(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 August 2017 (24.08.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/141202 Al

(51) International Patent Classification:
C07D 407/12 (2006.01) *A61P 3/00* (2006.01)
A61K 31/351 (2006.01)

(21) International Application Number:
PCT/IB20 17/050904

(22) International Filing Date:
17 February 2017 (17.02.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201621005573 17 February 2016 (17.02.2016) IN

(71) Applicant: **LUPIN LIMITED** [IN/IN]; Kalpataru Inspire, 3rd Floor, Off Western Express Highway, Santacruz (East), Maharashtra, Mumbai 400 055 (IN).

(72) Inventors: **AGARKAR, Amit, Madan;** Lupin Limited (Research Park), 46A / 47A, Village Nande, Taluka Mulshi, Maharashtra, Pune 4121 15 (IN). **MITRA, Rangan;** Lupin Limited (Research Park), 46A / 47A, Village Nande, Taluka Mulshi, Maharashtra, Pune 4121 15 (IN). **RANANAWARE, Umesh, Babanrao;** Lupin Limited (Research Park), 46A / 47A, Village Nande, Taluka Mulshi, Maharashtra, Pune 4121 15 (IN). **GODBOLE, Himanshu, Madhav;** Lupin Limited (Research Park), 46A / 47A, Village Nande, Taluka Mulshi, Maharashtra, Pune 412 115 (IN). **SINGH, Girij, Pal;** Lupin Limited (Research Park), 46A / 47A, Village Nande, Taluka Mulshi, Maharashtra, Pune 4121 15 (IN).

(74) Agents: **MAJUMDAR, Subhatosh** et al; S. Majumdar & Co., 5 Harish Mukherjee Road, State of West Bengal, Kolkata 700 025 (IN).

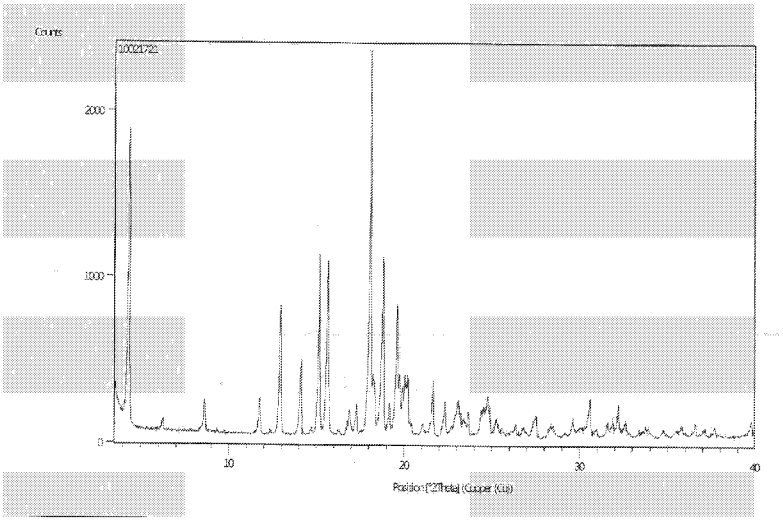
(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

[Continued on nextpage]

(54) Title: COMPLEX OF SGLT2 INHIBITOR AND PROCESS FOR PREPARATION THEREOF

Figure-1: The PXRD pattern of crystalline Form A of Empagliflozin-L-Proline Complex



(57) Abstract: The present invention relates to a crystalline Form **A** of complex of Empagliflozin with L-Proline and process for preparation thereof. The present invention further relates to a method of preparing pure crystalline Empagliflozin via formation of the said complex.

