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(54) **Title:** CRYSTALLINE FORM OF LCZ-696

(57) **Abstract:** The present application relates to crystalline form of a supra-molecular complex of valsartan and sacubitril which is known as LCZ-696 and process for preparation thereof.



WO 2016/151525 A1

CRYSTALLINE FORM OF LCZ-696

FIELD OF INVENTION

The present application relates to crystalline form of a supra-molecular complex of valsartan and sacubitril and process for preparation thereof.

BACKGROUND OF INVENTION

US Patent No. 8877938 discloses a crystalline form of supra-molecular complex of valsartan and sacubitril. It is known in the literature as LCZ-696 (Tetrahedron Letters 53, 2012, 275–276). The US'938 patent characterizes the crystalline form of LCZ-696 by XRD having peaks at 4.5, 5.5, 5.6, 9.9, 12.8, 15.7, 17.0, 17.1, 17.2, 18.3, 18.5, 19.8, 21.5, 21.7, 23.2, 23.3, 24.9, 25.3, 27.4, 27.9, 28.0 and 30.2 °2 θ . But the US'938 patent does not provide the XRD figure of the compound. Tetrahedron Letters 53, 2012, 275–276 discloses the XRD figure of LCZ-696.

In general, polymorphism refers to the ability of a substance to exist as two or more crystalline phases that have different spatial arrangements and/or conformations of molecules in their crystal lattices. Thus, “polymorphs” refer to different crystalline forms of the same pure substance in which the molecules have different spatial arrangements of the molecules, atoms, and/or ions forming the crystal. Different polymorphs may have different physical properties such as melting points, solubilities, etc. The variation in solid forms may appreciably influence the pharmaceutical properties, such as bioavailability, handling properties, dissolution rate, and stability, and in turn such properties can significantly influence the processing, shelf life, and commercial acceptance of a polymorphic form. For these reasons, regulatory authorities require drug manufacturing companies to put efforts into identifying all solid forms, e.g., crystalline, amorphous, solvates, stable dispersions with a pharmaceutically acceptable carriers, etc., of new drug substances.

The existence and possible numbers of polymorphic forms for a given compound cannot be predicted, and there are no “standard” procedures that can be used to prepare polymorphic forms of a substance. This is well-known in the art, as reported, for example, by A. Goho, “Tricky Business,” Science News, Vol. 166(8), August 2004.

Hence, there remains a need for alternate polymorphic forms of LCZ-696 and process for preparing them.

SUMMARY OF INVENTION

One aspect of the present application relates to a crystalline form I of LCZ-696 characterized by its powder X-ray diffraction (PXRD) pattern having peaks at about 4.24, 5.05, 9.96, 12.68 and $14.88 \pm 0.2^\circ 2\theta$.

Another aspect of the present application relates to a crystalline form I of LCZ-696 that can be characterized by a PXRD pattern having peaks located substantially as illustrated in the pattern of Figure 1 or Figure 2 or Figure 3.

Yet another aspect of the present application relates to a crystalline form I of LCZ-696 that can be characterized by a DSC pattern as illustrated in the Figure 4 or Figure 5.

Still another aspect of the present application relates to a crystalline form I of LCZ-696 that can be characterized by a TGA pattern as illustrated in the Figure 6.

Another aspect of the present application relates to a process for preparing a crystalline form I of LCZ-696 comprising the steps of:

- (i) adding an ether solvent to LCZ-696;
- (ii) stirring the reaction mixture of step (i) for sufficient time;
- (iii) isolating the precipitated material from step (ii).

Still another aspect of the present application relates to a pharmaceutical composition comprising a crystalline form I of LCZ-696 and at least one pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is an illustration of a PXRD pattern of crystalline form I of LCZ-696 as obtained from Example 1.

Figure 2 is an illustration of a PXRD pattern of crystalline form I of LCZ-696 as obtained from Example 2.

Figure 3 is an illustration of a PXRD pattern of crystalline form I of LCZ-696 as obtained from Example 3.

Figure 4 is an illustration of a DSC pattern of crystalline form I of LCZ-696 as obtained from Example 2.

Figure 5 is an illustration of a DSC pattern of crystalline form I of LCZ-696 as obtained from Example 3.

Figure 6 is an illustration of a TGA pattern of crystalline form I of LCZ-696 as obtained from Example 2.

