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(54) Title: A CRYSTALLINE FORM OF A SALT OF SACUBITRIL AND A PROCESS OF ITS PREPARATION

(57) Abstract: The present invention provides a process for the preparation of a salt of sacubitril. Specifically, the present invention provides a process for the preparation of a sodium salt of sacubitril. The present invention further provides a crystalline Form I of sodium salt of sacubitril and its process of preparation.

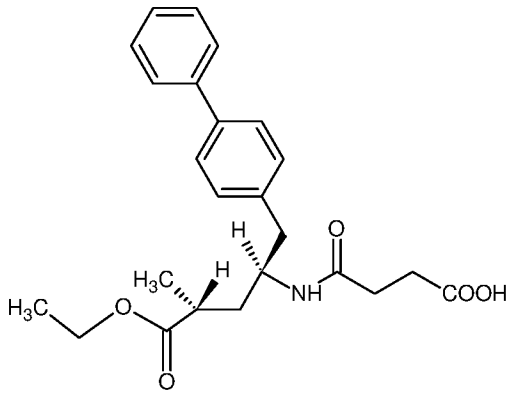
A CRYSTALLINE FORM OF A SALT OF SACUBITRIL AND A PROCESS OF ITS PREPARATION

Field of the Invention

The present invention provides a process for the preparation of a salt of sacubitril. Specifically, the present invention provides a process for the preparation of a sodium salt of sacubitril. The present invention further provides a crystalline Form I of sodium salt of sacubitril and its process of preparation.

Background of the Invention

U.S. Patent No. 5,217,996, PCT Publication Nos. WO 2008/031567, WO 2008/083967, WO 2009/090251, WO 2012/025502, WO 2012/025501, WO 2013/026773, and WO 2014/032627 provide processes for the preparation of sacubitril of Formula I or salts thereof.



FORMULA I

Summary of the Invention

The present invention provides a simple, industrially viable, and cost effective process for the preparation of a salt of sacubitril. Specifically, the present invention provides a process for the preparation of a sodium salt of sacubitril. The sodium salt of sacubitril produced by following the process disclosed herein, is non-hygroscopic, has better yield, purity, and flowability. The sodium salt of sacubitril produced by following the process disclosed herein is also easy to handle and is found to be stable. The present

invention further provides a crystalline Form I of sodium salt of sacubitril and its process of preparation.

Brief Description of the Drawings

Figure 1 depicts an X-ray Powder Diffraction (XRPD) pattern of a crystalline Form I of the sodium salt of sacubitril as prepared according to Example 1(a).

Figure 2 depicts an X-ray Powder Diffraction (XRPD) pattern of a crystalline Form I of the sodium salt of sacubitril as prepared according to Example 1(a) after 1 month of storage at 30°C ± 2°C at a relative humidity of 75% ± 5%.

Figure 3 depicts a Differential Scanning Calorimetry (DSC) pattern of a crystalline Form I of the sodium salt of sacubitril as prepared according to Example 1(a).

Detailed Description of the Invention

The term "about," as used herein, refers to any value, which lies within the range defined by a number up to ±10% of the value.

The term "ambient temperature," as used herein, refers to the temperature in the range of 25°C to 35°C.

The term "treating," "reacting," or "converting," as used herein, includes combining, mixing, triturating, suspending, contacting, or a combination thereof.

The term "stable," as used herein, refers to a salt of sacubitril, which does not convert to any other polymorphic form upon storage at 30°C ±2°C and 75% ±5% relative humidity and for which the chromatographic purity does not decrease on storage.

A first aspect of the present invention provides a process for the preparation of a sodium salt of sacubitril, wherein the process comprises treating sacubitril with a sodium salt of an organic acid.

Sacubitril is prepared by any method known in the art, for example, according to the processes disclosed in U.S. Patent No. 5,217,996 or *J. Med. Chem.* 1995, *38*, 1689-1700.

The sodium salt of an organic acid is selected from the group consisting of sodium 2-ethyl hexanoate, sodium octanoate, sodium formate, sodium acetate, sodium propionate, sodium butyrate, sodium valerate, sodium caproate, sodium oxalate, sodium lactate, sodium malate, sodium citrate, sodium benzoate, sodium succinate and a mixture thereof.

The treatment of sacubitril with the sodium salt of an organic acid is carried out in a solvent.