WO 2017/141202 A1

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Hi))*

Published:

— *with international search report (Art. 21(3))*

COMPLEX OF SGLT2 INHIBITOR AND PROCESS FOR PREPARATION THEREOF

Field of the invention

The present invention relates to a complex of Empagliflozin with amino acids and process for preparation thereof. More specifically, the present invention provides crystalline forms of a complex of Empagliflozin with L-Proline, specifically crystalline Form-A of Empagliflozin L-Proline complex and process for preparation thereof. The present invention further relates to a method of preparing pure crystalline Empagliflozin via the complex of Empagliflozin with L-Proline, specifically the crystalline Form-A of Empagliflozin L-Proline complex.

Background of the invention

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of diabetic medications indicated only for the treatment of type 2 diabetes. In conjunction with exercise and a healthy diet, they can improve glycemic control.

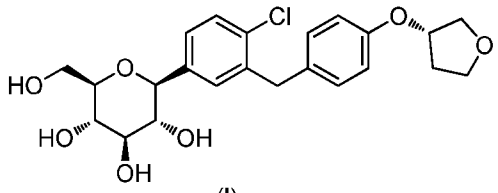
One of the classes of compound useful for inhibiting SGLT2 includes C-glucoside derivatives such as those described in U.S. Pat. No. 6,414,126, US20040138439, US20050209166, US20050233988, WO2005085237, U.S. Pat. No. 7,094,763, US20060009400, US20060019948, US20060035841, US20060122126, US20060234953, WO2006108842, US20070049537 and WO2007136116.

U.S. Pat. No. 6,774,112 discloses preparation of amino acid complexes of amorphous C-aryl glucosides formed from both the **D**- or L-enantiomers of natural amino acids which are useful for the treatment of type II diabetes.

The PCT publication WO2016/131431 discloses amorphous and crystalline complex of Empagliflozin with L-proline.

Empagliflozin, a C-aryl glucoside derivative, is an orally-active inhibitor of the sodium-glucose co-transporter 2 (SGLT2). It is chemically chemically described as D-Glucitol, 1,

5-anhydro-l-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3furanyl] oxy] phenyl] methyl] phenyl]-, (IS) and structurally represented by formula (I) as given below.



(I)

Empagliflozin has been approved as Jardiance ™, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Furthermore it has been indicated to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

U.S. Patent No. 7,579,449 (US'449) discloses Empagliflozin and process for its preparation.

U.S. Patent No. 7,772,191 (US' 191) discloses a process for preparation of Empagliflozin. The processes disclosed in US'449 and US' 191 either involves chromatographic purification or purification involving chemical transformation i.e. protection followed by deprotection in the final or penultimate step to obtain chemically and/or stereoisomerically pure final compound.

It is well known to one skilled in the art that for pharmaceutical use highly pure active pharmaceutical ingredient (API) are desired. Therefore there is a need to identify means to obtain Empagliflozin as a pure crystalline compound in high yield without involving chemical transformations for purification or chromatographic purification or simply an additional purification step.

Object of the invention

It is an object of the present invention to provide a crystalline Empagliflozin amino acid complex, specifically a crystalline Form-A of Empagliflozin L-Proline complex.

It is another object of the present invention to provide a process for preparation of the crystalline Empagliflozin amino acid complex, specifically a crystalline Form-A of Empagliflozin L-Proline complex.

It is another object of the present invention to provide means of obtaining pure crystalline Empagliflozin using the Empagliflozin amino acid complex as an intermediate, specifically the crystalline Form-A of Empagliflozin L-Proline complex.

It is yet another object of the present invention to provide means of obtaining a stereochemical^ and chemically pure crystalline Empagliflozin using the Empagliflozin amino acid complex as an intermediate, specifically the crystalline Form-A of Empagliflozin L-Proline complex.

It is yet another object of the present invention to provide pharmaceutical composition comprising an effective amount of the pure crystalline Empagliflozin and crystalline Form-A of Empagliflozin L-Proline complex.

