tetraalkylphosphonium) salt is not higher than 16. Preferably, the total carbon atoms number in the alkyl groups of the trialkylsulfonium salt does not exceed 12. Especially advantageous salts for the conversion of other modifications of strontium ranelate into form X are sodium, potassium and strontium salts, most preferably in combination with the chloride anion. Out of semi-strong bases a suitable cation includes, above all, the ammonium cation; however, salts of primary, secondary or tertiary organic amines with suitable acids can also be used. It is preferable to operate, during conversion of the modifications, at about neutral pH or at an alkaline pH, e.g., in the range of 6.5 - 9.0, since in an acidic environment the solubility of strontium ranelate increases and the released ranelic acid tends to decarboxylate. Since salts of semi-strong bases with strong acids, such as ammonium chloride, produce slightly acidic pH due to hydrolysis in an aqueous environment, it is preferable, when such a salt is used, to adjust a suitable working pH by addition of a base, or to use a salt with a weak acid instead that of a strong acid, such as ammonium acetate, where the pH change caused by the hydrolysis is essentially compensated by the hydrolysis of the weak acid anion acting in the opposite direction. The acetate is a suitable anion in combination with cations of all the prospective bases, not only semi-strong, but also strong ones.

The required time of the action of the salt solution on the suspension of strontium ranelate depends on the temperature. It is preferable to use temperatures above 25°C, and at temperatures exceeding 50°C complete conversion of the known forms of strontium ranelate to form X can be achieved in less than 24 hours. Due to the risk of decomposition reactions of the ranelate in hot solutions the applied temperature should not exceed 100 °C. From the practical point of view the temperature for the preparation of form X should be most preferably selected within the range of 40 – 70 °C.

The conversion rate is enhanced by the increasing concentration of the salt present in the solution acting on the suspension, such that it is preferable to work with a concentration of the salt solution near to saturation of the solution at the selected operating temperature.

5 A preferable embodiment of the method according to the invention consists in treatment of suspended strontium ranelate with a solution of the salt under stirring.

As has been shown in comparative experiments, form X of strontium ranelate dissolves in water much faster than the tetrahydrate, heptahydrate or the alpha form. This finding has unexpectedly opened the possibility of using the new form of strontium ranelate for the preparation of solid pharmaceutical compositions of strontium ranelate that will provide a clear solution after being stirred in water unlike all the hitherto known forms of this substance. The possibility of administering strontium ranelate in the form of a clear solution means a better guarantee of swallowing and absorption of the whole dose of the drug both for the patient and the attending physician as compared to a suspension, which may more easily and to a higher extent stick to the bottom or walls of the vessel.

15 Used experimental procedures and techniques:

The alpha form was prepared in accordance with EP 1 642 897, the heptahydrate form was prepared in accordance with CN 2006-10014798 and the tetrahydrate was prepared by drying of the alpha of heptahydrate form at 50 °C at a reduced pressure.

20 The nuclear magnetic resonance spectra of solid samples (¹³C ss NMR) were measured in a 400WB AVANCE III NMR spectrometer (Bruker) using a 4 mm cuvette, with the rotation speed of 13 kHz and contact time of 2 ms.

The various crystalline modifications exhibited the following chemical shifts of ¹³C carbon:
alpha form: 181.6; 178.8; 177.9; 167.1; 166.4; 139.6; 120.1; 87.2; 60.4; 58.3; 37.1;
heptahydrate: 180.2; 178.4; 165.4; 164.5; 141.1; 119.0; 118.0; 87.2; 58.9; 37.4;
25 tetrahydrate: 186.3; 184.1; 180.7; 179.6; 179.3; 170.2; 166.6; 165.5; 164.9; 140.7; 139.7;
119.5; 117.8; 88.9; 87.8; 64.5; 62.0; 61.1; 38.7; 38.2;
form X: 180.9; 178.8; 176.3; 165.4; 137.9; 121.0; 86.2; 59.2; 38.0 ppm.

30 XRPD was measured in an X'PERT PRO MPD PANalytical diffractometer with a graphite monochromator, using radiation of CuKα (λ=1.542 Å), excitation voltage: 45 kV, anode current: 40 mA, measured range: 2 - 40° 2θ, increment: 0.01° 2θ, a flat sample with the 10/0.5

mm area/thickness was used for the measurement. For the setting of the primary optical equipment programmable divergence slits with the irradiated area of the sample of 10 mm, 0.02 Soller slits and a $\frac{1}{4}^\circ$ anti-diffusion slit were used. For the setting of the secondary optical equipment an X'Celerator detector with maximum opening of the detection slot, 0.02 Soller
 5 slits and a 5.0 mm anti-diffusion slit were used.

Various crystalline modifications exhibited the following characteristic peaks:

alpha form: 7.6; 8.0; 8.6; 11.3; 12.0 a $13.5^\circ 2\theta \pm 0.1^\circ 2\theta$;

heptahydrate: 7.9; 8.3; 8.9; 13.1; 17.9 a $19.1^\circ 2\theta \pm 0.1^\circ 2\theta$;

tetrahydrate: 8.8; 9.0; 10.8; 14.3 and $17.6^\circ 2\theta \pm 0.1^\circ 2\theta$;

10 form X: 8.5; 8.6; 8.8; 12.0; 13.1; 16.3; 17.4; 22.8 and $24.9^\circ 2\theta \pm 0.1^\circ 2\theta$.

Table of the diffraction peaks of form X of strontium ranelate:

Position [2θ]	d-interplanar distance [Å] (1 Å = 0.1 nm)	Relative intensity [%]
8.54	10.343	50.4
8.64	10.224	100.0
8.79	10.053	40.0
11.98	7.381	76.4
13.14	6.734	48.5
15.06	5.877	13.6
15.25	5.806	14.7
15.71	5.638	2.1
16.30	5.435	59.9
17.35	5.107	54.4
17.70	5.008	7.9
18.81	4.713	7.2
18.95	4.679	6.4
19.38	4.576	11.5
20.74	4.279	18.1
21.51	4.128	5.6
22.16	4.008	30.9
22.77	3.902	62.7
23.27	3.819	34.4
23.77	3.741	9.0
24.13	3.685	18.0
24.91	3.571	48.1
25.18	3.534	6.9
25.41	3.503	5.4
25.86	3.443	14.0
25.98	3.427	24.9
26.59	3.349	30.2
27.14	3.283	21.9
27.39	3.254	18.9

27.64	3.225	33.6
27.78	3.208	15.5
28.06	3.177	11.3
28.78	3.100	25.5
29.30	3.046	4.2
29.61	3.014	13.3
29.82	2.994	23.1
30.11	2.965	5.2
30.35	2.943	6.8
31.09	2.874	6.9
31.30	2.856	11.6
31.69	2.821	11.9
31.84	2.808	10.8
32.39	2.762	8.1
32.92	2.719	23.0
33.45	2.676	9.0
34.37	2.607	10.6
35.22	2.546	21.4
35.57	2.522	10.7
35.96	2.496	7.1
36.22	2.478	5.2
36.81	2.440	9.3
37.01	2.427	9.5
37.84	2.376	19.7
38.35	2.345	7.1
38.86	2.315	10.0
39.86	2.260	14.9

TGA (thermogravimetric analysis) was performed using a TGA 6 device (Perkin Elmer). The used heat-up rate was 10 °C/min from 22 °C to 250 °C. The samples were analyzed in an N₂ atmosphere with a weighed charge of about 20 mg.