The solvent is selected from the group consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated hydrocarbons, aliphatic hydrocarbons, polar aprotic solvents, and mixtures thereof. Examples of aromatic hydrocarbons include toluene or benzene. Examples of ketones include acetone or methyl ethyl ketone. Examples of esters include ethyl acetate, n-propyl acetate, isopropyl acetate, or n-butyl acetate. Examples of ethers include methyl *t*-butyl ether or tetrahydrofuran. Examples of alkanols include primary, secondary, and tertiary alcohols having from one to six carbon atoms. Suitable alkanols include methanol, ethanol, 1-propanol, 2-propanol, or butanol. Examples of halogenated hydrocarbons include dichloromethane, chloroform, or 1,2-dichloroethane. Examples of aliphatic hydrocarbons include n-pentane, n-hexane, n-heptane, cyclohexane, or cycloheptane. Examples of polar aprotic solvents include N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile, or N-methylpyrrolidone.

Sacubitril is treated with the sodium salt of an organic acid at a temperature of about 10°C to about 60°C, for example, at about 20°C to about 55°C.

Sacubitril is treated with the sodium salt of an organic acid for about 2 hours to about 15 hours, for example, for about 2 hours to about 14 hours.

The sodium salt of sacubitril may be isolated by methods including concentration, distillation, decantation, filtration, evaporation, centrifugation, or a combination thereof, and may further be dried.

A second aspect of the present invention provides crystalline Form I of the sodium salt of sacubitril characterized by an X-ray powder diffraction (XRPD) pattern having peaks at d-spacings of about 14.1, 4.4, and 3.7 Å.

The crystalline Form I of sodium salt of sacubitril is further characterized by an XRPD pattern having additional peaks at d-spacings of about 7.4, 6.9, 5.4, 4.1, 3.4 and 3.3 Å.

The crystalline Form I of sodium salt of sacubitril is further characterized by an XRPD pattern as depicted in Figure 1.

Table 1 provides XRPD peak values (2θ), their corresponding d-spacing values (Å), and the relative intensities of the crystalline Form I of the sodium salt of sacubitril as prepared according to Example 1(a).

Position (±0.2° 2θ)	**d-spacing [Å]**	**Relative Intensity (%)**
3.1	28.2	8.6
6.3	14.1	37.0
7.3	12.2	8.8
7.8	11.3	5.3
9.3	9.5	1.4
12.0	7.4	14.0
12.5	7.1	8.3
12.8	6.9	10.6
13.0	6.8	3.1
13.8	6.4	10.2
15.6	5.7	6.4
16.5	5.4	12.8
16.9	5.2	3.9
17.3	5.1	3.7
17.6	5.0	4.1
18.4	4.8	9.9
18.7	4.7	5.5
19.1	4.6	6.3
20.0	4.4	100.0
21.6	4.1	12.9
22.0	4.0	4.4
22.4	4.0	10.0
22.7	3.9	5.5
23.8	3.7	26.5
24.2	3.7	12.6
25.0	3.6	10.1
26.3	3.4	22.1
26.9	3.3	12.4
27.8	3.2	8.3
28.6	3.1	7.7
29.5	3.0	2.5
30.3	2.9	2.9
31.4	2.8	6.6
31.8	2.8	6.6
32.2	2.8	6.1
33.9	2.6	1.3
35.9	2.5	7.4
37.1	2.4	3.1
37.8	2.4	1.0

The crystalline Form I of the sodium salt of sacubitril prepared by the present invention is found to be stable after storing at 30°C ±2°C/ 75% ±5% RH for 1 month as depicted in Figure 2.

The crystalline Form I of the sodium salt of sacubitril is characterized by a differential scanning calorimetry (DSC) thermogram as depicted in Figure 3.

The crystalline Form I of the sodium salt of sacubitril is characterized by a DSC thermogram having endothermic peaks at about 161.8°C and 247.2°C.

A third aspect of the present invention provides a process for the preparation of a crystalline Form I of the sodium salt of sacubitril, wherein the process comprises treating sacubitril with a sodium containing reagent.

Sacubitril is prepared by any method known in the art, for example, according to methods disclosed in U.S. Patent No. 5,217,996 or *J. Med. Chem.* 1995, *38*, 1689-1700.

The sodium containing reagent is selected from the group consisting of sodium methoxide, sodium carbonate, sodium bicarbonate, sodium chloride, sodium bromide, sodium 2-ethyl hexanoate, sodium octanoate, sodium formate, sodium acetate, sodium propionate, sodium butyrate, sodium valerate, sodium caproate, sodium oxalate, sodium lactate, sodium malate, sodium citrate, sodium benzoate, sodium succinate and a mixture thereof.