Brief description of the drawing

Figure-1: The PXRD diffractogram of crystalline Form-A of Empagliflozin L-Proline Complex

Figure-2: The DSC thermogram of crystalline Form-A of Empagliflozin L-Proline Complex

Figure-3: The Infra-Red (IR) spectrum of crystalline Form-A of Empagliflozin L-Proline Complex

Figure-4: ^{1}H NMR of crystalline Form-A of Empagliflozin L-proline complex

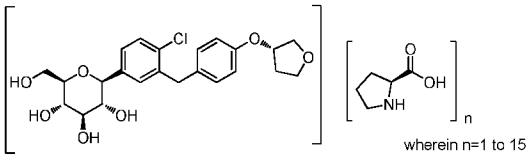
Figure-5: The PXRD diffractogram of crystalline Empagliflozin Tryptophan Complex

Figure-6: The PXRD diffractogram of crystalline Empagliflozin L-hydroxyproline Complex

Description of the invention

The present invention relates to a complex of Empagliflozin with amino acid. The amino acid is selected from the group consisting of L-proline, L-hydroxyproline, L-phenylalanine, L-aspartamine, L-arginine, Tryptophan and the like.

The present invention relates to a complex of Empagliflozin with L-Proline. More specifically, the invention provides a crystalline Form-A of Empagliflozin L-Proline complex of formula (II).



(II)

The crystalline form A of Empagliflozin L-Proline complex of the present invention is characterized by powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC) and infra-red spectroscopy.

The crystalline Form-A of Empagliflozin L-Proline complex of the present invention is characterized by powder X-ray diffraction (PXRD) diffractogram substantially as illustrated by Figure- 1.

The crystalline Form-A of Empagliflozin L-proline complex is characterized by X-ray diffraction peaks at 2Θvalues of 4.32, 6.24, 8.62, 11.77, 12.94, 14.12, 15.17, 15.64, 16.26, 16.90, 17.27, 18.06, 18.23, 18.78, 19.14, 19.58, 19.82, 20.19, 21.63, 22.30, 23.06, 24.74, 24.87 and 30.57 (2Θ± 0.2) degree.

The crystalline Form-A of Empagliflozin L-proline complex is further characterized by PXRD pattern having characteristic X-ray diffraction peaks at 2Θ values of 4.32, 6.24, 8.62, 11.77, 12.94, 14.12, 15.17, 15.64, 18.06, 18.78, 19.58, 21.63, 22.30 and 24.74 (2Θ± 0.2) degree.

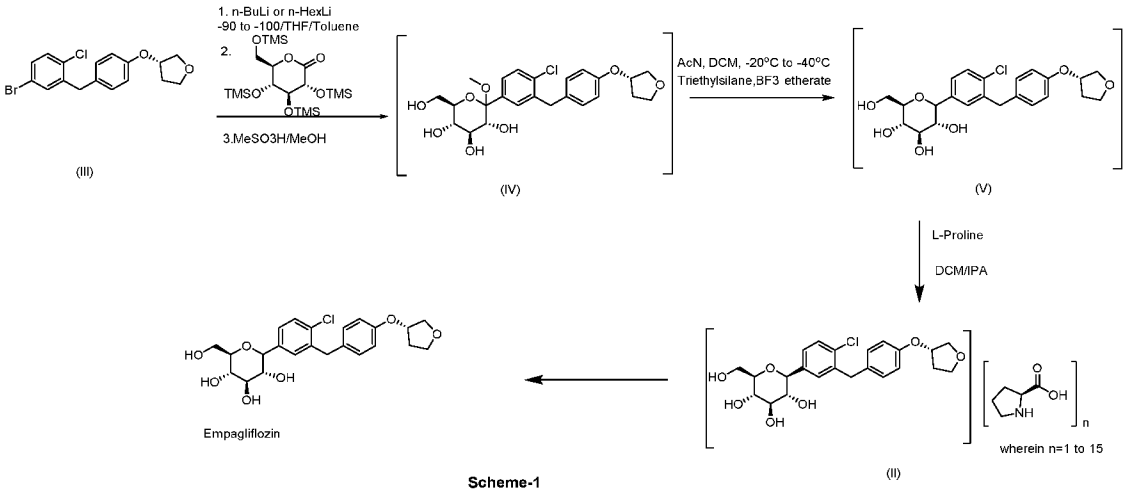
In a preferred embodiment, the crystalline Form-A of Empagliflozin L-proline complex is further characterized by PXRD pattern having characteristic X-ray diffraction peaks at 2Θ values of 4.32, 6.24, 8.62, 11.77, 12.94, 14.12, 15.17, 15.64, 18.06, 18.78, 19.58 and 21.63 (2Θ± 0.2) degree.

