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(54) **Title:** CRYSTALLINE FORMS OF CANAGLIFLOZIN

(57) **Abstract:** The present invention relates to crystalline forms of canagliflozin, processes for their preparation, and their use for the treatment of type 2 diabetes mellitus. A crystalline Form R1of canagliflozin emihydrate. The crystalline Form R1 of canagliflozin hemihydrate of claim 1, characterized by an X-ray powder diffraction peaks having d-spacing values at about 3.1, 3.7, 4.6, and 8.9 A.

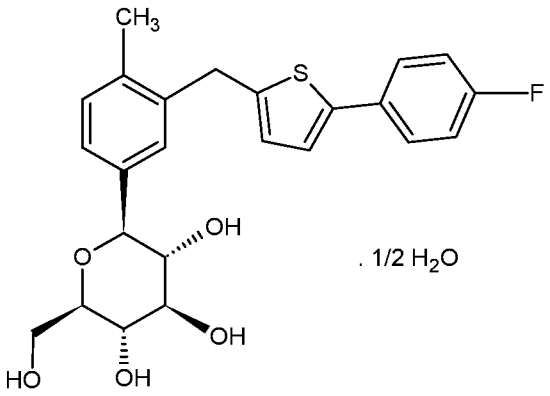
CRYSTALLINE FORMS OF CANAGLIFLOZIN

Field of the Invention

The present invention relates to crystalline forms of canagliflozin, processes for their preparation, and their use for the treatment of type 2 diabetes mellitus.

Background of the Invention

Canagliflozin hemihydrate, chemically designated as (1*S*)-1,5-anhydro-1-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-D-glucitol hemihydrate, is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Its chemical structure is represented by Formula I.



Formula I

U.S. Patent Nos. 7,943,582 and 8,513,202 disclose crystalline forms of canagliflozin hemihydrate.

PCT Publication No. WO 2009/035969 discloses a crystalline form of canagliflozin, designated as I-S.

PCT Publication No. WO 2013/064909 discloses crystalline complexes of canagliflozin with L-proline, D-proline, and L-phenylalanine, and the processes for their preparation.

PCT Publication No. WO 2014/180872 discloses crystalline non-stoichiometric hydrates of canagliflozin (HxA and HxB), and the process for their preparation.

PCT Publication No. WO 2015/071761 discloses crystalline Forms B, C, and D of canagliflozin.

Chinese Publication Nos. CN 103980262, CN 103936726, CN 103936725, CN 103980261, CN 103641822, CN 104230907, CN 104447722, CN 104447721, and CN 104130246 disclose different crystalline polymorphs of canagliflozin.

In the pharmaceutical industry, there is a constant need to identify critical physicochemical parameters of a drug substance such as novel salts, polymorphic forms, and co-crystals, that affect the drug's performance, solubility, and stability, and which may play a key role in determining the drug's market acceptance and success.

The discovery of new forms of a drug substance may improve desirable processing properties of the drug, such as ease of handling, storage stability, and ease of purification. Accordingly, the present invention provides novel crystalline forms of canagliflozin having enhanced stability over known crystalline forms of canagliflozin.

Summary of the Invention

The present invention relates to crystalline forms of canagliflozin, processes for their preparation, and their use for the treatment of type 2 diabetes mellitus.

Brief Description of the Figures

Figure 1 depicts an X-Ray Powder Diffraction (XRPD) pattern of a crystalline Form R1 of canagliflozin hemihydrate.

Figure 2 depicts a Differential Scanning Calorimetry (DSC) thermogram of a crystalline Form R1 of canagliflozin hemihydrate.

Figure 3 depicts an XRPD pattern of a crystalline Form R2 of canagliflozin monohydrate.

Figure 4 depicts a DSC thermogram of a crystalline Form R2 of canagliflozin monohydrate.

Figure 5 depicts an X-Ray Powder Diffraction (XRPD) pattern of a crystalline Form R3 of canagliflozin hydrate.

Figure 6 depicts a Differential Scanning Calorimetry (DSC) thermogram of a crystalline Form R3 of canagliflozin hydrate.

Figure 7 depicts a Thermogravimetic Analysis (TGA) of crystalline Form R3 of canagliflozin hydrate.

Figure 8 depicts a Scanning Electron Microscope (SEM) image of crystalline Form R3 of canagliflozin.

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 "treating," as used herein, refers to an act of bringing together two or more components by any means, such as contacting, suspending, dissolving, mixing, blending, slurrying, stirring, or combinations thereof.

The term "room temperature," as used herein, refers to a temperature of about 20°C to about 30°C.

The term "elevated temperature," as used herein, refers to a temperature that is more than room temperature. More specifically, the "elevated temperature" should be more than 30°C.

The term "ionic additive," as used herein, refers to organic and inorganic salts of ammonium, alkali metals, and alkaline earth metals. Preferably, the ionic additive for the purpose of the present invention is selected from the group comprising ammonium formate, sodium formate, potassium formate, ammonium acetate, sodium acetate, potassium acetate, triammonium citrate, trisodium citrate, tripotassium citrate, and sodium chloride.

The term "canagliflozin monohydrate," as used herein, refers to canagliflozin having one molar equivalent of water. More specifically, the amount of water in the canagliflozin monohydrate ranges from 3.5% to 4.5%.

The term "canagliflozin hemihydrate," as used herein, refers to canagliflozin having 0.5 molar equivalents of water. More specifically, the amount of water in the canagliflozin hemihydrate ranges from 1.5% to 2.5%.

The term "canagliflozin hydrate," as used herein, refers to canagliflozin having water ranging from about 8% to about 16%.

The term "standard conditions," as used herein, refers to a temperature of about 40°C and relative humidity (RH) of about 75%.

The term "bound water," as used herein, refers to the water contained within the crystal lattice of a compound particularly held by hydrogen bonding or capillary action, and which cannot be removed easily.

The term "surface water," as used herein, refers to the water adsorbed on the crystal lattice of a compound and which can be removed easily, such as by keeping the compound in dry air.

The term "triple layer package," as used herein, refers to the canagliflozin being packed in a polyethylene bag, then inserted and heat sealed in a bag made of a mixture of polyethylene s, and then further inserted and heat sealed into an outer bag made of a mixture of polyester film and aluminum foil/polyethylene.

A first aspect of the present invention provides a crystalline Form R1 of canagliflozin hemihydrate.

In one embodiment of this aspect, the crystalline Form R1 of canagliflozin hemihydrate is characterized by X-Ray Powder Diffraction peaks having d-spacing values at about 3.1, 3.7, 4.6, and 8.9 A.

In another embodiment of this aspect, the crystalline Form R1 of canagliflozin hemihydrate is further characterized by additional X-ray powder diffraction peaks having d-spacing values at about 3.1, 3.4, 3.5, 3.6, 3.7, 4.0, 4.1, 4.3, 4.6, 4.9, 5.3, 5.5, 5.7, 5.9, 6.2 6.7, 7.0, 7.4, 8.9, and 13.3, A.

In another embodiment of this aspect, the crystalline Form R1 of canagliflozin hemihydrate is characterized by X-ray powder diffraction peaks having values at 10.0, 19.5, 24.0, and 28.5 ± 0.2° 2Θ

In yet another embodiment of this aspect, the crystalline Form R1 of canagliflozin hemihydrate is further characterized by X-ray powder diffraction peaks having values at 6.7, 10.0, 12.0, 12.7, 13.2, 14.2, 14.9, 15.4, 16.1, 16.7, 18.1, 19.5, 20.8, 21.4, 22.2, 24.0, 24.4, 25.4, 26.2, and 28.5 ± 0.2° 2Θ.