The treatment of sacubitril with a sodium containing reagent is carried out in a solvent.

The solvent is selected from the group consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated hydrocarbons, aliphatic hydrocarbons, polar aprotic solvents, and mixtures thereof. Examples of aromatic hydrocarbons include toluene or benzene. Examples of ketones include acetone or methyl ethyl ketone. Examples of esters include ethyl acetate, n-propyl acetate, isopropyl acetate, or n-butyl acetate. Examples of ethers include methyl *t*-butyl ether or tetrahydrofuran. Examples of alkanols include primary, secondary, and tertiary alcohols having from one to six carbon atoms. Suitable alkanols include methanol, ethanol, 1-propanol, 2-propanol, or butanol. Examples of halogenated hydrocarbons include dichloromethane, chloroform, or 1,2-dichloroethane. Examples of aliphatic hydrocarbons include n-pentane, n-hexane, n-heptane, cyclohexane, or cycloheptane. Examples of polar aprotic solvents include N,N-

dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile, or N-methylpyrrolidone.

Sacubitril is treated with the sodium containing reagent at a temperature of about 10°C to about 60°C, for example, at about 20°C to about 55°C.

Sacubitril is treated with the sodium containing reagent for about 2 hours to about 15 hours, for example, for about 2 hours to about 14 hours.

The crystalline Form I of the sodium salt of sacubitril may be isolated by methods including concentration, distillation, decantation, filtration, evaporation, centrifugation, or a combination thereof, and may further be dried.

A fourth aspect of the present invention provides use of a crystalline Form I of the sodium salt of sacubitril for the preparation of a pharmaceutical active agent.

A fifth aspect of the present invention provides use of a crystalline Form I of the sodium salt of sacubitril for the preparation of a pharmaceutical composition comprising solid forms of valsartan and sacubitril.

A sixth aspect of the present invention provides use of a crystalline Form I of the sodium salt of sacubitril for the preparation of a medicament for treating or preventing a cardiovascular or renal condition or a medical condition responsive to valsartan and/or sacubitril in a patient in need thereof.

A seventh aspect of the present invention provides use of a crystalline Form I of the sodium salt of sacubitril for the preparation of a medicament comprising a solid form of sacubitril and valsartan for treating or preventing a cardiovascular or renal condition or a medical condition responsive to valsartan and/or sacubitril in a patient in need thereof.

While the present invention has been described in terms of its specific aspects and embodiments, certain modifications and equivalents will be apparent to those skilled in the art, and are intended to be included within the scope of the present invention.

Methods

XRPD of the samples was determined by using a PANalytical® instrument; Model X'pert PRO; Detector: X'celerator®.

DSC was recorded using Mettler Toledo DSC 82le.

The following examples are for illustrative purposes only and should not be construed as limiting the scope of the invention in any way.

EXAMPLE

Example 1: Preparation of a sodium salt of sacubitril

(a) Sacubitril (24 g) was added to methyl *t*-butyl ether (350 mL) at 20°C to 25°C and the mixture was stirred for 30 minutes. Sodium-2-ethyl hexonoate (10.84 g) was added to the mixture. The reaction mixture was heated to 50°C to 55°C for 2.5 hours. The reaction mixture was cooled to 20°C to 25°C and stirred for 3 hours. The reaction mixture was filtered under nitrogen atmosphere. The reaction mixture was washed with methyl *t*-butyl ether (50 mL) under nitrogen atmosphere. The product obtained was dried under nitrogen atmosphere for 10 minutes and then dried under 650 mm Hg to 680 mm Hg of pressure for 24 hours at 40°C to 45°C to obtain the title compound.

Yield: 19 g.

Chromatographic purity (Initial): 99.85%

Initial X-ray Powder Diffraction (XRPD) pattern is depicted in Figure 1.

Chromatographic purity after 1 month of storage (at 30°C ±2°C/75% ±5% RH): 99.76%.

X-ray Powder Diffraction (XRPD) pattern after 1 month of storage is depicted in Figure 2.