The crystalline Form-A of Empagliflozin L-proline complex is characterized by a differential scanning calorimetry thermogram having endothermic onsets at 47.57°C, 60.83°C and 155.54 °C ± 3°C.

The crystalline Form-A of Empagliflozin L-proline complex is further characterized by a differential scanning calorimetry thermogram substantially as illustrated by Figure-2.

The crystalline Form-A of Empagliflozin L-proline complex is further characterized by infra-red spectrum substantially as illustrated by Figure-3.

The crystalline Form-A of Empagliflozin L-proline complex of the present invention is prepared by reacting Empagliflozin with L-proline in a suitable solvent. The present inventors have also found that isolation of crystalline Form-A of Empagliflozin L-proline complex of formula (II) is also possible by reacting Empagliflozin of formula (V) in situ with L-proline as per the reaction sequence depicted in the following Scheme-1.



Scheme-1

In one aspect the present invention provides a process for the preparation of the crystalline Form-A of Empagliflozin L-Proline complex comprising:

(a) preparing a mixture of L-proline in a solvent A;

(b) contacting Empagliflozin in a solvent B and the mixture of step (a);

(c) heating the reaction mass of step (b);

(d) cooling the reaction mass of step (c) to obtain crystalline Form-A of Empagliflozin L-proline complex;

(e) isolating the crystalline Form-A of Empagliflozin L-Proline complex; and

(f) drying the isolated crystalline Form-A of Empagliflozin L-Proline complex.

The solvent A and solvent **B** is selected from the group consisting of alcohol, ketone, chlorinated hydrocarbon, ester, nitrile, water and a combination thereof in a suitable proportion. The preferred alcohol is methanol, ethanol, propanol, isopropanol, butanol, 2-butanol, 1-pentanol and the like, the preferred ketone is acetone and methyl ethyl ketone and the like ,the preferred chlorinated hydrocarbon is dichloromethane and the like, the preferred ester is ethyl acetate, isopropyl acetate and the like and the preferred nitrile is acetonitrile and the like.

The preferred solvent A is selected from the group consisting of alcohol, such as methanol, ethanol, propanol, isopropanol, butanol, 2-butanol, 1-pentanol and the like.

The preferred alcohol is isopropanol.

The preferred solvent **B** is selected from the group consisting of alcohol, such as methanol, ethanol, propanol, isopropanol, butanol, 2-butanol, 1-pentanol and the like and chlorinated hydrocarbon, such as dichloromethane and a combination thereof.

The preferred solvent **B** is dichloromethane, isopropanol or a combination thereof.

In step (c), the reaction mass of step (b) is heated to about 30 °C to about 90 °C, preferably to about 50 °C to about 80 °C, more preferably to about 30 °C to about 40 °C. In step (d) the reaction mass of step (c) is cooled to about -5 °C to 15 °C, more preferably to about 0 °C to 10 °C to obtain the crystalline Form A of Empagliflozin L-Proline complex. In step (e), the crystalline Form A of Empagliflozin L-Proline complex is isolated by techniques known in the art such as decantation, filtration by gravity or suction or centrifugation. In step (f), the crystalline Form A of Empagliflozin L-Proline

complex is dried at a suitable temperature and pressure for a suitable time. The suitable temperature for drying is about 30 °C to about 70°C, preferably is about 40 °C to about 50°C, and more preferably is not more than 45 °C.