- 5 DVS (Dynamic Vapour Sorption) was measured with a DVS Advantage 1 (Surface Measurement System) device. A sample of strontium ranelate (60-100 mg) was loaded with two cycles with a change of relative humidity (RH) in the range of 0-90-0 % of RH in a nitrogen atmosphere at the temperature of 25 °C. After execution of a cycle (0 % RH) the polymorphous structure was verified by means of XRPD; the sample was also subject to
- 10 XRPD analysis after loading with 90% RH for 3 hours. Form X proved to be stable against drying and wetting – both the cycles occurred without a change of the polymorphous structure. On the basis of these experiments as well as comparison to the behaviour of the other forms during several days' exposure to high of low humidity it can be concluded that form X is the most stable polymorphous form of strontium ranelate as regards the influence of variable air
- 15 humidity.

Dissolution was measured with a SOTAX CE7 smart dissolution device. For the analysis a cell for powders and granulates was used into which 20 mg of strontium ranelate was weighed. The charge in the cell was covered with a conical sieve with balls for homogenization of the active substances. The dissolution vessels contained 900 ml of water. The media flowed
5 through the cell at the rate of 8 ml/min for 95 minutes. Absorbance was measured continuously at 320 nm in 1 cm cuvettes. The absorbance values recalculated to % of the dissolved substance are presented in Fig. 16.

Brief Description of Drawings

Figure 1: X-ray diffraction pattern of the alpha form of strontium ranelate

10 Figure 2: X-ray diffraction pattern of strontium ranelate heptahydrate

Figure 3: X-ray diffraction pattern of strontium ranelate tetrahydrate

Figure 4: X-ray diffraction pattern of form X of strontium ranelate

Figure 5: ^{13}C ss NMR spectrum of the alpha form of strontium ranelate

Figure 6: ^{13}C ss NMR spectrum of strontium ranelate heptahydrate

15 Figure 7: ^{13}C ss NMR spectrum of strontium ranelate tetrahydrate

Figure 8: ^{13}C ss NMR spectrum of form X of strontium ranelate

Figure 9: DVS record of strontium ranelate heptahydrate

Figure 10: DVS record of the alpha form of strontium ranelate

Figure 11: DVS record of form X of strontium ranelate

20 Figure 12: TGA record of strontium ranelate tetrahydrate

Figure 13: TGA record of strontium ranelate heptahydrate

Figure 14: TGA record of the alpha form of strontium ranelate

Figure 15: TGA record of form X of strontium ranelate

Figure 16. Dissolution curves of the hydrates of strontium ranelate in water

Specific Working Examples

The invention are illustrated in more detail in the examples below, which however do not have any influence on the protection scope defined by the claims. The percentage data, unless specified otherwise in particular cases, mean % by weight.

Example 1 (comparative). Preparation of strontium ranelate tetrahydrate:

Drying of strontium ranelate of the alpha form prepared in accordance with EP 1 642 897 at 50 °C and the pressure of 0.01MPa for 3 hours provided the tetrahydrate crystalline form with the water content of 12.7 %.

5 Example 2.

By stirring of a suspension of strontium ranelate of the alpha form prepared in accordance with EP 1 642 897 in a 5% aqueous solution of NaCl at 65 °C for 5 hours after aspiration of the solid fraction and its drying freely in the air form X was prepared with the water content of 18.9 %.

10 Example 3.

By stirring of a suspension of strontium ranelate of the alpha form prepared in accordance with EP 1 642 897 in a 20% aqueous solution of NaCl at 65 °C for 5 hours, aspiration of the solid fraction and its drying freely in the air form X was prepared with the water content of 18.7 %.

Example 4.

- 15 By stirring of a suspension of strontium ranelate tetrahydrate prepared in accordance with Example 1 in a 5% aqueous solution of NaCl at 65 °C for 5 hours after aspiration of the solid fraction and its drying freely in the air form X was prepared with the water content of 18,8 %.

Example 5.

- 20 By stirring of a suspension of strontium ranelate tetrahydrate prepared in accordance with Example 1 in a 20% solution of NaCl at 65 °C for 5 hours, aspiration of the solid fraction and its drying freely in the air form X was prepared with the water content of 19,0 %.

Example 6. Drying of form X of strontium ranelate:

- 25 Form X of strontium ranelate prepared in accordance with Example 2 was left in an exsiccator with controlled RH ($RH < 5\%$) for 3 days. The weight loss was 1.5 % (the resulting water content calculated on the basis of the weight changes was 16.3 %) and after drying the polymorphous structure was verified with the use of XRPD. The polymorphous structure did not change during the experiment.

Example 7. Wetting of form X of strontium ranelate:

The dried form X of strontium ranelate prepared in accordance with Example 6 was left in an exsiccator with controlled relative humidity ($RH > 90\%$) for 1 day or 7 days, respectively.

- 5 The weight increase after 1 day was 5.0 % (the resulting water content calculated on the basis of the weight changes was 21.3 %), the total increase after 7 days was 21.6 % (the resulting water content calculated on the basis of the weight changes was 42.6 %). Then, the polymorphous structure was verified with the use of XRPD. The polymorphous structure did not change during the experiment.

Example 8 (comparative). Drying of strontium ranelate heptahydrate:

- 10 Strontium ranelate heptahydrate prepared in accordance with CN 10014798 was left in an exsiccator with controlled RH ($RH < 5\%$) for 3 days. The weight loss was 6.8 % (the resulting water content calculated on the basis of the weight changes was 13.9 %) and after drying the polymorphous structure was verified with the use of XPRD. During the experiment the polymorphous structure changed to the tetrahydrate crystalline form.

- 15 Example 9 (comparative). Wetting of the tetrahydrate crystalline form obtained by drying of strontium ranelate heptahydrate:

The dried form of strontium ranelate prepared in accordance with Example 8 was left in an exsiccator with controlled RH ($RH > 90\%$) for 1 day or 7 days, respectively. The weight increase after 1 day was 13.9 % (the resulting water content calculated on the basis of the

- 20 weight changes was 27.8 %), after 7 days the weight increase was 17.4 % (the resulting water content calculated on the basis of the weight changes was 31.3 %). Then, the polymorphous structure was verified with the use of XRPD. During the experiment the polymorphous structure changed to the alpha crystalline form.

Example 10 (comparative). Drying of the alpha form of strontium ranelate:

- 25 The alpha crystalline form of strontium ranelate prepared in accordance with EP 1 642 897 was left in an exsiccator with controlled RH ($RH < 5\%$) for 3 days. The weight loss was 10.9 % (the resulting water content calculated on the basis of the weight changes was 13.9 %) and after drying the polymorphous structure was verified in accordance with XRPD. During the experiment the polymorphous structure changed to the tetrahydrate crystalline form.