(b) Sacubitril (50 g) was added to methyl *t*-butyl ether (600 mL) at 20°C to 25°C and the mixture was stirred for 20 minutes. Sodium-2-ethyl hexonoate (20.2 g) was added to the mixture. The reaction mixture was heated to 50°C to 55°C for 2 hours. Methyl *t*-butyl ether (200 mL) was added to the reaction mixture and cooled to 20°C to 25°C. The reaction mixture was stirred at 20°C to 25°C for 1 hour. The reaction mixture was filtered under nitrogen atmosphere. The reaction mixture was washed with methyl *t*-butyl ether (100 mL) under nitrogen atmosphere. The product obtained was dried under nitrogen atmosphere for 30 minutes and then dried under 650 mm Hg to 680 mm Hg of pressure for 20 hours to obtain the title compound.

Yield: 47 g.

(c) Sacubitril (10 g) was added to methyl *t*-butyl ether (100 mL) at 20°C to 25°C and the mixture was stirred for 15 minutes. Sodium-2-ethyl hexonoate (3.9 g) was added to the mixture. The reaction mixture was heated to 50°C to 55°C for 2 hours. The reaction mixture was cooled to 40°C to 45°C. The reaction mixture was filtered under nitrogen atmosphere and then washed with methyl *t*-butyl ether (50 mL) under nitrogen atmosphere. The product obtained was dried under 650 mm Hg to 680 mm Hg of pressure for 16 hours at 40°C to 45°C to obtain the title compound.

Yield: 8.5 g.

(d) Sodium-2-ethyl hexanoate (4 g) was added to toluene (100 mL) and toluene was recovered at 123°C to 135°C. The mixture was cooled to 40°C to 45°C. Sacubitril (10 g) in methyl *t*-butyl ether (150 mL) was added to the reaction mixture. The reaction mixture was heated to 50°C to 55°C and then stirred for 2 hours. The reaction mixture was filtered under nitrogen atmosphere at 20°C to 25°C. The reaction mixture was washed with methyl *t*-butyl ether (50 mL) under nitrogen atmosphere. The product obtained was dried under 650 mm Hg to 680 mm Hg of pressure for 16 hours at 40°C to 45°C to obtain the title compound.

Yield: 5.5 g.

(e) Sacubitril (50 g) was added to methyl *t*-butyl ether (500 mL) at 20°C to 25°C and the mixture was stirred for 15 minutes. Sodium-2-ethyl hexonoate (21.6 g) was added to the mixture. The reaction mixture was heated to 50°C to 55°C for 14 hours. The reaction mixture was cooled to 35°C to 40°C. The reaction mixture was filtered under nitrogen atmosphere. The reaction mixture was washed with methyl *t*-butyl ether (400 mL) under nitrogen atmosphere. The product obtained was dried under 650 mm Hg to 680 mm Hg of pressure for 16 hours at 40°C to 45°C to obtain the title compound.

Yield: 49 g.

We Claim:

1. A process for the preparation of a sodium salt of sacubitril, wherein the process comprises treating sacubitril with a sodium salt of an organic acid.

2. The process according to claim 1, wherein the sodium salt of an organic acid is selected from the group consisting of sodium 2-ethyl hexanoate, sodium octanoate, sodium formate, sodium acetate, sodium propionate, sodium butyrate, sodium valerate, sodium caproate, sodium oxalate, sodium lactate, sodium malate, sodium citrate, sodium benzoate, sodium succinate and a mixture thereof.

3. The process according to claim 1, wherein the treatment of sacubitril with the sodium salt of an organic acid is carried out in a solvent.

4. The process according to claim 3, wherein the solvent is selected from the group consisting of water, an aromatic hydrocarbon, a ketone, an ester, an ether, an alkanol, a halogenated hydrocarbon, an aliphatic hydrocarbon, a polar aprotic solvent, and a mixture thereof.

5. The process according to claim 4, wherein the aromatic hydrocarbon is selected from the group consisting of toluene and benzene.

6. The process according to claim 4, wherein the ketone is selected from the group consisting of acetone and methyl ethyl ketone.

7. The process according to claim 4, wherein the ester is selected from the group consisting of ethyl acetate, n-propyl acetate, isopropyl acetate, and n-butyl acetate.

8. The process according to claim 4, wherein the ether is selected from the group consisting of methyl *t*-butyl ether and tetrahydrofuran.

9. The process according to claim 4, wherein the alkanols are selected from the group consisting of primary, secondary, and tertiary alcohols having from one to six carbon atoms.

10. The process according to claim 4, wherein the halogenated hydrocarbon is selected from the group consisting of dichloromethane, chloroform, and 1,2-dichloroethane.

11. The process according to claim 4, wherein the aliphatic hydrocarbon is selected from the group consisting of n-pentane, n-hexane, n-heptane, cyclohexane, and cycloheptane.