DETAILED DESCRIPTION OF INVENTION

One aspect of the present application relates to a crystalline form I of LCZ-696 characterized by its powder X-ray diffraction (PXRD) pattern having peaks at about 4.24, 5.05, 9.96, 12.68 and $14.88 \pm 0.2^\circ 2\theta \pm 0.2^\circ 2\theta$.

Another aspect of the present application relates to a crystalline form I of LCZ-696 that can be characterized by a PXRD pattern having peaks located substantially as illustrated in the pattern of Figure 1 or Figure 2 or Figure 3.

Yet another aspect of the present application relates to a crystalline form I of LCZ-696 that can be characterized by a DSC pattern as illustrated in the Figure 4 or Figure 5.

Still another aspect of the present application relates to a crystalline form I of LCZ-696 that can be characterized by a TGA pattern as illustrated in the Figure 6.

In one embodiment, the sodium content of the crystalline form I of LCZ-696 of the present application was measured by Atomic Absorption Spectroscopy (AAS). It is observed that content of sodium in the crystalline form I of LCZ-696 is about 7% w/w.

In another embodiment, the water content of the crystalline form I of LCZ-696 of the present application was measured by Karl-Fischer technique. It is observed that water content in the crystalline form I of LCZ-696 of the present application is about 5 % w/w to about 7.5 % w/w i.e. about 2.6 moles of water to about 4 moles of water per mole of LCZ-696. Specifically, the water content in the crystalline form I of LCZ-696 of the present application is about 6 % w/w to about 7 % w/w i.e. about 3.1 moles of water to about 3.7 moles of water per mole of LCZ-696. More specifically, the water content in the crystalline form I of LCZ-696 of the present application is about 6.5 % w/w i.e. about 3.5 moles of water per mole of LCZ-696.

In still another embodiment, the TGA pattern of form I of LCZ-696 of the present application shows about 5.6% of weight loss.

In another embodiment, the content of residual solvent was analyzed by Gas Chromatography (GC). It is observed that the organic volatile impurities in form I of LCZ-696 of the present application show presence of methyl tert-butyl ether as the only organic volatiles. Methyl tert-butyl ether is a Class 3 solvent. According to USP30-NF25 (United States Pharmacopoeia 30 – National Formulary 25) Class 3 residual solvents are limited to not more than 50 mg per day (corresponding to 5000 ppm or 0.5% under Option 1). The content of methyl tert-butyl ether in form I of LCZ-696 of the present application is below the limit of 5000 ppm. Specifically, the content of methyl tert-butyl ether in form I of LCZ-696 of the present application is below the limit of 1000 ppm. More specifically, content of methyl tert-butyl ether in form I of LCZ-696 of the present application is below the limit of 500 ppm.

The crystalline form I of LCZ-696 of the present application is stable and has excellent physico-chemical properties. The crystalline form I of LCZ-696 of the present application may be easily formulated into a pharmaceutical composition comprising LCZ-696.

Yet another aspect of the present application relates to a process for preparing a crystalline form I of LCZ-696 comprising the steps of:

- (i) adding an ether solvent to LCZ-696;
- (ii) stirring the reaction mixture of step (i) for sufficient time;
- (iii) isolating crystalline form I of LCZ-696.

The ether solvent of step (i) includes but not limited to diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran and the like. The LCZ-696 used in step (i) may be of any crystalline nature or a crude product. Alternatively, LCZ-696 used in step (i) may be obtained by a reaction of valsartan and sacubitril in an organic solvent or mixture thereof in presence of sodium hydroxide and evaporating the solvent.

The reaction mixture of step (i) may be stirred for about 5 minutes to about 15 hours at a temperature of about 15 °C to about boiling point of the solvent. Specifically, the reaction mixture of step (i) may be stirred for about 1 hour to about 12 hours at about 25 °C.

The resulted material of step (ii) may be isolated by techniques known in the art e.g. evaporation, distillation, filtration of isolated solid and the like. The solid may be washed with an ether solvent. Suitable temperatures for isolation may be less than about 25 °C, less than about 10 °C, or any other suitable temperatures. Filtration can be achieved by any means known in the art. The solid may optionally be dried. The drying may be carried out at atmospheric pressure or above, or under reduced pressures, specifically at temperatures less than about 80 °C and more specifically less than about 60 °C and most specifically at about 40 °C. The drying may be carried out for any time period

required for obtaining a desired product quality, such as from about 5 minutes to about 24 hours, or longer.