Example 11 (comparative). Wetting of the tetrahydrate crystalline form obtained by drying of the alpha form of strontium ranelate:

5 The dried crystalline form of strontium ranelate prepared in accordance with Example 10 was left in an exsiccator with controlled RH ($RH > 90\%$) for 1 day or 7 days, respectively. The weight increase after 1 day was 14.1 % (the resulting water content calculated on the basis of the weight changes was 28.0 %), after 7 days the weight increase was 18.8 % (the resulting water content calculated on the basis of the weight changes was 32.7 %). Then, the polymorphous structure was verified with the use of XRPD. During the experiment the polymorphous structure changed back to the alpha crystalline form.

CLAIMS

1. Crystalline form X of strontium ranelate, characterized by the following peaks in the X-ray powder diffraction pattern: 8.5; 8.6; 8.8; 12.0; 13.1; 16.3; 17.4; 22.8 and 24.9°
5 $2\theta \pm 0.1^\circ 2\theta$ or the following peaks in the ^{13}C ss NMR spectrum: 180.9; 178.8; 176.3; 165.4; 137.9; 121.0; 86.2; 59.2; 38.0 ppm.
2. A method for the preparation of the crystalline form X of strontium ranelate according to claim 1, characterized in that a suspension of another crystalline form of strontium ranelate is treated with an aqueous solution of a salt of a strong or semi-strong base and
10 after the required conversion is achieved, the resulting solid form X is separated from said solution of the salt.
3. The method according to claim 2, characterized in that said salt of a strong base is a salt of an alkali metal or strontium.
4. The method according to claim 2, characterized in that said salt of a semi-strong base
15 is an ammonium salt.
5. The method according to claim 3, characterized in that said salt of a strong base is sodium chloride, potassium chloride or strontium chloride.
6. The method according to any one of claims 2-4, characterized in that said salt of a strong or semi-strong base is an acetate.
7. The method according to claims 2-6, characterized in that said treatment with said salt
20 solution is performed at a temperature of from 25 to 100 °C.
8. The method according to claim 7, characterized in that said treatment is performed at a temperature of from 40 to 70 °C.
9. A solid pharmaceutical composition, containing strontium ranelate and at least one
25 excipient, characterized in that strontium ranelate is in the form X according to claim 1 and said composition is designed for preparation of a solution.
10. The composition according to claim 9, characterized in that said solution is designed for oral administration.