12. The process according to claim 4, wherein the polar aprotic solvent is selected from the group consisting of N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile, and N-methylpyrrolidone.

13. The process according to claim 1, wherein the treatment of sacubitril with the sodium salt of the organic acid is performed at a temperature of about 10°C to about 60°C.

14. Crystalline Form I of a sodium salt of sacubitril characterized by an X-ray powder diffraction (XRPD) pattern having peaks at d-spacings of about 14.1, 4.4, and 3.7 Å.

15. The crystalline Form I of the sodium salt of sacubitril, according to claim 14, further characterized by an XRPD pattern having peaks at d-spacings of about 7.4, 6.9, 5.4, 4.1, 3.4 and 3.3 Å.

16. A crystalline Form I of a sodium salt of sacubitril characterized by an XRPD pattern as depicted in Figure 1.

17. A crystalline Form I of a sodium salt of sacubitril characterized by a differential scanning calorimetry (DSC) thermogram as depicted in Figure 3.

18. A crystalline Form I of a sodium salt of sacubitril characterized by a DSC thermogram having endothermic peaks at about 161.8°C and 247.2°C

19. A process for the preparation of a crystalline Form I of a sodium salt of sacubitril, wherein the process comprises treating sacubitril with a sodium containing reagent.

20. The process according to claim 19, wherein the sodium containing reagent is selected from the group consisting of sodium methoxide, sodium carbonate, sodium bicarbonate, sodium chloride, sodium bromide, sodium 2-ethyl hexanoate, sodium octanoate, sodium formate, sodium acetate, sodium propionate, sodium butyrate, sodium valerate, sodium caproate, sodium oxalate, sodium lactate, sodium malate, sodium citrate, sodium benzoate, sodium succinate and a mixture thereof.

21. The process according to claim 19, wherein the treatment of sacubitril with a sodium containing reagent is carried out in a solvent.

22. The process according to claim 21, wherein the solvent is selected from the group consisting of water, an aromatic hydrocarbon, a ketone, an ester, an ether, an alkanol, a halogenated hydrocarbon, an aliphatic hydrocarbon, a polar aprotic solvent, and a mixture thereof.

23. The process according to claim 22, wherein the aromatic hydrocarbon is selected from the group consisting of toluene and benzene.

24. The process according to claim 22, wherein the ketone is selected from the group consisting of acetone and methyl ethyl ketone.

25. The process according to claim 22, wherein the ester is selected from the group consisting of ethyl acetate, n-propyl acetate, isopropyl acetate, and n-butyl acetate.

26. The process according to claim 22, wherein the ether is selected from the group consisting of methyl *t*-butyl ether and tetrahydrofuran.

27. The process according to claim 22, wherein the alkanols is selected from the group consisting of primary, secondary, and tertiary alcohols having from one to six carbon atoms.

28. The process according to claim 22, wherein the halogenated hydrocarbon is selected from the group consisting of dichloromethane, chloroform, and 1,2-dichloroethane.

29. The process according to claim 22, wherein the aliphatic hydrocarbon is selected from the group consisting of n-pentane, n-hexane, n-heptane, cyclohexane, and cycloheptane.

30. The process according to claim 22, wherein the polar aprotic solvent is selected from the group consisting of N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile, and N-methylpyrrolidone.

31. The process according to claim 19, wherein the treatment of sacubitril with a sodium containing reagent is performed at a temperature of about 10°C to about 60°C.

32. Use of a crystalline Form I of sodium salt of sacubitril for the preparation of a pharmaceutical active agent.

33. Use of a crystalline Form I of sodium salt of sacubitril for the preparation of a pharmaceutical composition comprising solid forms of valsartan and sacubitril.

34. Use of a crystalline Form I of sodium salt of sacubitril for the preparation of a medicament for treating or preventing cardiovascular or renal condition or a medical condition responsive to valsartan and/or sacubitril in a patient in need thereof.

35. Use of a crystalline Form I of sodium salt of sacubitril for the preparation of a medicament comprising solid form of sacubitril and valsartan for treating or preventing cardiovascular or renal condition or a medical condition responsive to valsartan and/or sacubitril in a patient in need thereof.

Figure 1 depicts an X-ray Powder Diffraction (XRPD) pattern of a sodium salt of sacubitril as prepared according to Example 1(a).