The obtained crystalline form I of LCZ-696 may optionally be subjected to a particle size reduction procedure to produce desired particle sizes and distributions. Milling or micronization may be performed before drying, or after the completion of drying of crystalline form I of LCZ-696. Equipment that may be used for particle size reduction includes but not limited to ball mill, roller mill, hammer mill, and jet mill.

Yet another aspect of the present application relates to a pharmaceutical composition comprising a crystalline form I of LCZ-696 and at least one pharmaceutically acceptable excipient. Crystalline form I of LCZ-696 together with one or more pharmaceutically acceptable excipients of the present application may be formulated as: solid oral dosage forms such as, but not limited to, powders, granules, pellets, tablets, and capsules; liquid oral dosage forms such as, but not limited to, syrups, suspensions, dispersions, and emulsions; and injectable preparations such as, but not limited to, solutions, dispersions, and freeze dried compositions. Formulations may be in the forms of immediate release, delayed release, or modified release. Further, immediate release compositions may be conventional, dispersible, chewable, mouth dissolving, or flash melt preparations, and modified release compositions that may comprise hydrophilic or hydrophobic, or combinations of hydrophilic and hydrophobic, release rate controlling substances to form matrix or reservoir or combination of matrix and reservoir systems. The compositions may be prepared using any one or more of techniques such as direct blending, dry granulation, wet granulation, and extrusion and spheronization. Compositions may be presented as uncoated, film coated, sugar coated, powder coated, enteric coated, and modified release coated.

Pharmaceutically acceptable excipients that are useful in the present application include, but are not limited to: diluents such as starches, pregelatinized starches, lactose, powdered celluloses, microcrystalline celluloses, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar, and the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinylpyrrolidones, hydroxypropyl celluloses,

hydroxypropyl methyl celluloses, pregelatinized starches, and the like; disintegrants such as starches, sodium starch glycolate, pregelatinized starches, croscopoidones, croscarmellose sodium, colloidal silicon dioxide, and the like; lubricants such as stearic acid, magnesium stearate, zinc stearate, and the like; glidants such as colloidal silicon dioxide and the like; solubility or wetting enhancers such as anionic, cationic, or neutral surfactants; complex forming agents such as various grades of cyclodextrins and resins; and release rate controlling agents such as hydroxypropyl celluloses, hydroxymethyl celluloses, hydroxypropyl methylcelluloses, ethylcelluloses, methylcelluloses, various grades of methyl methacrylates, waxes, and the like. Other pharmaceutically acceptable excipients that are useful include, but are not limited to, film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants, and the like.

The PXRD conditions for the measurement of PXRD peaks of crystalline form I of LCZ-696 as obtained from Example 1 of the present application are as follows:

Range: $3^{\circ} 2\theta$ to $40^{\circ} 2\theta$ in conventional reflection mode

Instrument: PANalytical X-ray Diffractometer

Detector: X'celerator

Source: Copper K-alpha radiation (1.5418 Angstrom).

The PXRD conditions for the measurement of PXRD peaks of crystalline form I of LCZ-696 as obtained from Example 2 and Example 3 of the present application are as follows:

Range: $3^{\circ} 2\theta$ to $40^{\circ} 2\theta$ in conventional reflection mode

Instrument: Bruker AXS D8 Advance Powder X-ray Diffractometer

Detector: Lynxeye

Source: Copper K-alpha radiation (1.5418 Angstrom).

DEFINITIONS

The following definitions are used in connection with the present application unless the context indicates otherwise.

The terms "about," "general, 'generally," and the like are to be construed as modifying a term or value such that it is not an absolute. Such terms will be defined by the circumstances and the terms that they modify as those terms are understood by those of skill in the art. This includes, at very least, the degree of expected experimental error, technique error and instrument error for a given technique used to measure a value.

A name used herein to characterize a crystalline form should not be considered limiting with respect to any other substance possessing similar or identical physical and chemical characteristics, but rather it should be understood that these designations are mere identifiers that should be interpreted according to the characterization information also presented herein.