Table 1 provides XRPD peak values (°2Θ), their corresponding d-spacing values (A), and their relative intensities for the crystalline Form R1 of canagliflozin hemihydrate.

Table 1

Position (°2θ)	d-spacing (Å)	Relative Intensity
3.3	26.7	3.3
5.4	16.5	5.3
6.7	13.3	36.7
10.0	8.9	4.8
10.7	8.2	1.5
12.0	7.4	4.3
12.7	7.0	7.4
13.2	6.7	13.5
14.2	6.2	6.5
14.9	5.9	10.2
15.4	5.7	15.4
16.1	5.5	20.2
16.7	5.3	12.8
18.1	4.9	12.8
19.5	4.6	100
20.8	4.3	15.0
21.4	4.1	13.1
22.2	4.0	8.8
24.0	3.7	42.2
24.5	3.6	20.1
25.4	3.5	7.5
26.2	3.4	7.0
28.5	3.1	27.7
31.7	2.8	1.3
33.5	2.7	2.1
35.4	2.5	2.4

In another embodiment of this aspect, the crystalline Form R1 of canagliflozin hemihydrate is characterized by a DSC thermogram having an endotherm at about 86°C.

A second aspect of the present invention provides a crystalline Form R2 of canagliflozin monohydrate.

In one embodiment of this aspect, the crystalline Form R2 of canagliflozin monohydrate is characterized by X-ray powder diffraction peaks having d-spacing values at about 3.1, 3.7, 4.5, and 7.1 Å.

In another embodiment of this aspect, the crystalline Form R2 of canagliflozin monohydrate is further characterized by additional X-ray powder diffraction peaks having d-spacing values at about 3.0, 3.1, 3.2, 3.5, 3.7, 3.8, 4.0, 4.2, 4.3, 4.5, 4.6, 4.8, 5.1, 5.3, 5.6, 5.9, 6.4, 6.7, 7.1, 9.3, 12.1, 13.3, and 14.0 Å.

In another embodiment of this aspect, the crystalline Form R2 of canagliflozin monohydrate characterized by X-ray powder diffraction peaks having values at 12.4, 19.6, 24.1, and 28.8 ± 0.2° 2Θ.

In another embodiment of this aspect, the crystalline Form R2 of canagliflozin monohydrate is further characterized by X-ray powder diffraction peaks having values at, 6.3, 6.7, 7.3, 9.5, 12.4, 13.2, 13.7, 15.0, 15.8, 16.7, 17.4, 18.2, 19.0, 19.6, , 20.6, 21.4, 22.2, 23.3, 24.1, 25.3, 27.3, 28.8, and 29.5± 0.2° 2Θ.

Table 2 provides XRPD peak values (°2Θ), their corresponding d-spacing values (A), and their relative intensities for the crystalline Form R2 of canagliflozin monohydrate.

Table 2

Position (°2θ)	d-spacing (Å)	Relative Intensity
5.3	16.6	2.1
6.3	14.0	16.9
6.7	13.3	14.8
7.3	12.1	2.9
9.5	9.3	5.9
12.4	7.1	14.6
13.2	6.7	6.7
13.7	6.4	15.7
15.0	5.9	10.7
15.8	5.6	25.0
16.7	5.3	17.2
17.4	5.1	14.4
18.2	4.9	14.4
19.0	4.7	17.6
19.6	4.5	100
20.6	4.3	17.0
21.4	4.2	15.4
22.2	4.0	18.6
23.3	3.8	13.3
24.1	3.7	49.1
25.3	3.5	13.2
27.3	3.3	7.5
28.8	3.1	32.3
29.5	3.0	8. 2
33.6	2.7	3.6
35.0	2.6	2.7
37.0	2.4	2.3

In another embodiment of this aspect, the crystalline Form R2 of canagliflozin monohydrate is characterized by a DSC thermogram having endotherms at about 57°C, 76°C, and 102°C.

A third aspect of the present invention provides a process for the preparation of a crystalline Form R1 of canagliflozin hemihydrate comprising treating an amorphous form of canagliflozin with an aqueous solution of an ionic additive at room temperature to obtain a suspension, then drying the suspension under vacuum at an elevated temperature.

In one embodiment of this aspect, the ionic additive is sodium formate.

In another embodiment of this aspect, the crystalline Form R1 of canagliflozin hemihydrate is prepared by treating an amorphous form of canagliflozin with an aqueous solution of sodium formate, then drying the suspension under vacuum at about 60°C.

In yet another embodiment of this aspect, the crystalline Form R1 of canagliflozin hemihydrate is prepared by drying crystalline Form R2 of canagliflozin monohydrate at an elevated temperature for more than 25 hours.

A fourth aspect of the present invention provides a process for the preparation of a crystalline Form R2 of canagliflozin monohydrate comprising treating an amorphous form of canagliflozin with an aqueous solution of an ionic additive to obtain a suspension, then drying the suspension under vacuum at room temperature.

In one embodiment of this aspect, the ionic additive is sodium formate.

In another embodiment of this aspect, the crystalline Form R2 of canagliflozin monohydrate is prepared by treating an amorphous form of canagliflozin with an aqueous solution of sodium formate, then drying the suspension under vacuum at about 30°C.

A fifth aspect of the present invention provides a process for the preparation of a crystalline Form R2 of canagliflozin monohydrate comprising exposing a crystalline Form R1 of canagliflozin hemihydrate to moisture.

In one embodiment of this aspect, the process for the preparation of the crystalline Form R2 of canagliflozin monohydrate comprises treating the crystalline Form R1 of canagliflozin hemihydrate with water, then drying the material under vacuum at room temperature.

A sixth aspect of the present invention provides a crystalline Form R3 of canagliflozin hydrate.

In an embodiment of this aspect, the crystalline Form R3 of canagliflozin hydrate is characterized by a DSC thermogram having a broad endotherm at about 58.5°C and a sharp endotherm at about 80.9°C.

In another embodiment of this aspect, the crystalline Form R3 of canagliflozin hydrate is a stable form of canagliflozin hydrate. It is not converted to any other form of canagliflozin when kept under standard conditions for one month under triple layer package.

In another embodiment of this aspect, the crystalline Form R3 of canagliflozin hydrate may be isolated with a water content of about 8% to about 16% as determined by Karl Fischer (KF) method. The water content falls to about 6% with no change in its XRPD pattern in 6 hours at about 25°C or at room temperature and low relative humidity of about 35%.

In another embodiment of this aspect, the crystalline Form R3 of canagliflozin hydrate is characterized by a TGA which indicates two stages of weight loss; the first weight loss occurs at about 25°C which corresponds to about 4.5% or 1 mole equivalent of water and the second weight loss occurs at about 60°C which corresponds to about 1.4% or about 0.5 mole equivalent of water.

Table 3 provides the water content, XRD, and TGA of crystalline Form R3 of canagliflozin hydrate performed under different conditions. The study indicates that the crystal structure of crystalline Form R3 of canagliflozin hydrate is sesquihydrate with bound water of about 6% and may accommodate additional surface water of about 8% to about 10%.

Table 3

Condition	Technique	Observations
25°C/40 hours	XRD	XRD profile is comparable to initial profile
	KF	6.58%
	TGA	Weight loss 5.83 % in two parts: 4.515% and 1.315%.
25°C/42 hours	XRD	XRD profile is comparable to initial profile
	KF	6.04%
	TGA	Weight loss 5.74 % in two parts: 4.443% and 1.306%
25°C/44 hours	XRD	XRD profile is not comparable to initial profile
	KF	5.54 %
	TGA	Weight loss 5.804 % in two parts: 4.432% and 1.372%
25°C/46 hours	XRD	XRD profile is not comparable to initial profile
	KF	6.04%
	TGA	Weight loss 4.792 % in two parts: 3.471% and 1.321%
25°C/48 hours	XRD	XRD profile is not comparable to initial profile
	KF	5.82%
	TGA	Weight loss 5.507% in two parts: 4.153% and 1.354%

In another embodiment of this aspect, the crystalline Form R3 of canagliflozin hydrate is characterized by an X-ray powder diffraction peaks having d-spacing values at 3.2, 4.1, 4.5, and 7.2 A.