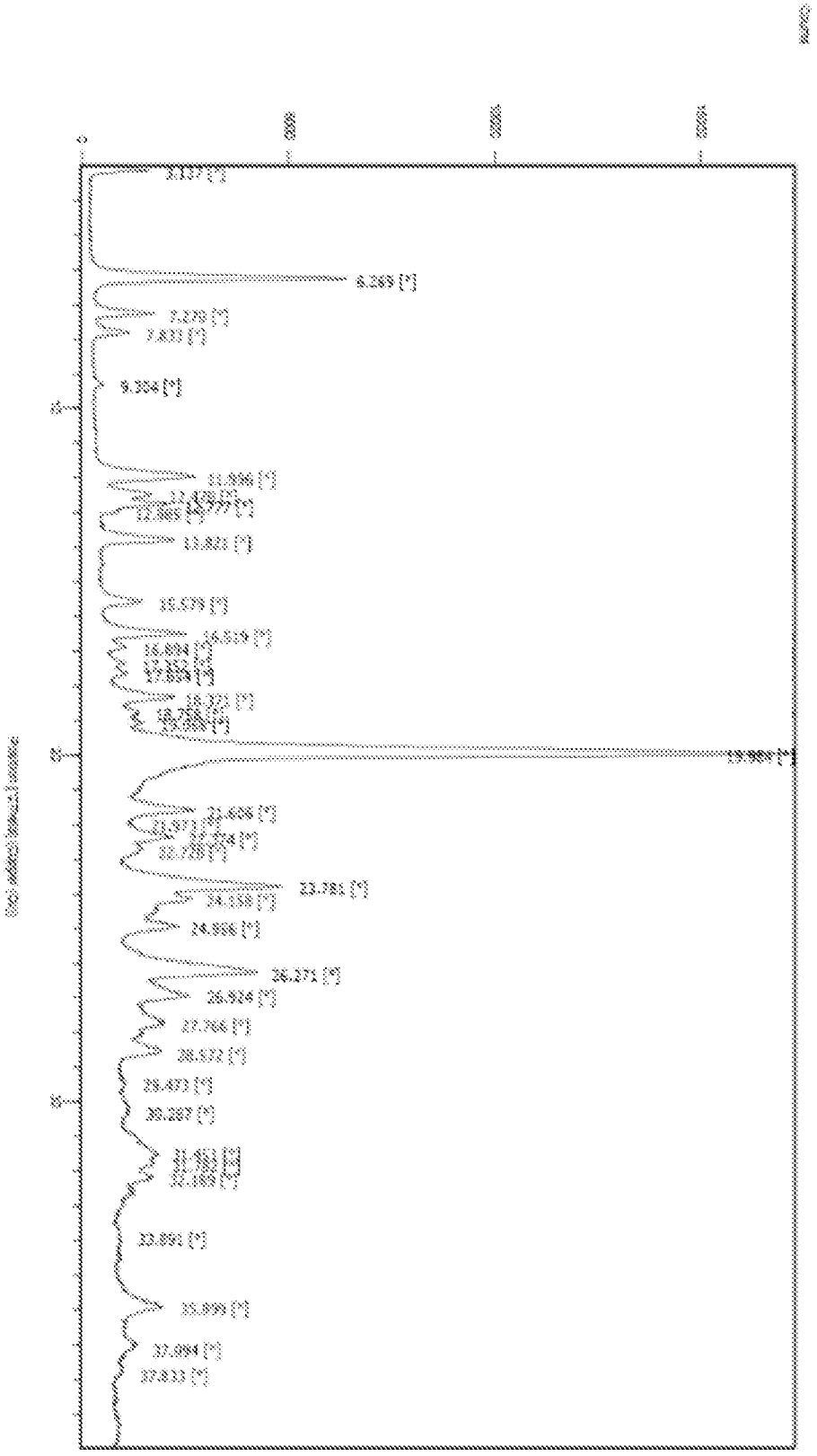


Figure 2 depicts an X-ray Powder Diffraction (XRPD) pattern of a sodium salt of sacubitril as prepared according to Example 1(a) after 1 month of storage at 40°C ±2°C at a relative humidity of 75% ±5%.