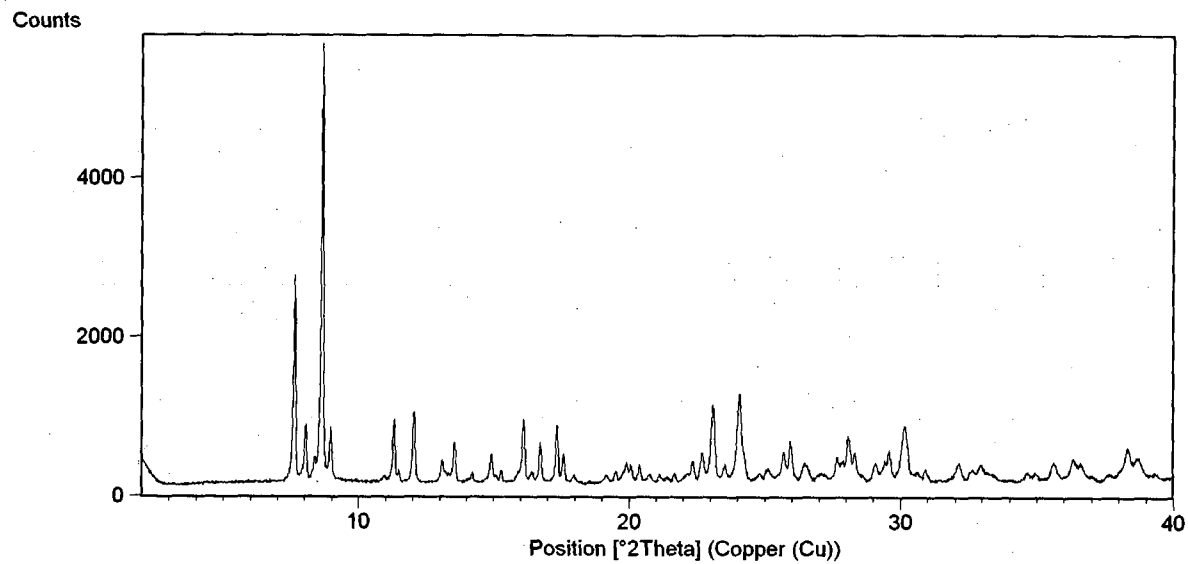


Figure 1

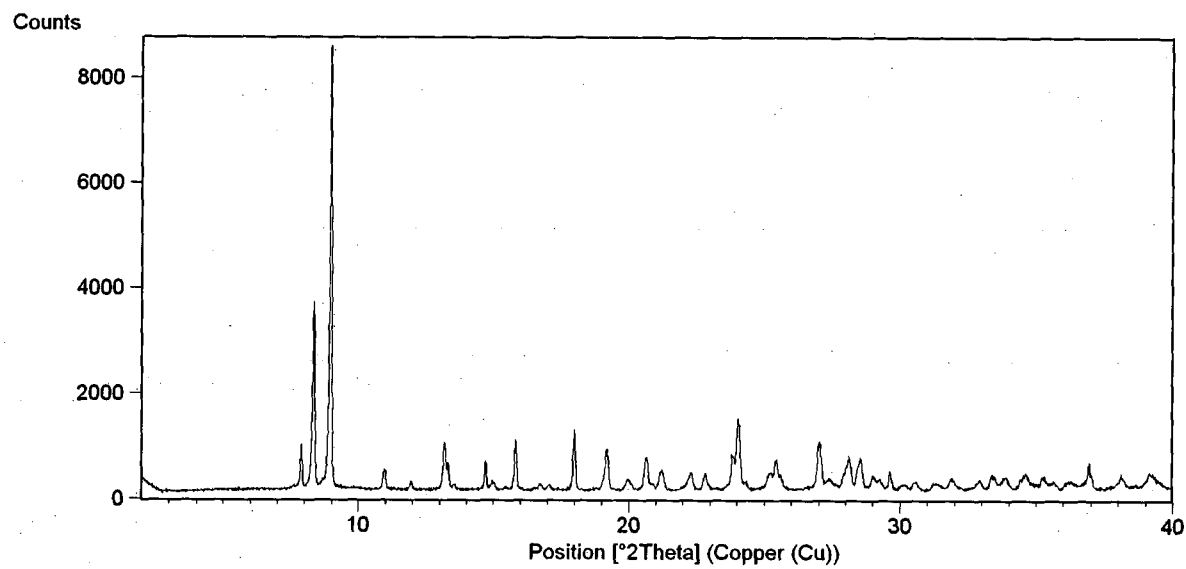


Figure 2

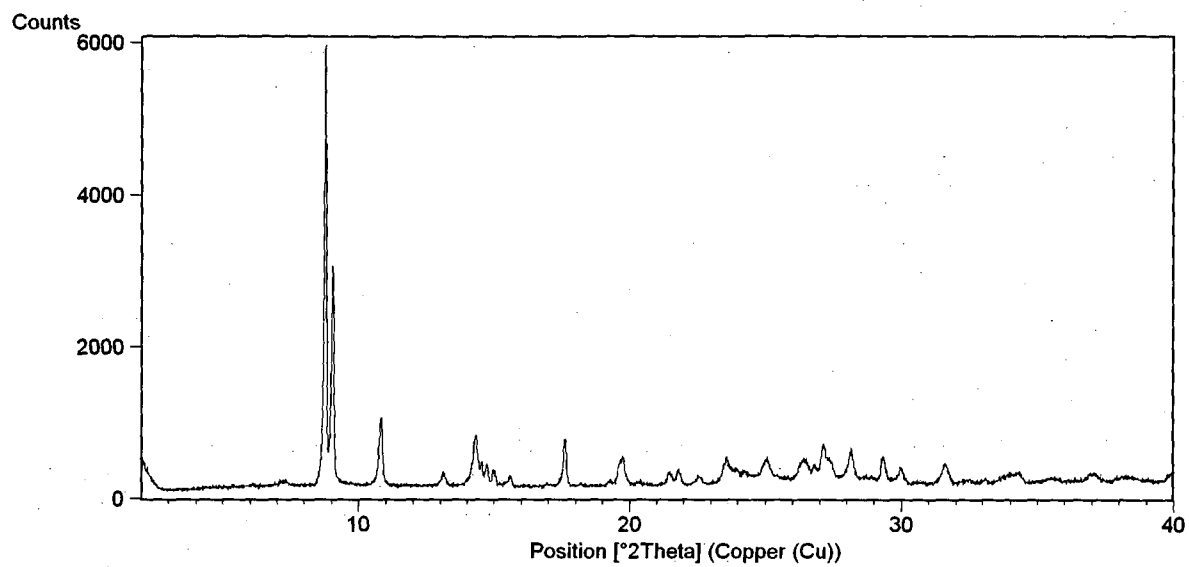


Figure 3

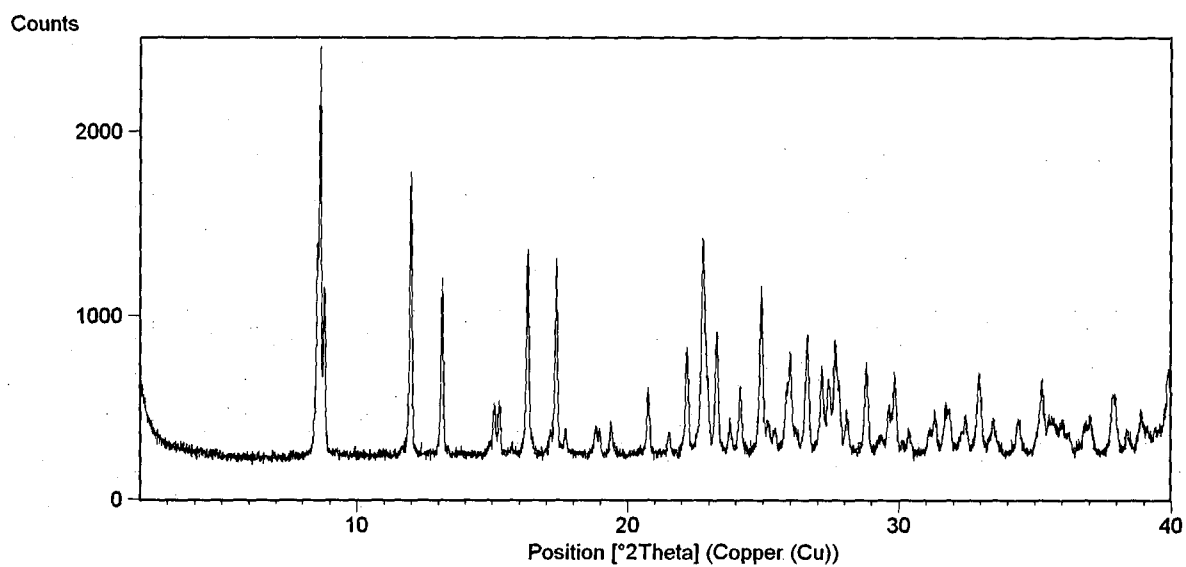


Figure 4

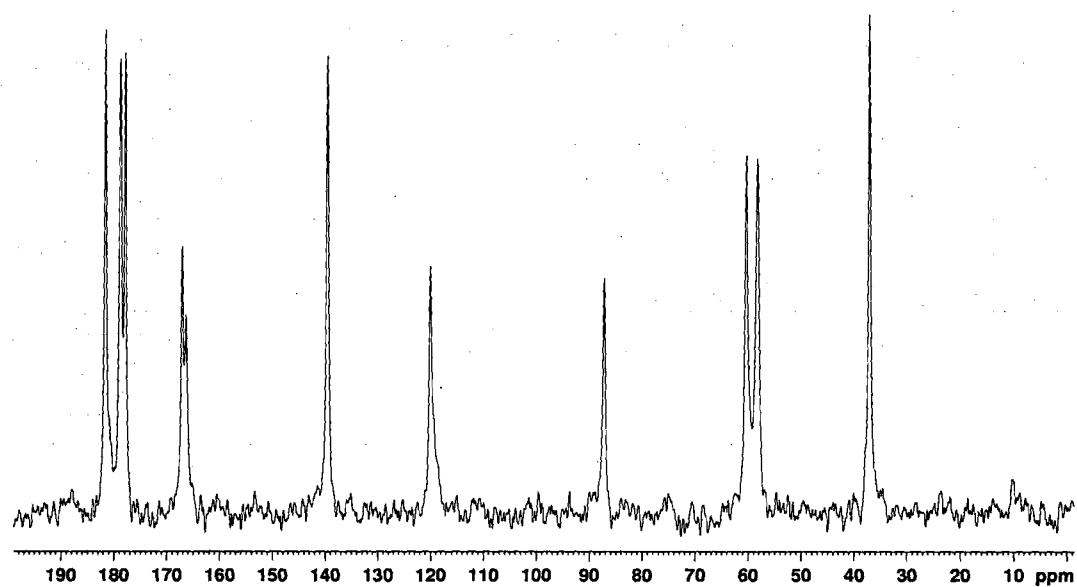


Figure 5