In yet another embodiment of this aspect, the crystalline Form R3 of canagliflozin hydrate is characterized by X-ray powder diffraction peaks having d-spacing values at about 3.0, 3.1, 3.2, 3.3, 3.5, 3.6, 3.7, 3.8, 4.0, 4.1, 4.2, 4.3, 4.5, 4.7, 4.9, 5.1, 5.3, 5.6, 5.7, 5.8, 6.5, 7.2, 9.3, and 14.0 A.

In another embodiment of this aspect, the crystalline Form R3 of canagliflozin is characterized by X-ray powder diffraction peaks having values at 12.4, 19.6, 21.8, and 28.2 ± 0.2° 2Θ

In another embodiment of this aspect, the crystalline Form R3 of canagliflozin hydrate is further characterized by additional X-ray powder diffraction peaks having values at 6.3, 9.5, 12.4, 13.7, 15.3, 15.5, 15.9, 16.4, 16.8, 17.5, 18.3, 19.0, 19.6, 20.7, 21.8, 22.2, 23.4, 24.3, 24.9, 25.2, 27.4, 28.2, 28.7, 29.5, and 31.5 ± 0.2° 2Θ.

Table 4 provides XRPD peak values (°2Θ), their corresponding d-spacing values (A), and relative intensities for the crystalline Form R3 of canagliflozin hydrate.

Table 4

Position (°2θ)	d-spacing (Å)	Relative Intensity
5.3	16.8	1.3
5.6	15.9	1.6
6.3	14.0	27.5
6.7	13.2	5.3
7.3	12.0	5.4
9.0	9.8	4.8
9.5	9.3	16.2
10.6	8.4	4.6
11.7	7.5	11.4
12.4	7.2	29.4
12.6	7.0	14.8
13.7	6.5	22.5
14.0	6.3	4.5
15.0	5.9	12.6
15.3	5.8	19.0
15.5	5.7	17.3
15.9	5.6	30.2
16.4	5.4	6.7
16.8	5.3	22.1
17.5	5.1	21.4
18.3	4.9	16.4
19.0	4.7	19.1
19.6	4.5	100.0
20.7	4.3	19.3
21.4	4.2	22.4
21.8	4.1	18.5
22.2	4.0	26.5
23.4	3.8	19.6
24.3	3.7	59.8
24.9	3.6	20.0
25.2	3.5	20.8
27.4	3.3	15.9
28.2	3.2	11.5
28.7	3.1	39.5
29.5	3.0	16.8
31.5	2.8	10.4
32.8	2.7	10.6
33.8	2.6	15.6
37.2	2.4	11.4
38.8	2.3	10.6

In yet another embodiment of this aspect, the crystalline Form R3 of canagliflozin hydrate has irregular plate-shaped crystals, as observed by the SEM image depicted in Figure 8.

A seventh aspect of the present invention provides a process for the preparation of a crystalline Form R3 of canagliflozin hydrate comprising treating an amorphous form of canagliflozin with an aqueous solution of sodium formate at room temperature to obtain a suspension. The suspension is then filtered, and then dried under vacuum at about 25°C to 35°C until a water content of about 8% to about 16% is attained.

The amorphous canagliflozin used for the preparation of the crystalline forms of the present invention can be obtained by methods known in the art, for example, the method described in U.S. Patent No. 7,943,788, which is incorporated herein by reference.

An eighth aspect of the present invention provides a pharmaceutical composition comprising a crystalline Form R1 of canagliflozin hemihydrate and one or more pharmaceutically acceptable carriers, diluents, or excipients.

A ninth aspect of the present invention provides a pharmaceutical composition comprising a crystalline Form R2 of canagliflozin monohydrate and one or more pharmaceutically acceptable carriers, diluents, or excipients.

A tenth aspect of the present invention provides a pharmaceutical composition comprising a crystalline Form R3 of canagliflozin hydrate and one or more pharmaceutically acceptable carriers, diluents, or excipients.

An eleventh aspect the present invention provides the use of a crystalline Form R1 of canagliflozin hemihydrate for the treatment of type 2 diabetes mellitus.

A twelfth aspect the present invention provides the use of a crystalline Form R2 of canagliflozin monohydrate for the treatment of type 2 diabetes mellitus.

A thirteenth aspect the present invention provides the use of a crystalline Form R3 of canagliflozin hydrate for the treatment of type 2 diabetes mellitus.

Methods:

The XRPD of the samples were determined by using a PANalytical®; Model X'Pert PRO; Detector: X'celerator®; Step size: 0.02; Scan Range: 3-40 degree 2 theta; CuKa radiation at 45kV and 40 mA.

The DSC was recorded using a Mettler-Toledo® 82 le. Data collection parameters: Scanning rate: 10°C/minute; Temperature: 30°C to 300°C.

The TGA was performed using a TA Instruments® Q500 at 10°C/min from room temperature to 300°C.

The SEM was performed using a Jeol® JSM-6010LV.

The water content was detected using a Metrohm® KF titrator and a methanol medium.

The below examples are illustrated to aid the understanding of the present invention but are not intended to and should not be construed to limit the scope of the invention in any way.

EXAMPLES

Example 1: Preparation of a crystalline Form R1 of canagliflozin hemihydrate

Amorphous canagliflozin (5 g) was suspended in an aqueous solution of sodium formate (80 mL of a solution prepared by dissolving 137.7 g of sodium formate in 180 mL of de-ionized water). The suspension was stirred at room temperature for 20 hours to obtain a reaction mixture. De-ionized water (100 mL) was added to the reaction mixture, and then the reaction mixture was stirred for 1.5 hours. De-ionized water (50 mL) was added to the reaction mixture, and then the reaction mixture was stirred for 30 minutes. The reaction mixture was filtered, then washed with de-ionized water (300 mL), and then dried under vacuum for 12 hours to obtain a solid. The solid was further dried under vacuum at 60°C for 6 hours.

Yield: 4.71 g

Example 2: Preparation of a crystalline Form R2 of canagliflozin monohydrate

Amorphous canagliflozin (5 g) was suspended in an aqueous solution of sodium formate (80 mL of a solution prepared by dissolving 137.7 g of sodium formate in 180 mL of de-ionized water). The suspension was stirred at room temperature for 20 hours to obtain a reaction mixture. De-ionized water (100 mL) was added to the reaction mixture, and then the reaction mixture was stirred for 1.5 hours. De-ionized water (50 mL) was added to the reaction mixture, and then the reaction mixture was stirred for 30 minutes. The reaction mixture was filtered, then washed with de-ionized water (300 mL), and then dried under vacuum for 12 hours at room temperature.

Yield: 4.71 g

Example 3: Preparation of a crystalline Form R2 of canagliflozin monohydrate

Canagliflozin hemihydrate (0.15 g; Form R1 obtained as per Example 1) was suspended in de-ionized water (3 mL). The suspension was stirred at room temperature for 24 hours. The reaction mixture was filtered, then dried at room temperature under vacuum for 5 hours.