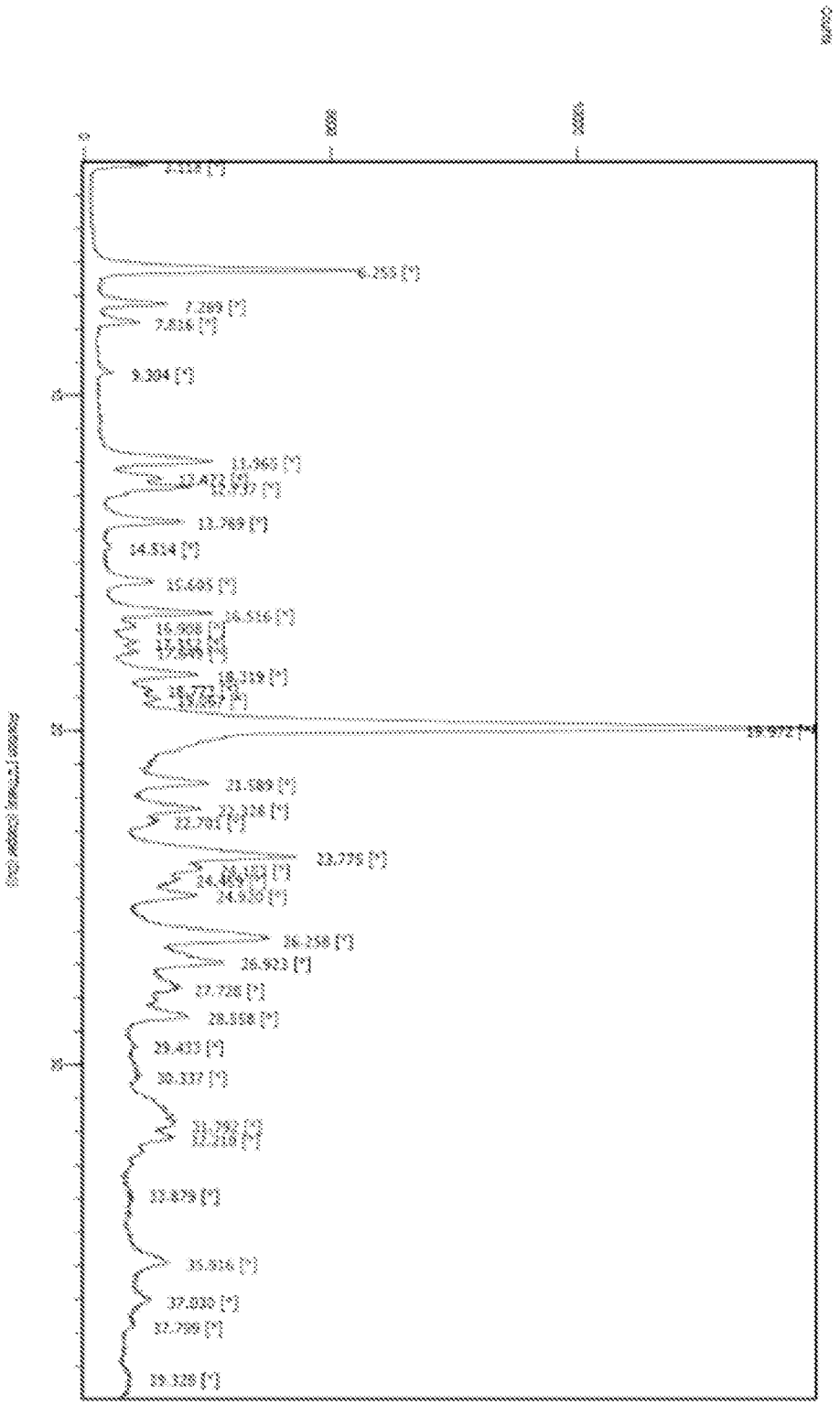
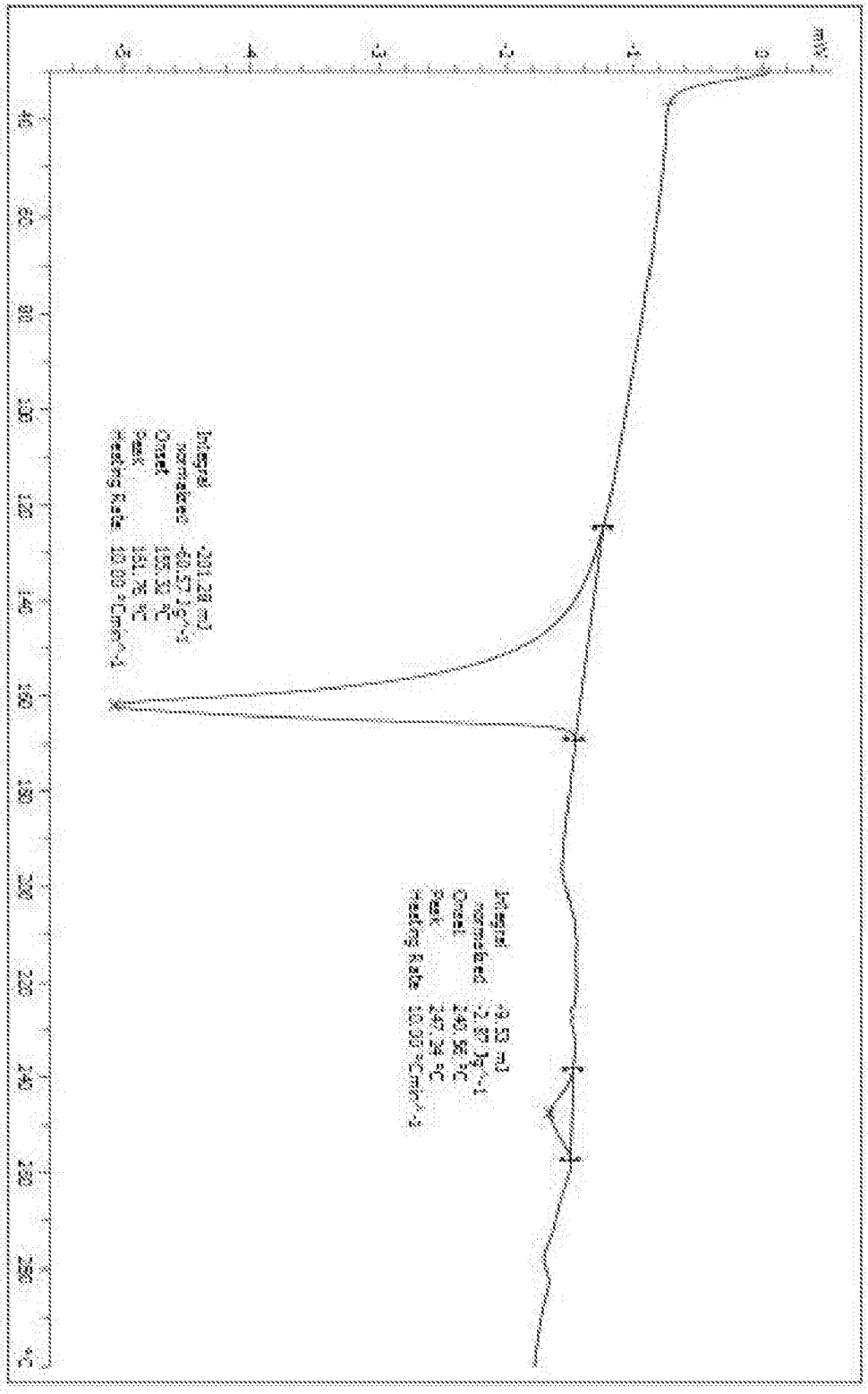