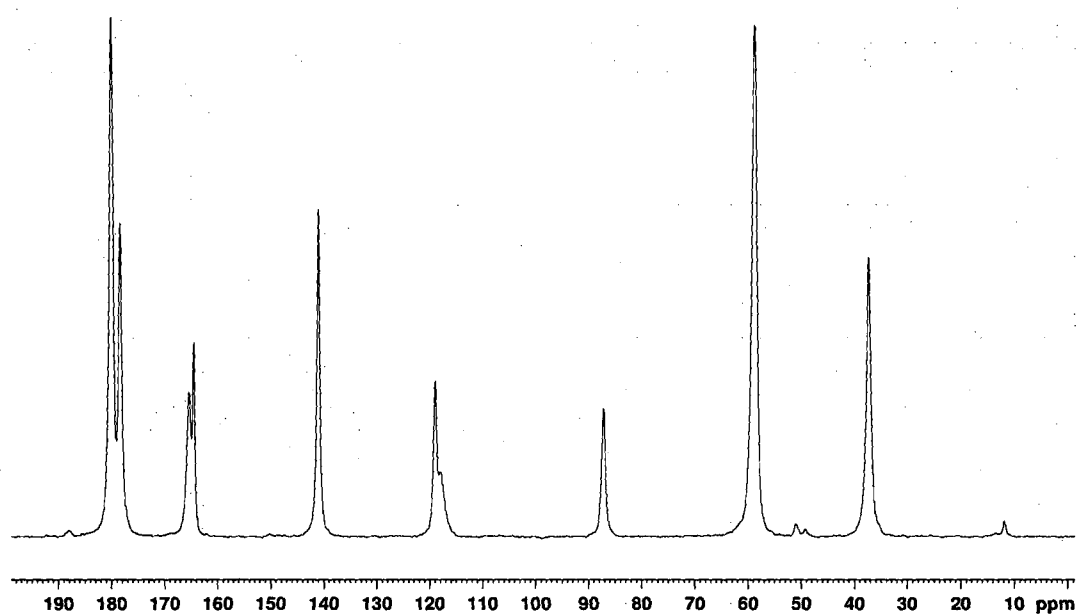


Figure 6

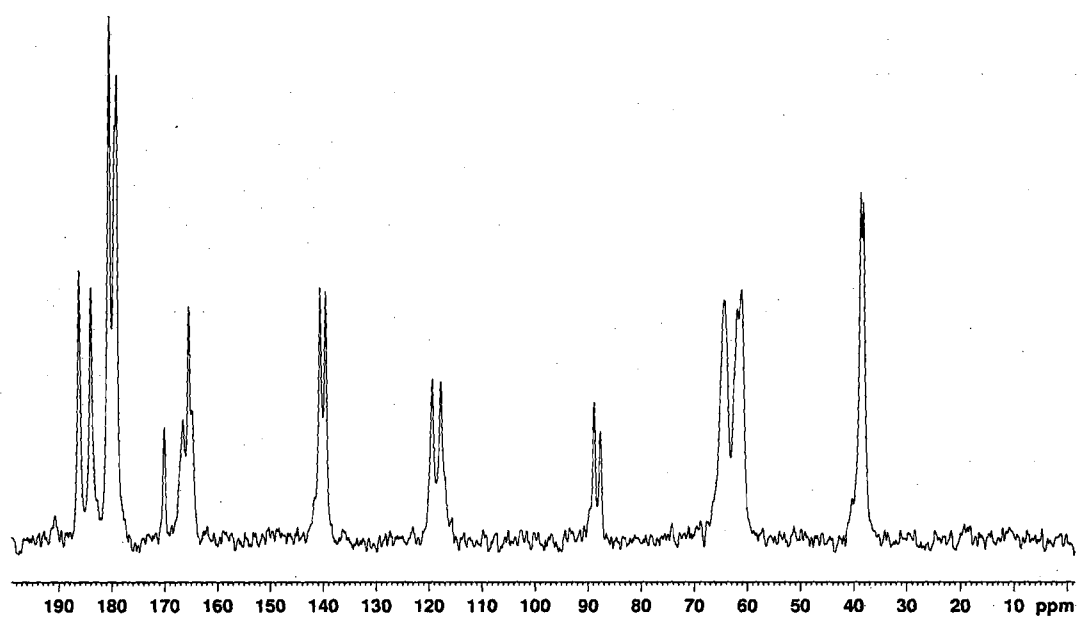


Figure 7

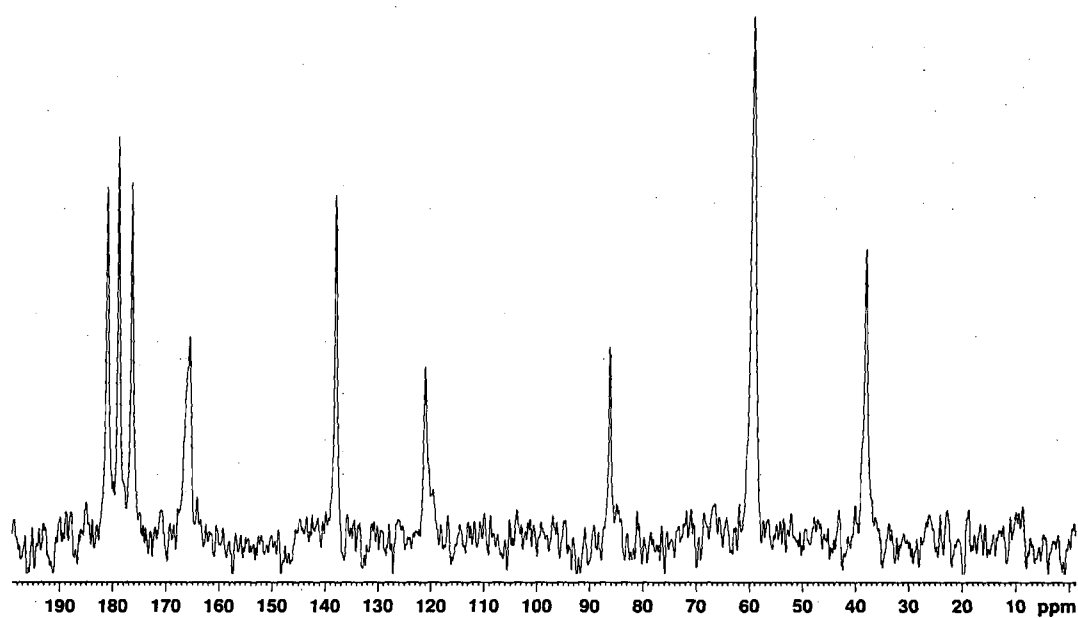


Figure 8

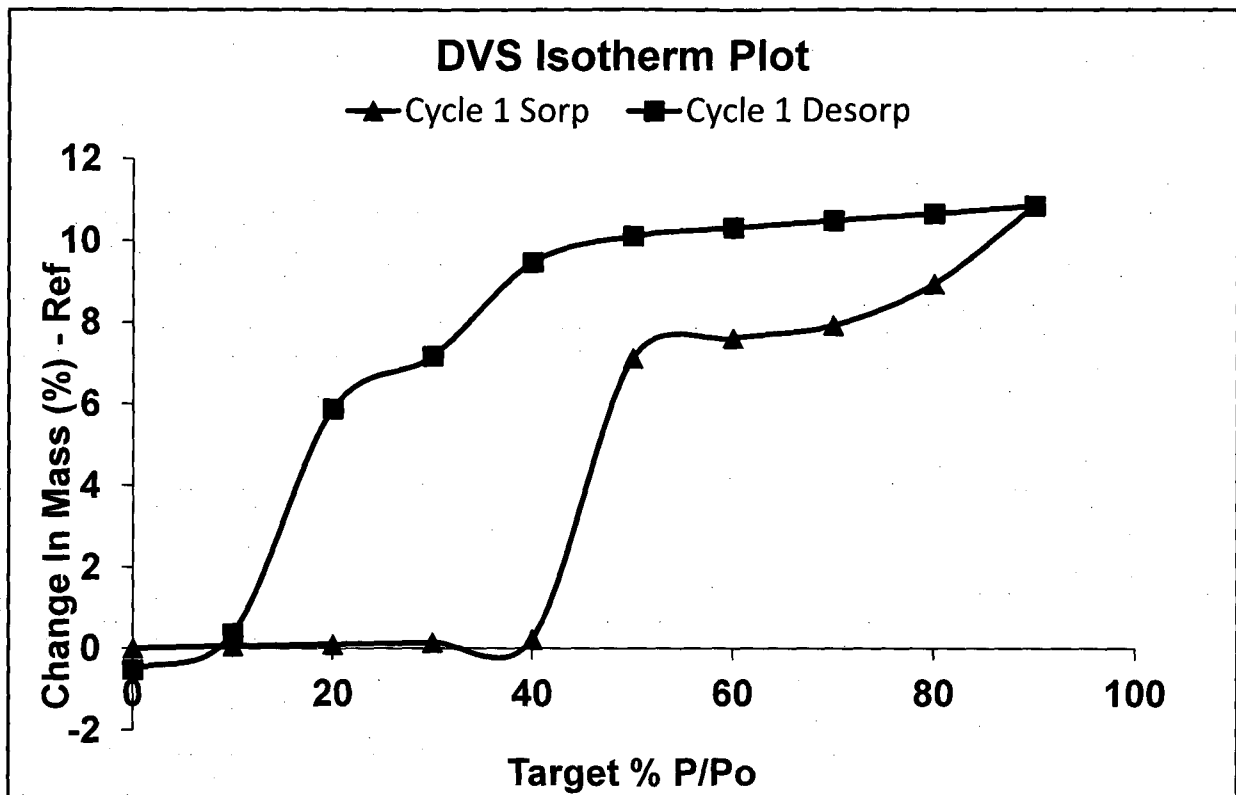


Figure 9

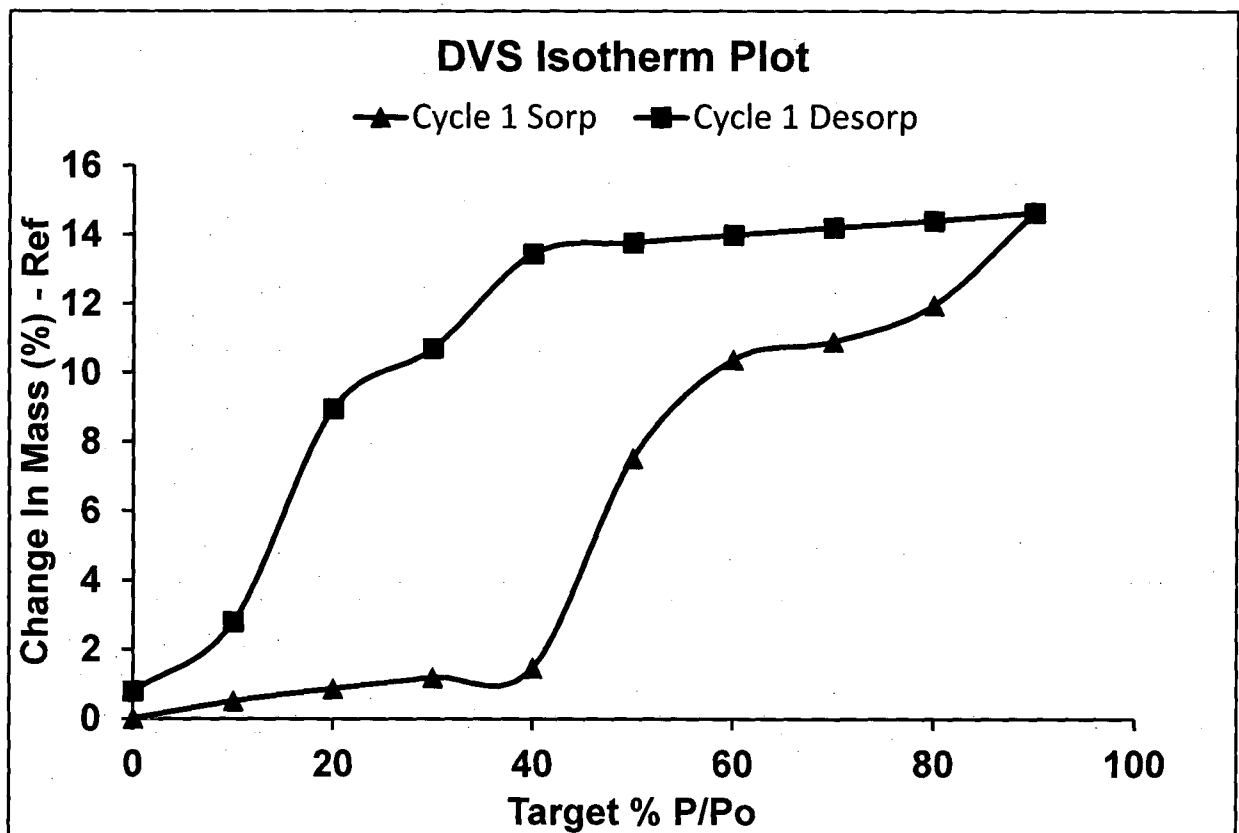


Figure 10

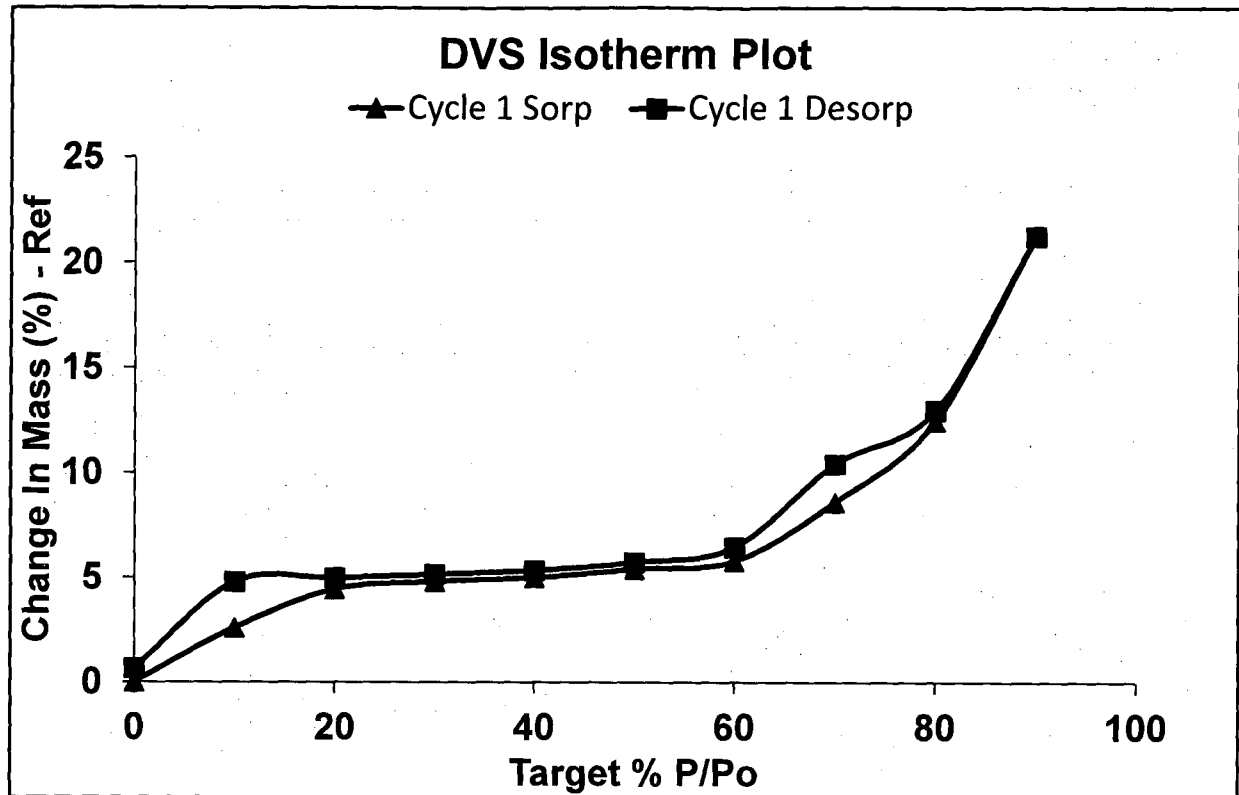