Yield: 0.143 g

Example 4: Preparation of a crystalline Form R3 of canagliflozin hydrate

Amorphous canagliflozin (100 g) was suspended in an aqueous solution of sodium formate (1224 g of sodium formate in 1600 mL of de-ionized water). The suspension was stirred at room temperature for 20 hours to obtain a reaction mixture. De-ionized water (2000 mL) was added to the reaction mixture, and then the reaction mixture was stirred for one hour. De-ionized water (1000 mL) was added to the reaction mixture, and then the reaction mixture was stirred for another one hour. The reaction mixture was filtered, then washed with de-ionized water (6000 mL), and then dried under vacuum for 30 minutes to obtain a solid. The solid was then dried under vacuum at 30°C to 35°C until a water content of 8% to 16% was attained.

Yield: 100 g

We claim:

1. A crystalline Form R1 of canagliflozin hemihydrate.

2. The crystalline Form R1 of canagliflozin hemihydrate of claim 1, characterized by an X-ray powder diffraction peaks having d-spacing values at about 3.1, 3.7, 4.6, and 8.9 A.

3. The crystalline Form R1 of canagliflozin hemihydrate of claim 2, characterized by X-ray powder diffraction peaks having d-spacing values at about 3.1, 3.4, 3.5, 3.6, 3.7, 4.0, 4.1, 4.3, 4.6, 4.9, 5.3, 5.5, 5.7, 5.9, 6.2 6.7, 7.0, 7.4, 8.9, and 13.3 A.

4. The crystalline Form R1 of canagliflozin hemihydrate of claim 1, characterized by X-ray powder diffraction peaks having values at 10.0, 19.5, 24.0, and 28.5 ± 0.2° 2Θ

5. The crystalline Form R1 of canagliflozin hemihydrate of claim 4, characterized by X-ray powder diffraction peaks having values at 6.7, 10.0, 12.0, 12.7, 13.2, 14.2, 14.9, 15.4, 16.1, 16.7, 18.1, 19.5, 20.8, 21.4, 22.2, 24.0, 24.5, 25.4, 26.2, and 28.5 ± 0.2° 2Θ.

6. The crystalline Form R1 of canagliflozin hemihydrate of claim 1, characterized by X-ray powder diffraction as shown in Figure 1.

7. The crystalline Form R1 of canagliflozin hemihydrate of claim 1, characterized by a DSC thermogram having an endotherm at about 86°C.

8. A process for the preparation of a crystalline Form R1 of canagliflozin hemihydrate comprising the steps of

a) treating an amorphous form of canagliflozin with an aqueous solution of an ionic additive to obtain a suspension; and

b) drying the suspension under vacuum at an elevated temperature.

9. The process of claims 8, wherein the ionic additive is sodium formate.

10. A crystalline Form R3 of canagliflozin hydrate.

11. The crystalline Form R3 of canagliflozin hydrate of claim 10, characterized by a DSC having a broad endotherm peak at 58.5°C and a sharp endotherm peak at 80.9°C.

12. The crystalline Form R3 of canagliflozin hydrate of claim 10, characterized in that it contains 8% to 16% of water content.

13. The crystalline hydrate of claim 10, characterized by an X-ray powder diffraction peaks having d-spacing values at 3.2, 4.1, 4.5, and 7.2 A.

14. The crystalline Form R3 of canagliflozin hydrate of claim 13, characterized by an X-ray powder diffraction peaks having d-spacing values at 3.0, 3.1, 3.2, 3.3, 3.5, 3.6, 3.7, 3.8, 4.0, 4.1, 4.2, 4.3, 4.5, 4.7, 4.9, 5.1, 5.3, 5.6, 5.7, 5.8, 6.5, 7.2, 9.3, and 14.0 A.

15. The crystalline Form R3 of canagliflozin hydrate of claim 10, characterized by X-ray powder diffraction peaks having values at 12.4, 19.6, 21.8 and 28.2 ± 0.2° 2Θ

16. The crystalline Form R3 of canagliflozin hydrate of claim 15, characterized by X-ray powder diffraction peaks having values at 6.3, 9.5, 12.4, 13.7, 15.3 15.5, 15.9, 16.4, 16.8, 17.5, 18.3, 19.0, 19.6, 20.7, 21.8, 22.2, 23.4, 24.3, 24.9, 25.2, 27.4, 28.2, 28.7, 29.5, and 31.5± O.2° 20..

17. The crystalline Form R3 of canagliflozin hydrate of claim 10, characterized by X-ray powder diffraction as shown in Figure 5.

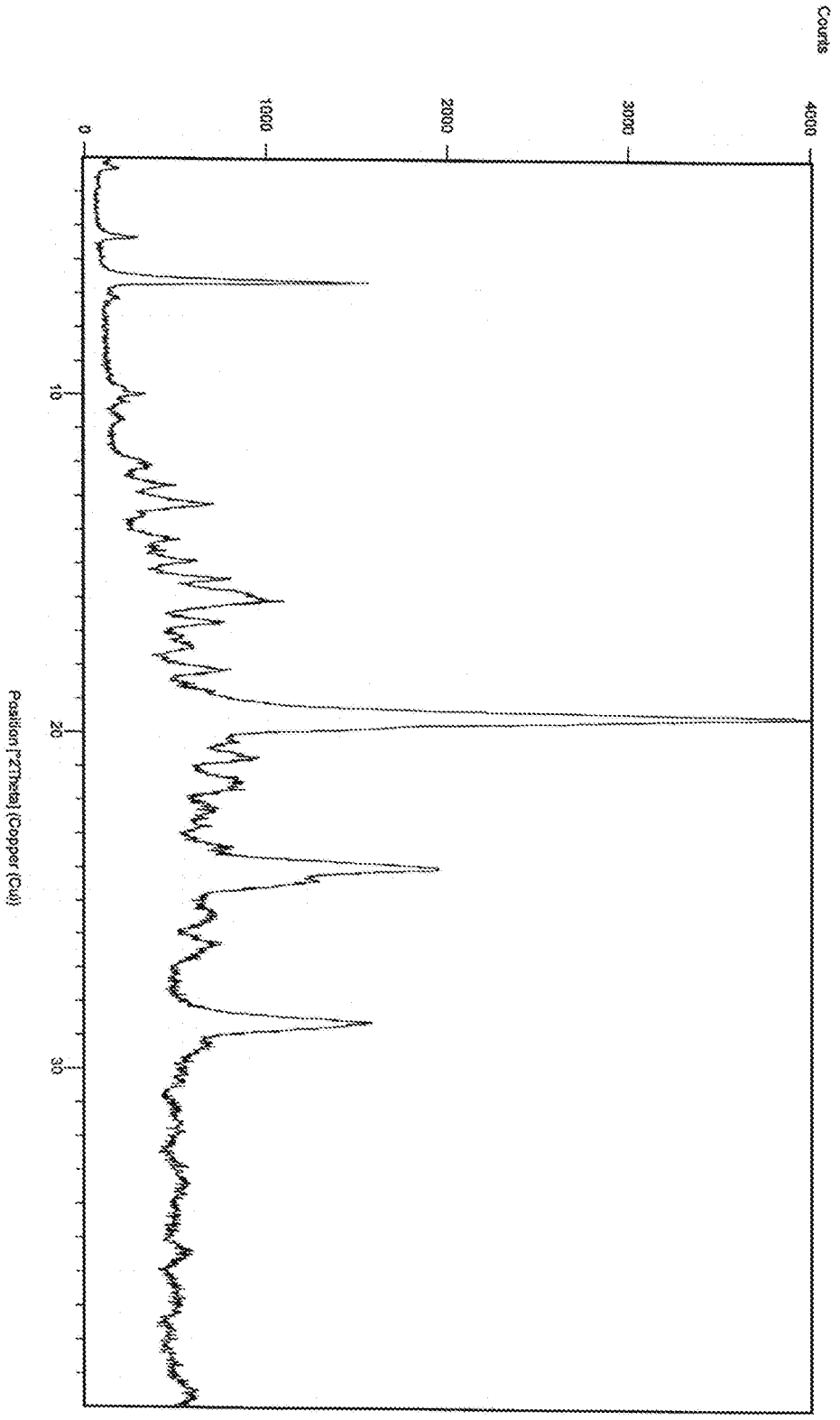
18. The crystalline Form R3 of canagliflozin hydrate of claim 10, characterized by TGA as depicted in Figure 7.