Figure 3 depicts a Differential Scanning Calorimetry (DSC) pattern of a crystalline Form I of sodium salt of sacubitril as prepared according to Example 1(a).



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB17/52673

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61P 9/12, 9/04; A61K 31/216; C07C 233/47, 231/24, 231/12 (2017.01)

CPC - A61K 31/216; C07C 233/47, 231/24, 231/12

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)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008/083967 A2 (NOVARTIS AG) 17 July 2008; page 40, scheme 5	1-13
Y	US 4277601 A (THOMPSON, E et al.) 7 July 1981; column 1, lines 65-68; column 2, lines 1-28	1-13
X, P	WO 2017/033212 A1 (ACTAVIS GROUP PTC EHF) 2 March 2017; entire document	19, 32-35
A	US 5217996 A (KSANDER, G) 8 June 1993; entire document	1-35
A	CN 105461587 A (SHANGHAI HANSEN BIOLOGICAL MEDICINE SCIENCE & TECH CO LTD) 6 April 2016; abstract; claim 1	14-31
A	WO 2016/051393 A2 (CRYSTAL PHARMATECH INC.) 7 April 2016; page 5, lines 26-28; figure 2	14-18
A	CN 105461647 A (SICHUAN HAISCO PHARMACEUTICAL CO LTD) 6 April 2016; abstract; paragraph [0009]	14-16, 19-35
A	US 2015/0057322 A1 (FENG, L et al.) 26 February 2015; claims 1-8	32-35

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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