All percentages and ratios used herein are by weight of the total composition and all measurements made are at about 25°C and about atmospheric pressure, unless otherwise designated. All temperatures are in degrees Celsius unless specified otherwise. As used herein, the terms "comprising" and "comprises" mean the elements recited, or their equivalents in structure or function, plus any other element or elements which are not recited. The terms "having" and "including" are also to be construed as open ended. All ranges recited herein include the endpoints, including those that recite a range between two values. Whether so indicated or not, all values recited herein are approximate as defined by the circumstances, including the degree of expected experimental error, technique error, and instrument error for a given technique used to measure a value.

The term “optional” or “optionally” is taken to mean that the event or circumstance described in the specification may or may not occur, and that the description includes instances where the event occurs and instances where it does not.

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the disclosure in any manner.

EXAMPLES

Example 1: Preparation of form I of LCZ-696

Valsartan (7.4 g, 0.0170 moles) was added to a mixture of sacubitril (7 g) and acetone (210 mL) at 25 °C to 30 °C. The reaction mixture was cooled to 20 °C and aqueous solution of sodium hydroxide (2 g in 7 mL water) was added. The reaction mixture was stirred for 2 hours at 25 °C to 30 °C. Acetone was completely distilled off under vacuum below 25 °C. Isopropyl acetate (135 mL) was added to the residue and distilled off under vacuum below 25 °C. Again isopropyl acetate (135 mL) was added to the residue and distilled off under vacuum below 25 °C. Methyl tert-butyl ether (135 mL) was added to the residue and the mixture was stirred for 1 hour at 25 °C to 30 °C. The precipitated solid was filtered and washed with methyl tert-butyl ether (36 mL). The solid was dried under vacuum at 25 °C to afford the desired product.

Yield: 11.4 g

Example 2: Preparation of form I of LCZ-696

Valsartan (5.12 g) was added to a mixture of sacubitril (5 g) and acetone (150 mL) at 28 °C and cooled to about 20-21 °C. An aqueous solution of sodium hydroxide (1.45 g in 5 mL water) was added. The reaction mixture was stirred for 2 hours at about 24 °C. Acetone was completely distilled off under vacuum below 25 °C. Isopropyl acetate (100 mL) was added to the residue and distilled off under vacuum below 25 °C. Again isopropyl acetate (100 mL) was added to the residue and distilled off under vacuum

below 25 °C. Methyl tert-butyl ether (100 mL) was added to the residue and the mixture was stirred for about 12.5 hours at 25 °C to 26 °C. The precipitated solid was filtered and washed with methyl tert-butyl ether (40 mL). The solid was dried under vacuum at 25 °C for 5 hours to afford the title compound.

Yield: 8.5 g

Purity (By HPLC): 98.75%

The XRPD peaks (error limit of $\pm 0.2^\circ 2\theta$) having more than 10% relative intensities are: 4.3, 5.0, 5.3, 5.4, 5.7, 10.0, 12.9, 13.7, 13.7, 14.7, 14.8, 15.0, 16.5 and 17.6.

Example 3: Preparation of form I of LCZ-696

Valsartan (5.12 g) was added to a mixture of sacubitril (5 g) and acetone (150 mL) at 27 °C and cooled to about 20 °C. An aqueous solution of sodium hydroxide (1.45 g in 5 mL water) was added. The reaction mixture was stirred for 2 hours at about 25 °C. Acetone was completely distilled off under vacuum below 25 °C. Isopropyl acetate (100 mL) was added to the residue and distilled off under vacuum at 25 °C. Again isopropyl acetate (100 mL) was added to the residue and distilled off under vacuum at 25 °C. Methyl tert-butyl ether (100 mL) was added to the residue and scratched the material with spatula. The reaction mixture was stirred for about 2 hours at 25 °C. The precipitated solid was filtered and washed with methyl tert-butyl ether (40 mL). The solid was dried under vacuum at 25 °C for about 1 hour to afford the title compound.

Yield: 9.2 g

Purity (By HPLC): 99.70%

Example 4: Determination of DSC of Form I of LCZ-696

The thermal analysis of crystalline form I of LCZ-696 as obtained from Example 2 and Example 3 were carried out by differential scanning calorimetry (DSC) (TA Instruments-Discovery DSC) equipped with refrigerated cooling accessory. Analysis was performed by taking 3 to 7 mg of sample into an open Tzero aluminum sample pan. The thermogram was recorded from 25°C to 250 °C under nitrogen atmosphere of 50

mL/min at a heating rate of 10 °C/min. Without being bound by any theory, two endothermic events were observed. The first endotherm starts at about 40 °C and ends at about 100 °C; whereas the second endotherm starts at about 115 °C and ends at about 140 °C.