19. The crystalline Form R3 of canagliflozin hydrate of claim 10, characterized by SEM image as depicted in Figure 8.

20. The crystalline Form R3 of canagliflozin hydrate of claim 10 is a sesquihydrate having bound water of about 6% and can accommodate additional surface water of about 10%.

21. A pharmaceutical composition comprising the crystalline form as claimed in claim 1 or claim 10, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

22. A method of using the crystalline form as claimed in claim 1 or claim 10 for the treatment of diabetes.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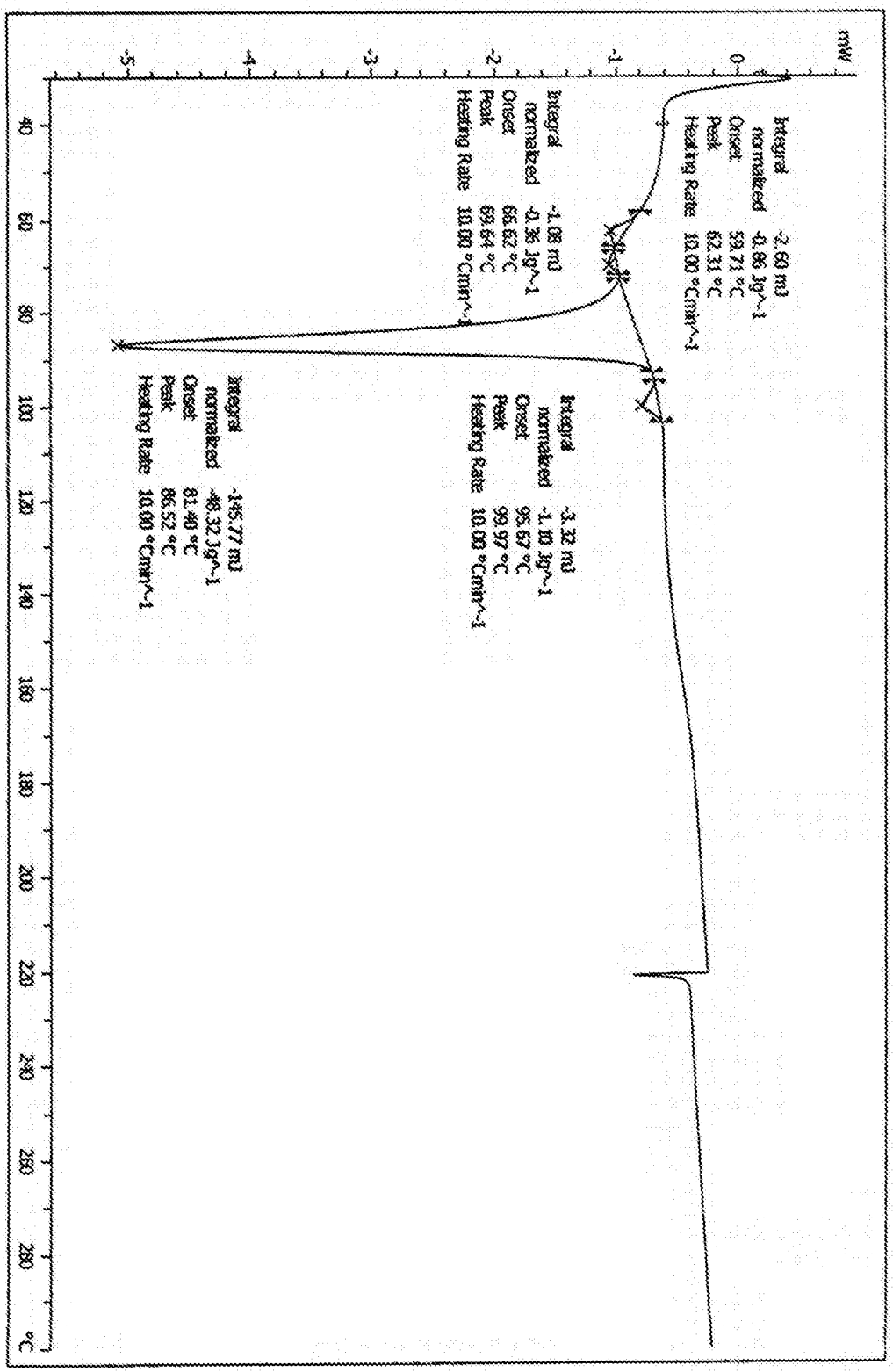
20
30
Position [°2Theta] (Copper (Cu))

Figure 1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normalized -0.86 Jg^-1
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Peak 62.31 °C
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Integral -1.08 mJ
normalized -0.36 Jg^-1
Onset 65.62 °C
Peak 69.64 °C
Heating Rate 10.00 °Cmin^-1
Integral -3.32 mJ
normalized -1.10 Jg^-1
Onset 95.67 °C
Peak 99.97 °C
Heating Rate 10.00 °Cmin^-1
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normalized -48.32 Jg^-1
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Heating Rate 10.00 °Cmin^-1