Figure 11

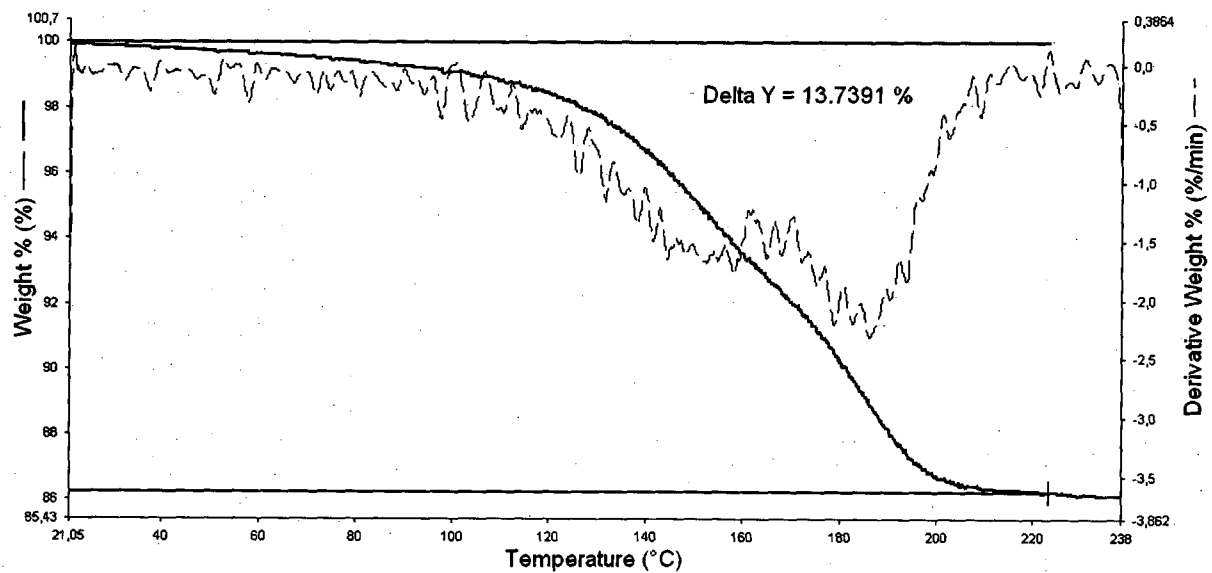


Figure 12

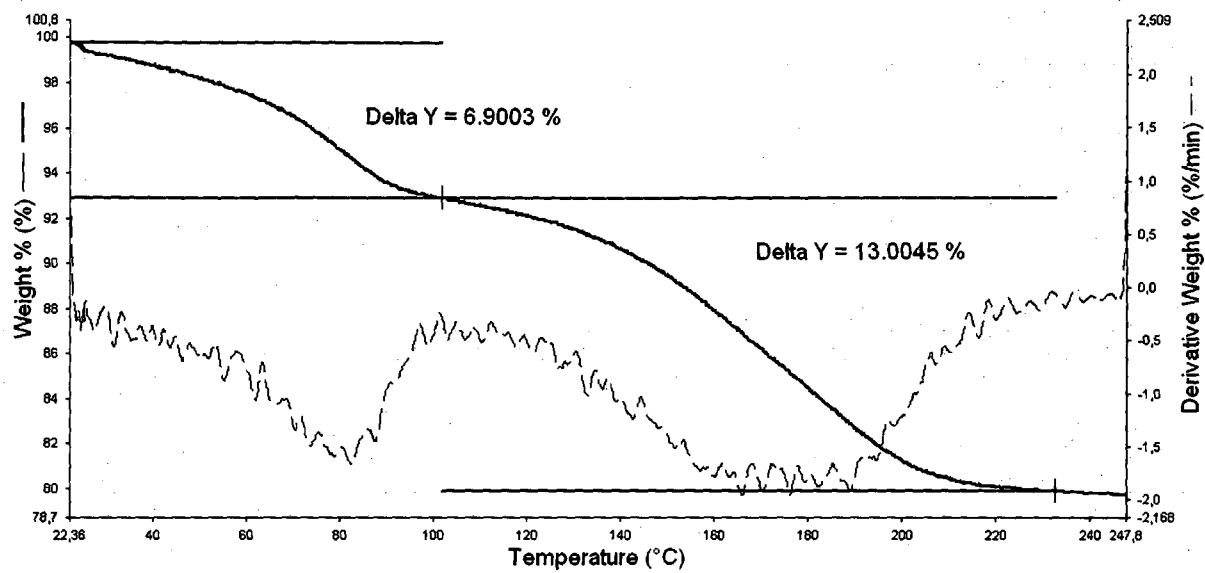


Figure 13

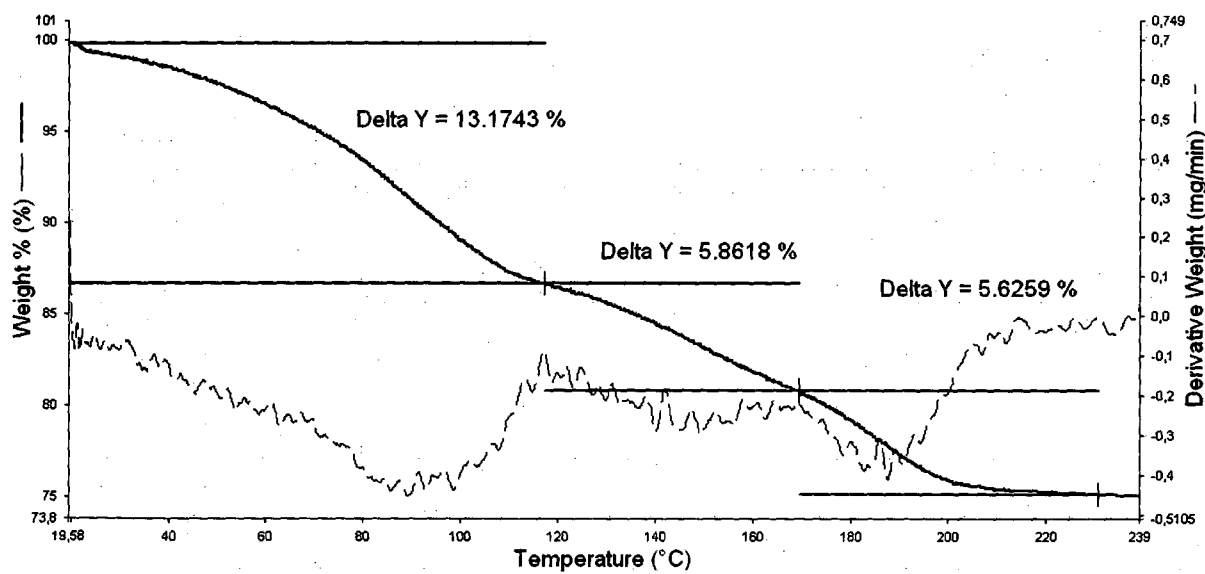


Figure 14

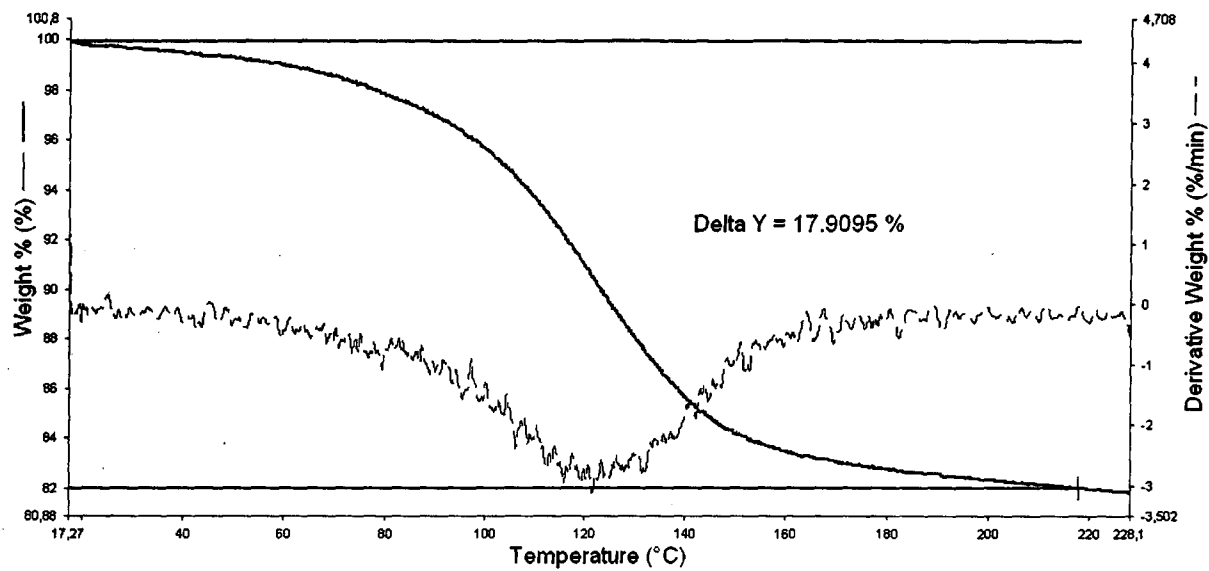


Figure 15

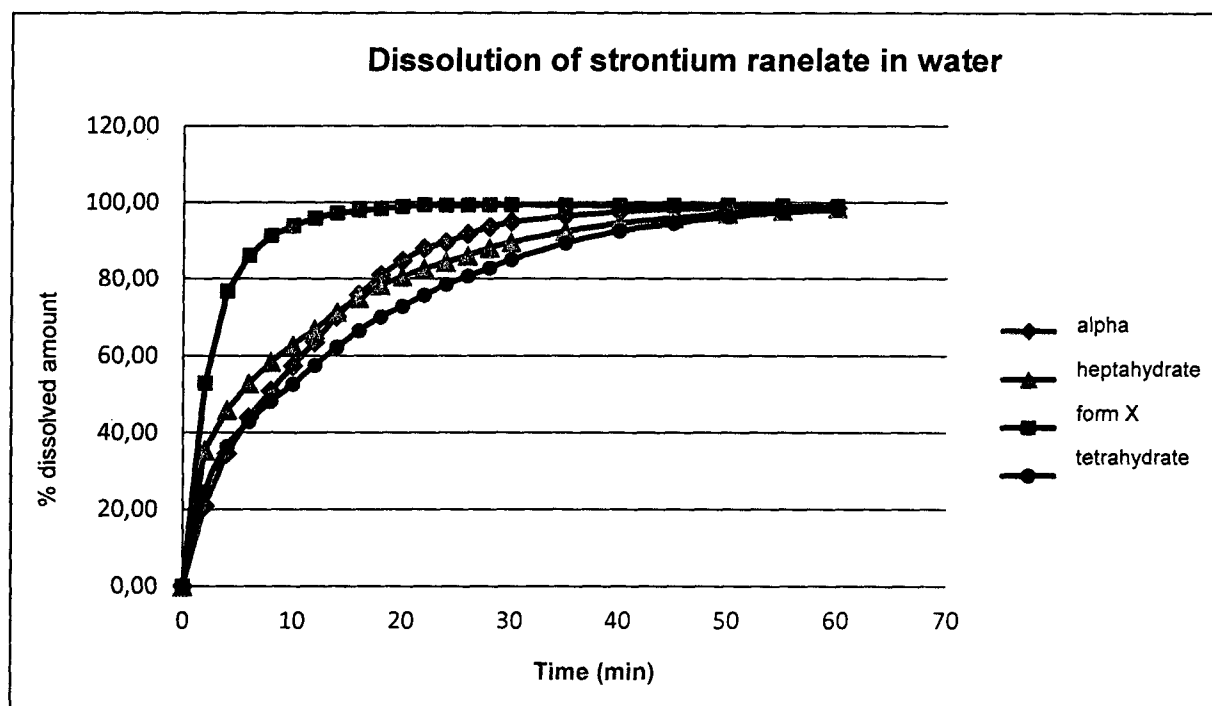


Figure 16

INTERNATIONAL SEARCH REPORT

International application No

PCT/CZ2012/000044

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D333/38

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

18 July 2012

Date of mailing of the international search report

27/07/2012

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Authorized officer

Jeanjean, Fabien

INTERNATIONAL SEARCH REPORT

International application No

PCT/CZ2012/000044

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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