Example 5: Determination of TGA of Form I of LCZ-696

Thermogravimetric analysis (TGA) was performed on TA Instruments model Q500. The sample (about 20-25 mg) was placed in a platinum pan previously tared. The weight loss of the sample was determined by heating the sample from room temperature to 200°C at a heating rate of 10°C/min under nitrogen atmosphere of 40 mL/min. The total weight loss of crystalline form I of LCZ-696 as obtained from Example 2 was found to be about 5.6 % w/w.

CLAIMS:

1. A crystalline form I of LCZ-696 characterized by its PXRD pattern having peaks located at about 4.24, 5.05, 9.96, 12.68 and $14.88 \pm 0.2^\circ 2\theta$.
2. A crystalline form I of LCZ-696 characterized by a PXRD pattern having peaks located substantially as illustrated in the pattern of Figure 1 or Figure 2 or Figure 3.
3. The crystalline form I of LCZ-696 of claim 1, having water content of about 6 % to about 7 %.
4. The crystalline form I of LCZ-696 of claim 3, having water content of about 6.5%.
5. The crystalline form I of LCZ-696 of claim 1, having sodium content of about 7%.
6. A process for preparing a crystalline form I of LCZ-696 comprising the steps of:
 - (i) adding an ether solvent to LCZ-696;
 - (ii) stirring the reaction mixture of step (i) for sufficient time;
 - (iii) isolating crystalline form I of LCZ-696.
7. The process of claim 6, wherein the ether solvent is selected from a group consisting of diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran.
8. The process of claim 6, wherein the ether solvent is methyl tert-butyl ether.
9. The process of claim 6, wherein the crystalline form I of LCZ-696 is further dried under vacuum.