Figure 2

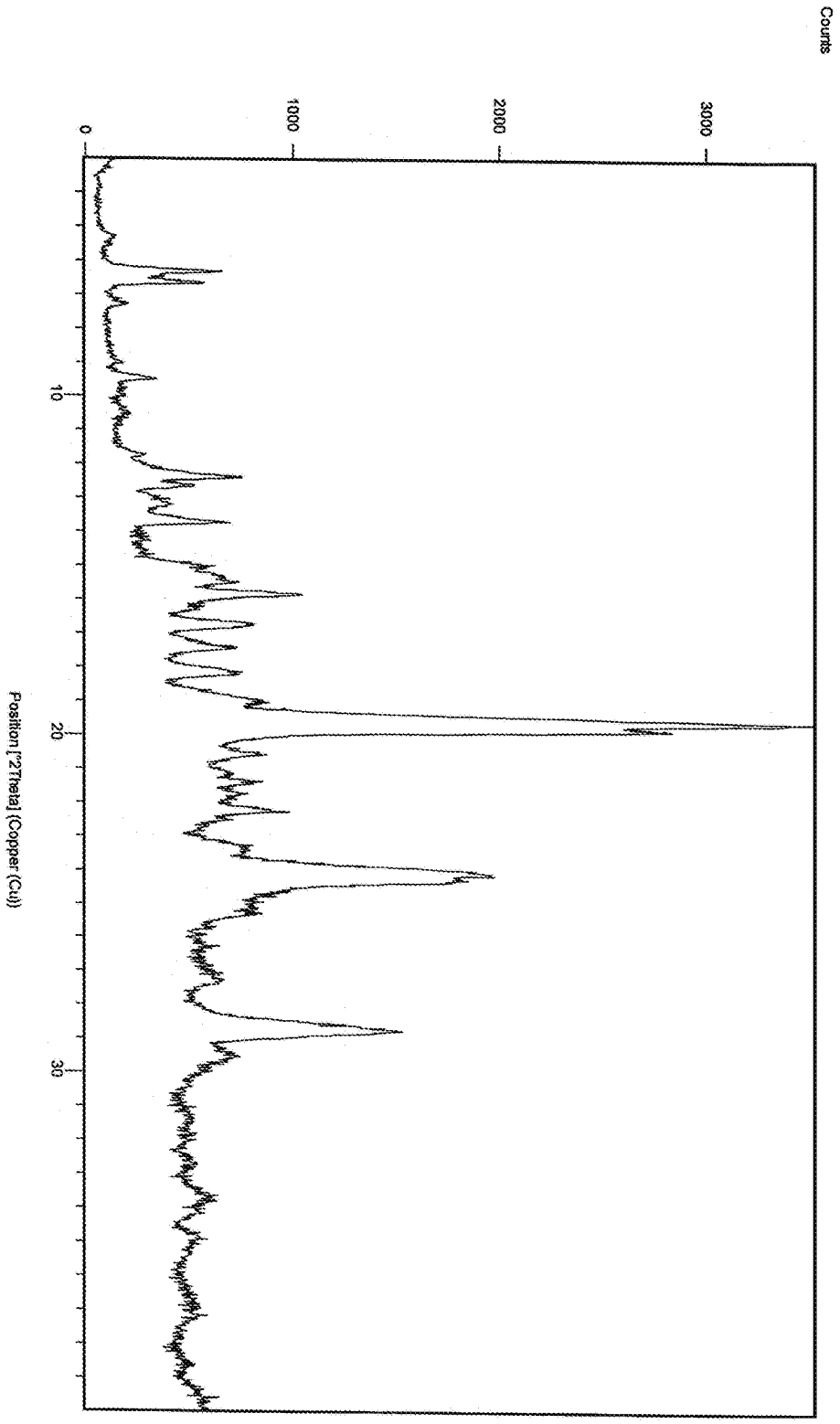
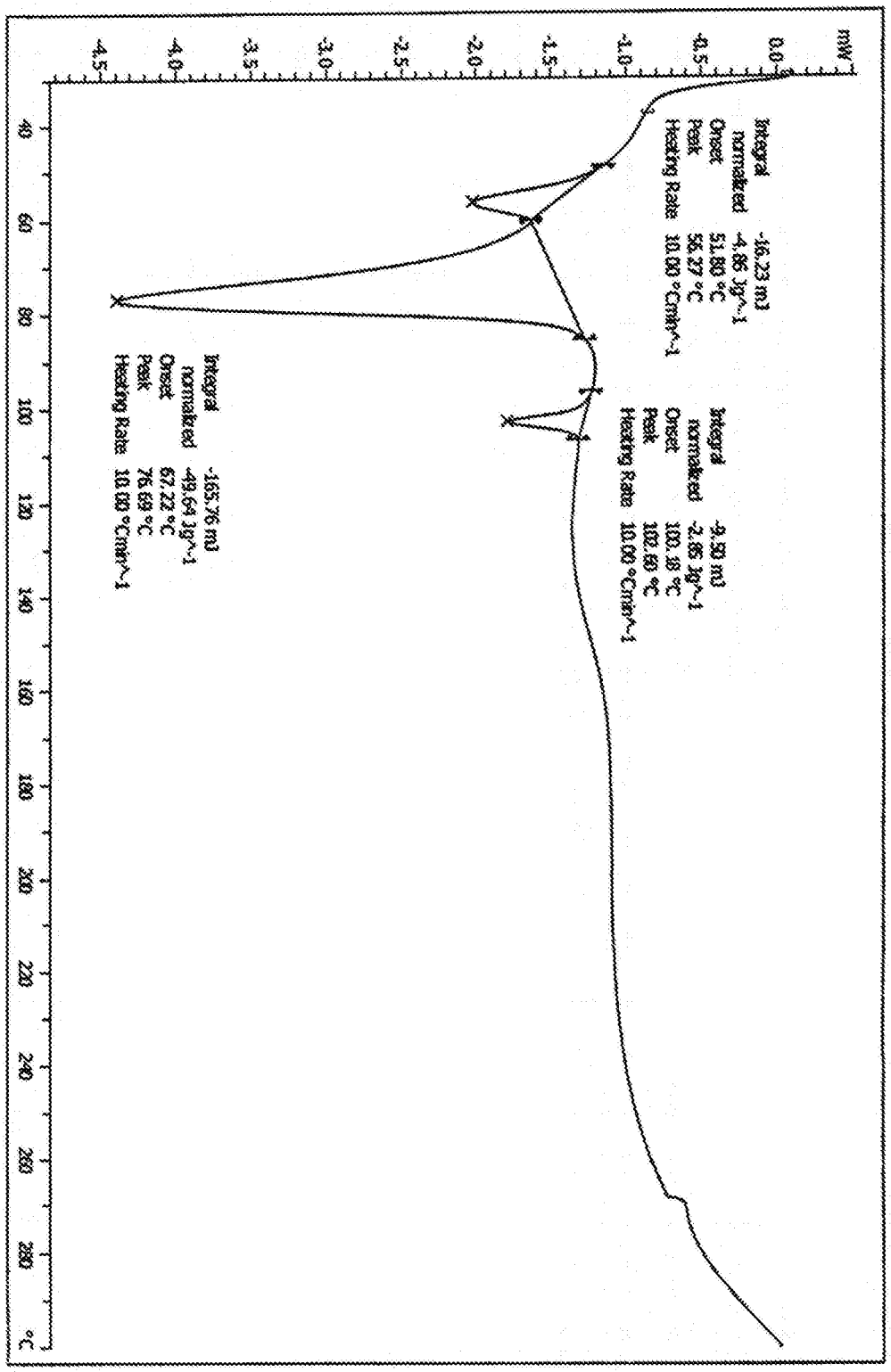


Figure 3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60
80
100
120
140
160
180
200
220
240
260
280
°C
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normalized -4.86 Jg^-1
Onset 51.80 °C
Peak 56.27 °C
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Integral -9.50 mJ
normalized -2.85 Jg^-1
Onset 100.18 °C
Peak 102.60 °C
Heating Rate 10.00 °Cmin^-1
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Heating Rate 10.00 °Cmin^-1

Figure 4

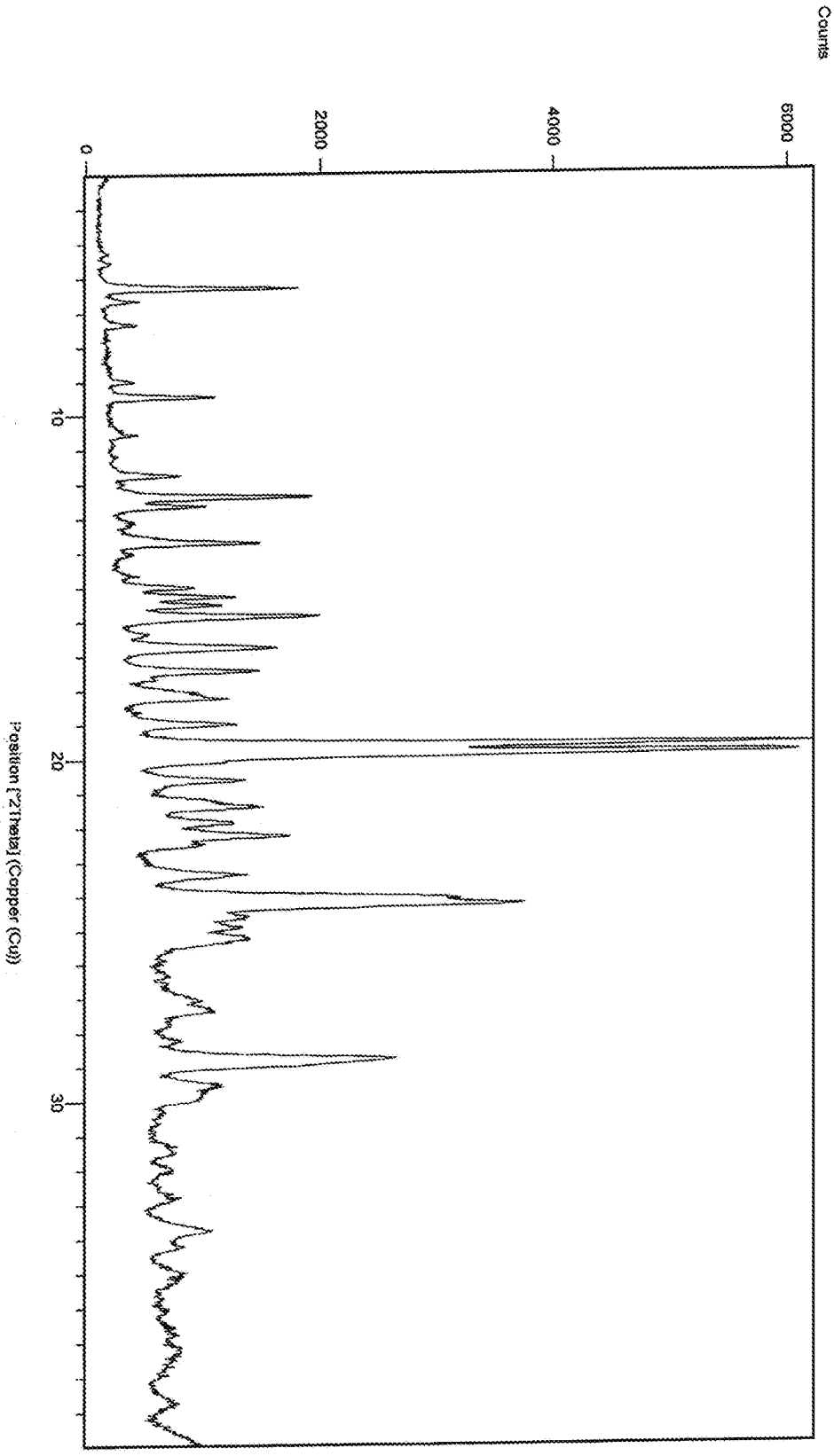
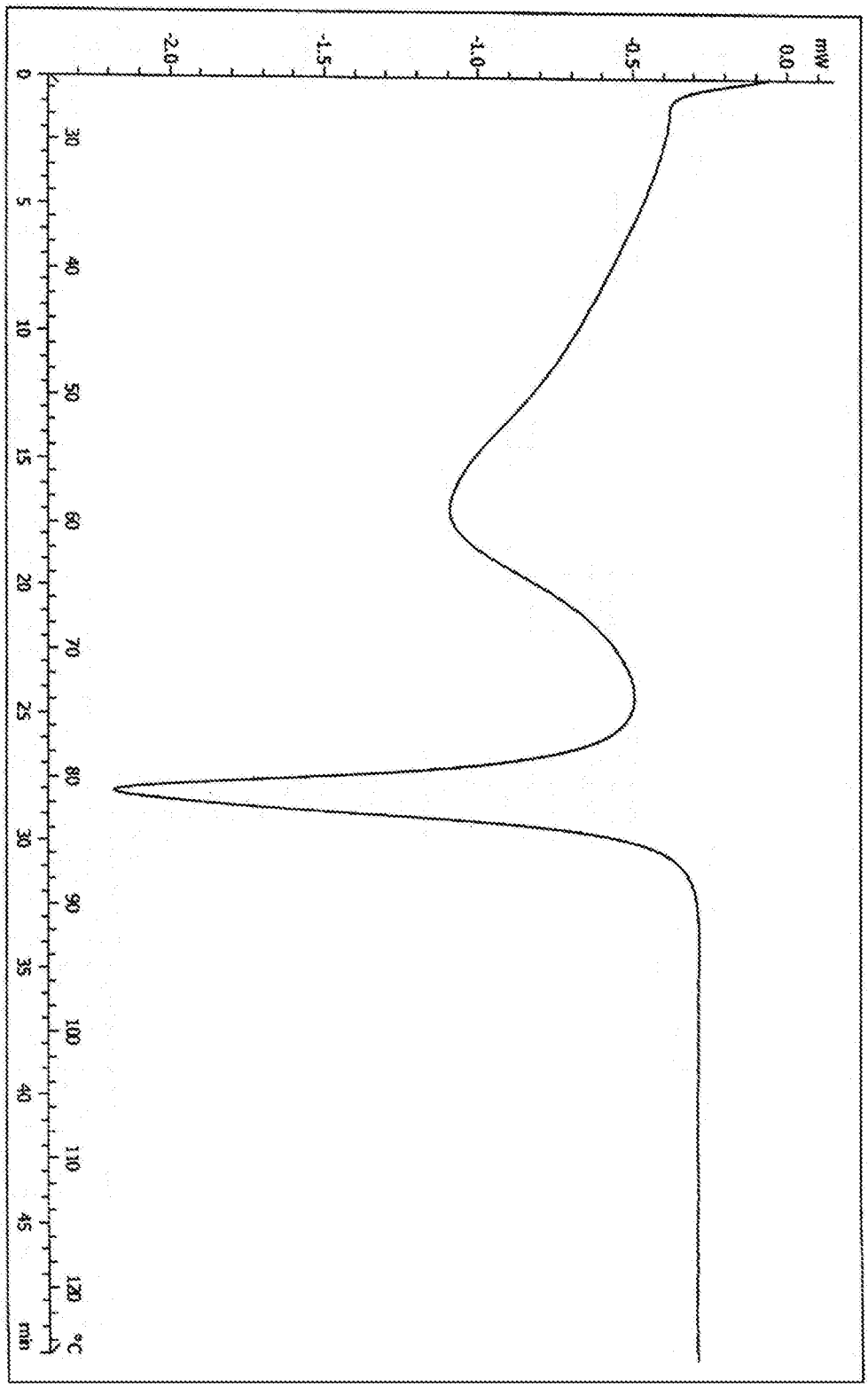


Figure 5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40
50
60
70
80
90
100
110
120
°C