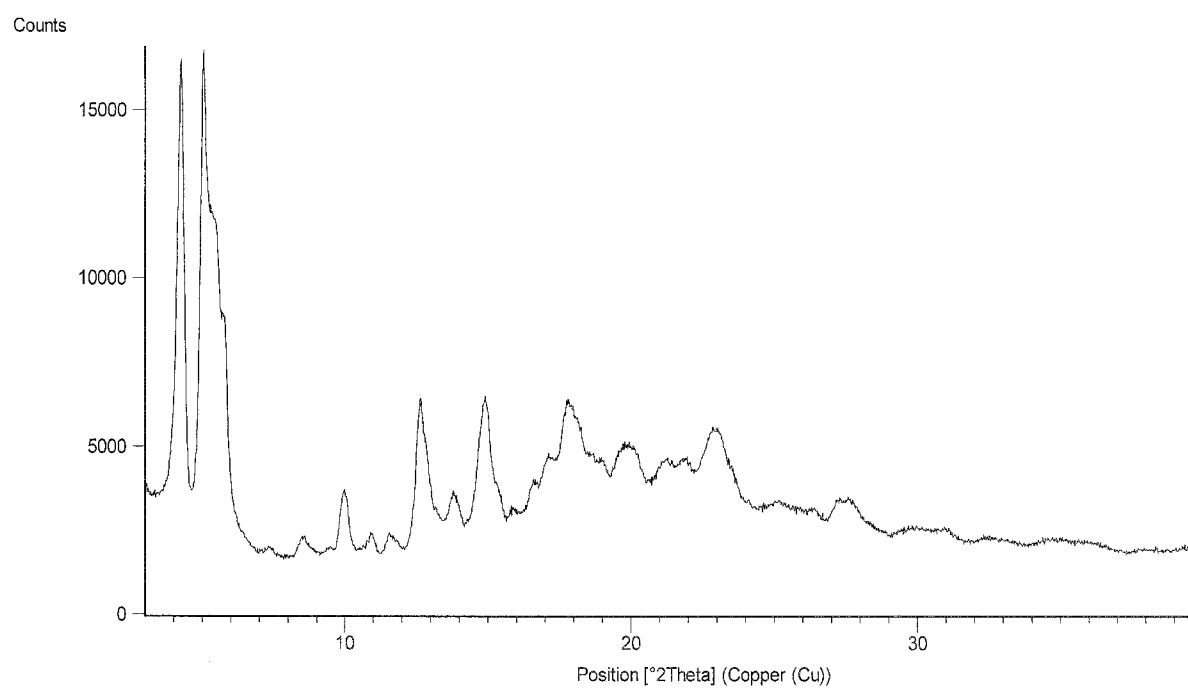


Figure. 1

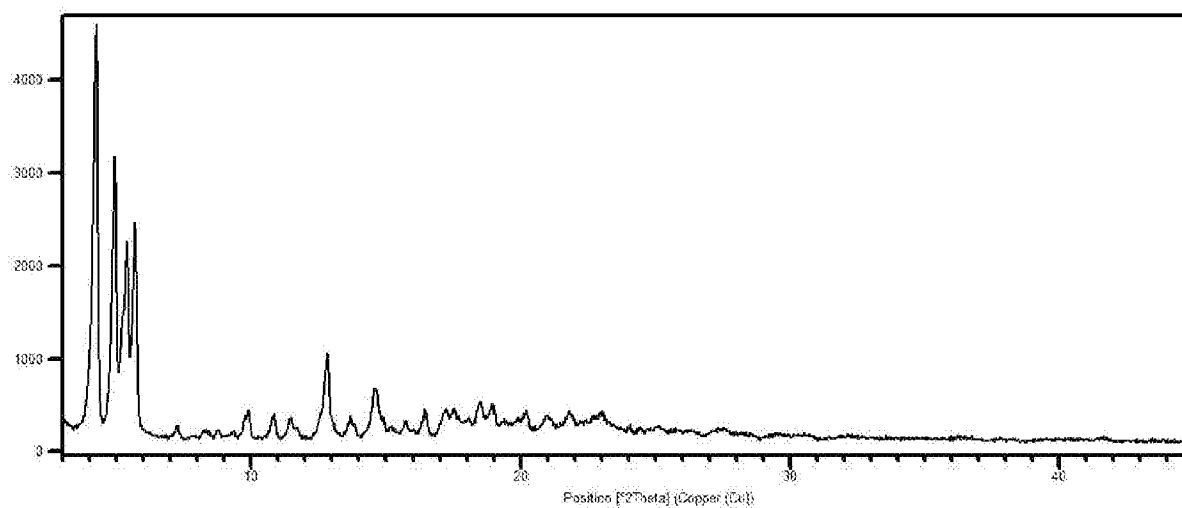


Figure. 2

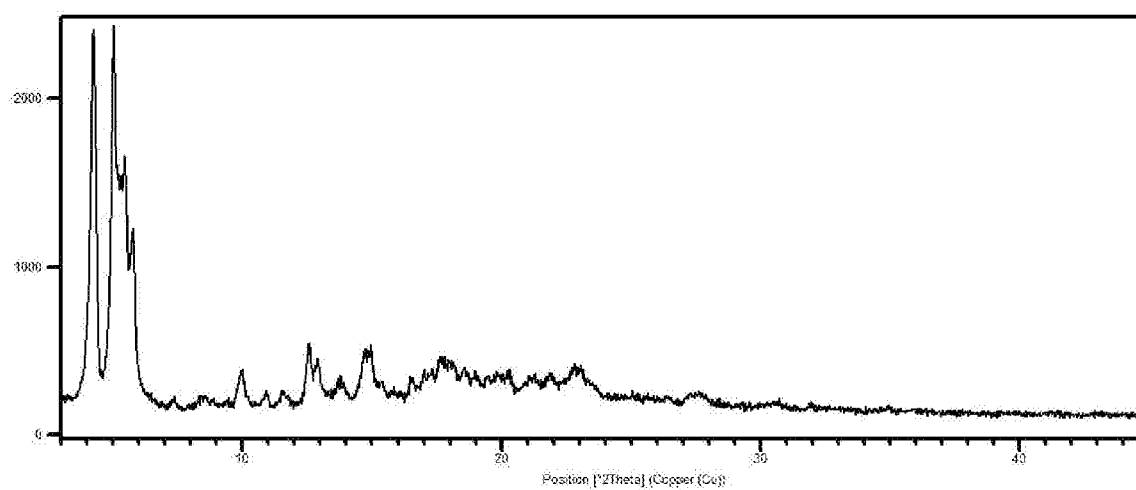


Figure. 3

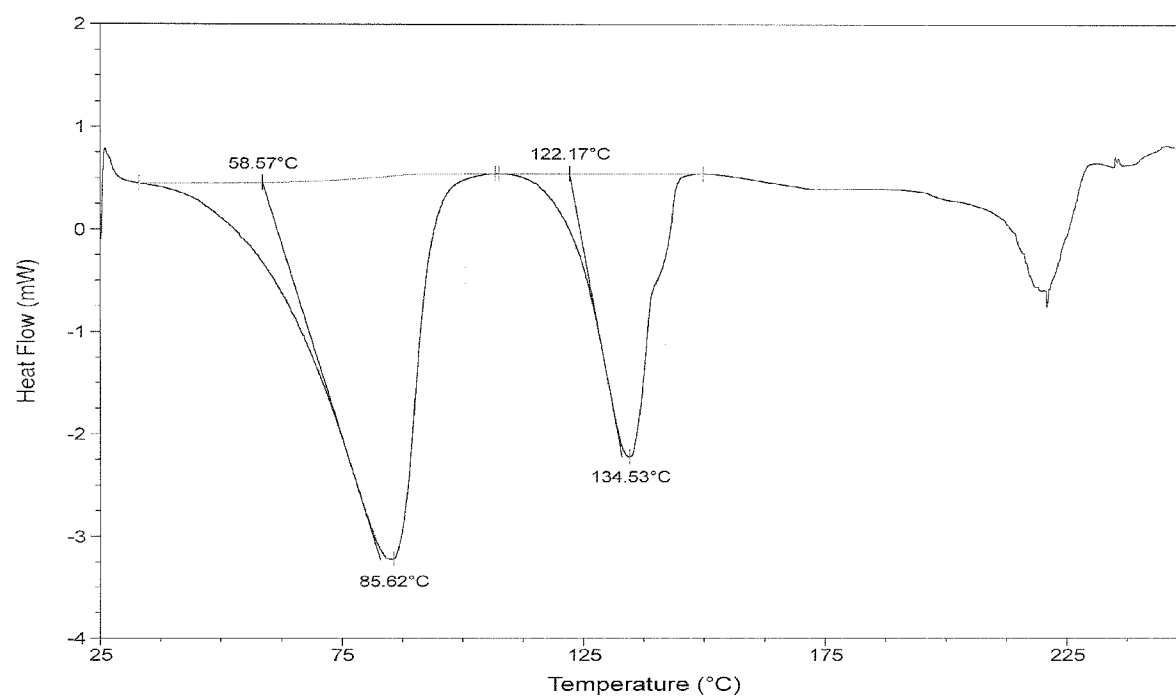


Figure. 4

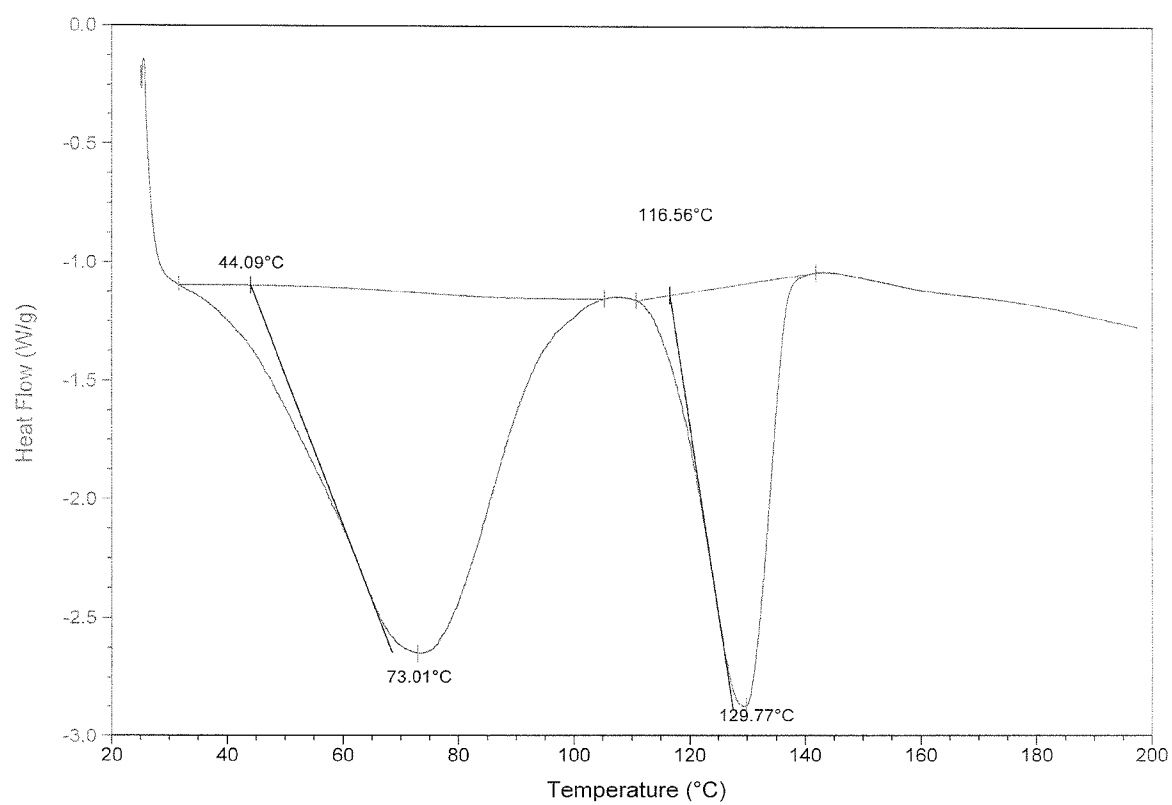


Figure. 5

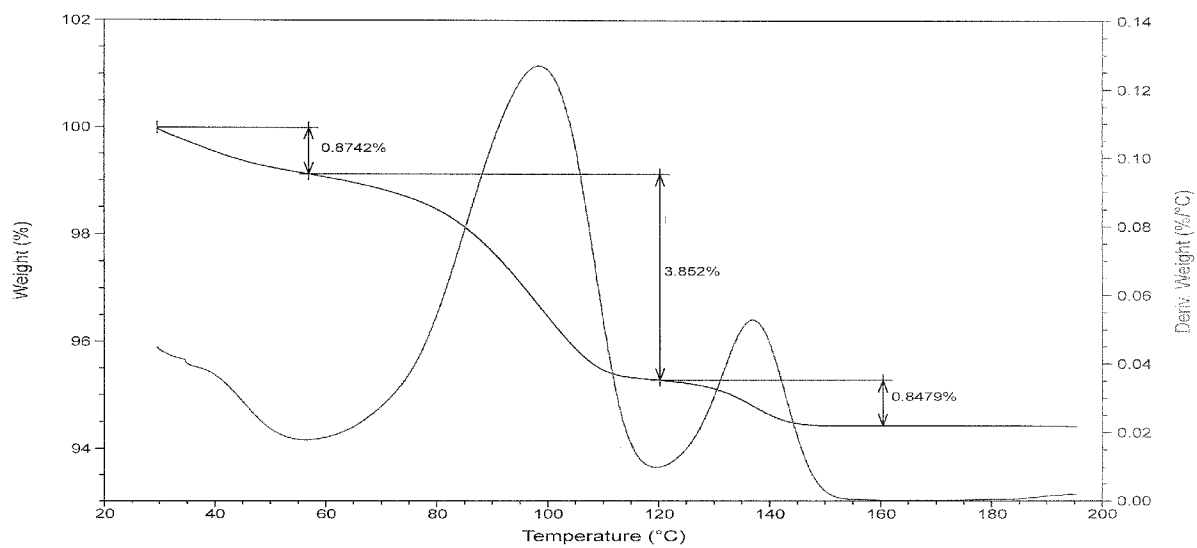


Figure. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/051680

A. CLASSIFICATION OF SUBJECT MATTER
A61K9/10 Version=2016.01

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)

C07D257/04, C07C233/47, A61K31/41

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)

Patseer, IPO Internal Database: Key words:crystalline form I of LCZ-696 ,
A process for preparing a crystalline form I of LCZ-696.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Tetrahedron Letters Volume 53, Issue 3, 18 January 2012, Pages 275-276. Abstract, Supplementary data -----	1-9
Y	US 8,877,938 B2 (FENG, Let al.) 04 November 2014 column 16, lines 14-46; column 17, lines 11-52; column 1R, lines 2-3; lines 8-11; table:claim 1	1-9

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

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search

16-08-2016

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16-08-2016

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2016/051680

Citation	Pub.Date	Family	Pub.Date
US 8877938 B2	04-11-2014	WO 2007056546 A1	18-05-2007
		EP 1948158 A1	30-07-2008