Figure 6

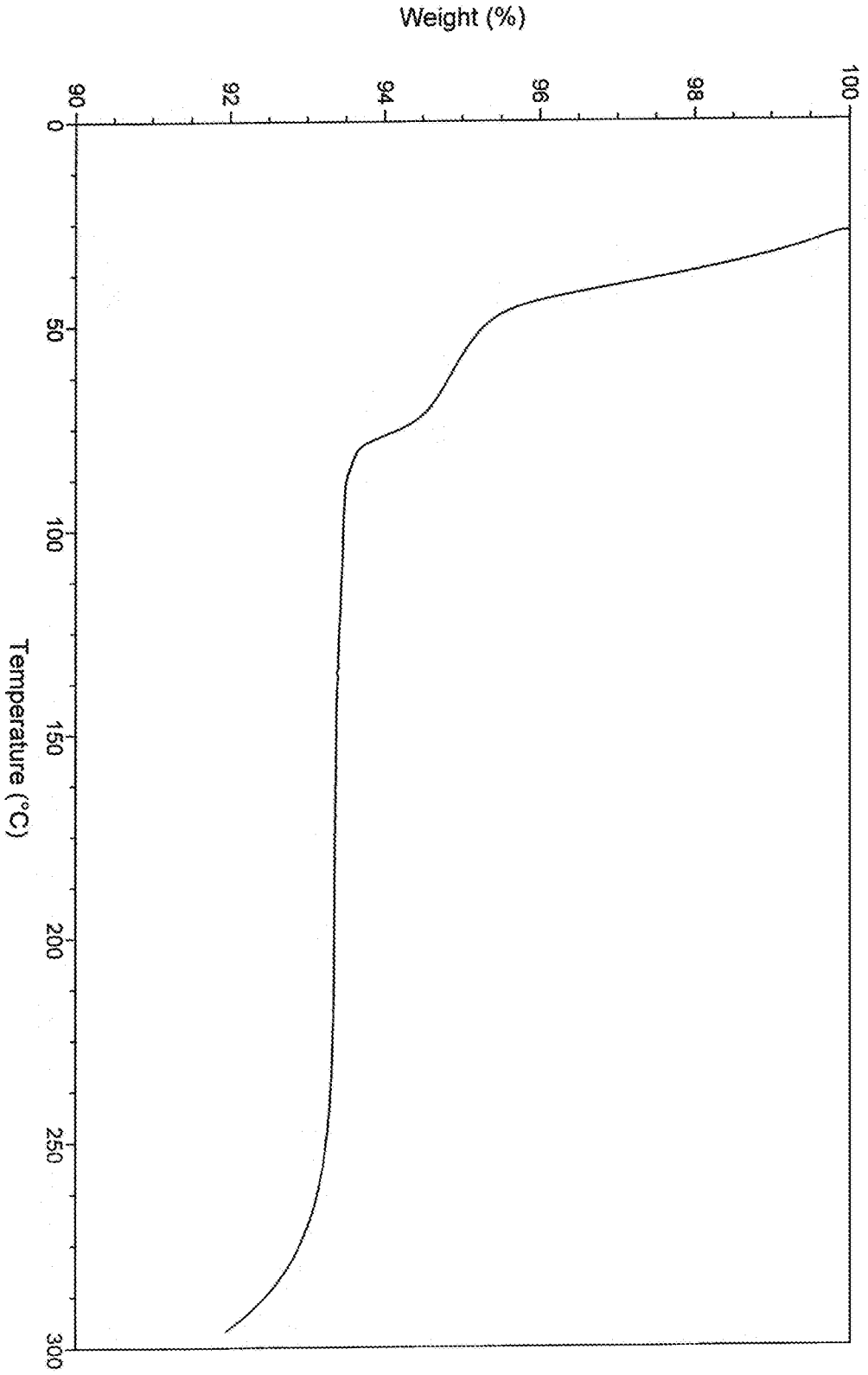
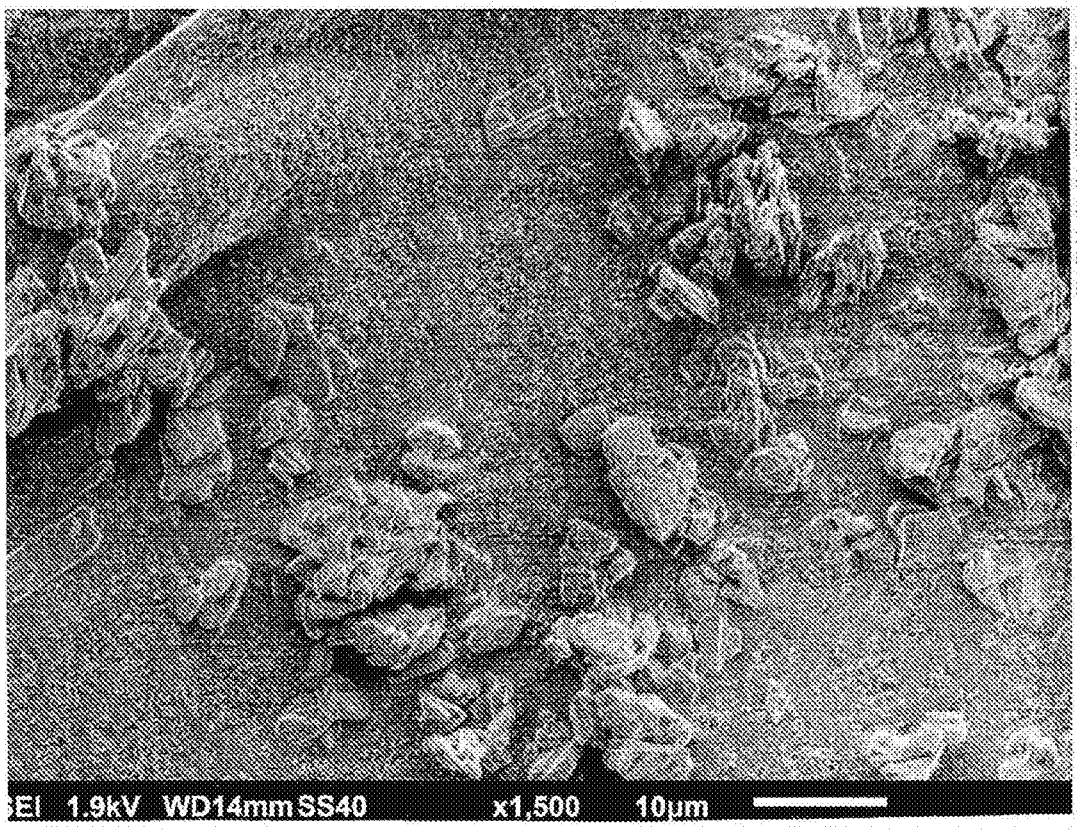


Figure 7

Figure 8



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB20 15/055559

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 409/10 (2015.01)
CPC - C07D 409/10 (2015.09)
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)
IPC(8) - A61K 31/331 , 31/7042; A61P 3/10; C07D 309/10, 409/10 (2015.01)
CPC - A61K 31/7042; C07D 309/10, 409/10 (2015.09)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/23; 536/122; IPC(8) - A61K 31/331 , 31/7042; A61 P 3/10; C07D 309/10, 409/10; CPC - A61K 31/7042; C07D 309/10, 409/10 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, STN, Google Patents, Google Scholar, SureChEMBL.
Search terms used: canagliflozin, "hydrate, TGA, thermogravimetric, dsc, calorimet*, x-ray, xrd, pxrd, sem, microscop*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2008/0146515 A1 (NOMURA et al) 19 June 2008 (19.06.2008) entire document	1-6, 8, 10, 13-18, 21, 22 --- 7, 11, 12, 19, 20
Y	CN 103936725 A (QILU PHARMACEUTICAL TIANJIN UNIVERSITY) 23 July 2014 (23.07.2014) entire document, see machine translation	7, 11, 19
Y	KATDARE et al. Characterization of Hydrates of Norfloxacin. Mikrochim. Acta 90(1): 1-12, 1986. [retrieved on 07 October 2015). Retrieved from the Internet. <URL: http://www.researchgate.net/profile/J_Guillory/publication/226618679_Characterization_of_hydrates_of_norfloxacin/links/0a85e533d9df74d4a0000000.pdf>. entire document	12, 20
P, A	WO 2014/180872 A1 (LEK PHARMACEUTICALS DD) 13 November 2014 (13.11.2014) entire document	1-22
P, A	CN 103980262 A (QILU PHARMACEUTICAL TIANJIN UNIVERSITY) 13 August 2014 (13.08.2014) entire doucment, see machine translation	1-22
P, A	CN 104130246 A (CHINA RESOURCES SAIKE PHARMACEUTICAL) 05 November 2014 (05.11.2014) entire document, see machine translation	1-22
P, A	WO 2015/071761 A2 (CRYSTAL PHARMATECH CO LTD) 21 May 2015 (21.05.2015) entire document	1-22

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

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"A" document defining the general state of the art which is not considered to be of particular relevance
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"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 2015	30 OCT 2015
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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