The molar ratio of L-Proline used for complex formation ranges from about 1.0 to 20.0 equivalents of L-Proline, preferably about 2 to 15 equivalents, more preferably about 1.5 to 9 equivalents of L-Proline relative to Empagliflozin of step (b).

In yet another aspect of the present invention a pure crystalline Empagliflozin is obtained from the crystalline Form A of Empagliflozin L-proline complex of formula (II) of the present invention.

The preparation of pure crystalline Empagliflozin from the crystalline Form-A of Empagliflozin L-Proline complex comprises of adding a mixture of water and a water immiscible organic solvent to the crystalline Form-A of Empagliflozin L-proline complex and stirring at temperature of about 30 °C to about 80 °C, more preferably at about 30 °C to about 50 °C.

In a preferred aspect of the present invention, said process for the preparation of pure crystalline Empagliflozin from the crystalline Form-A of Empagliflozin L-Proline complex of formula (II) comprises:

(a) preparing a mixture of crystalline Form-A of Empagliflozin L-proline complex in water and a water immiscible organic solvent;
(b) heating the mixture of step (a) to obtain a reaction mass;
(c) separating the layers of the reaction mass of step (b) to obtain an organic layer;
(d) cooling the organic layer of step (c);
(e) optionally seeding the organic layer of step (c);
(f) isolating the pure crystalline Empagliflozin.

In step (a) crystalline Form-A of Empagliflozin L-proline complex is mixed with water and a water immiscible organic solvent selected from the group consisting of chlorinated hydrocarbon and ester. The preferred chlorinated hydrocarbon is dichloromethane and the

preferred ester is ethyl acetate and isopropyl acetate or mixtures thereof, wherein the volume of organic solvent used is 5 to 20 times, preferably 10 to 15 times of the crystalline Form-A of Empagliflozin L-proline complex.

The preferred water immiscible organic solvent of step (a) is ethyl acetate wherein the ratio of ethylacetate to water is in the range of 3:1, preferably the ratio is 2:1(volume/volume).

In step (b), the reaction mass of step (a) is heated to about 40 °C to about 80 °C, preferably to about 55 °C to about 60 °C, more preferably to about 45 °C to about 50 °C. The reaction mass of step (b) is separated at 45 °C to about 50 °C to obtain an organic layer. The organic layer of step (c) is micron filtered to make it clear and free of unwanted particles. The organic layer of step (c) is cooled to about -5 °C to about 30 °C, more preferably the solution is cooled to about 0 °C to about 5 °C to obtain pure crystalline Empagliflozin.

The pure crystalline Empagliflozin is isolated by techniques known in the art such as decantation, filtration by gravity or suction or centrifugation. The isolated pure crystalline Empagliflozin is dried at a suitable temperature and pressure for a suitable time. The suitable temperature for drying is about 30 °C to about 70 °C, preferably is about 40 °C to about 50 °C, and more preferably is not more than 45 °C.

The processes of the present invention are particularly useful as they represent an efficient process for the preparation of SGLT2 inhibitor, pure crystalline Empagliflozin. In contrast to the processes illustrated in US'449 & US' 191, the methods of the present invention involve the reduction of an intermediate of formula (IV) to obtain Empagliflozin of formula (V) followed by complex formation with an amino acid, preferably L-Proline, wherein the complex is solid, typically crystalline, and is formed on large scale without intervening protection and deprotection steps. By eliminating the protection and deprotection steps, the final product can be produced in higher yield and in the absence of solvent impurities e.g., pyridine that are difficult to remove with the known processes. Furthermore, the formation of the crystalline Empagliflozin L-proline

complex of formula (II) is carried out without purification of the Empagliflozin intermediate compound of formula (V).

In an aspect of the invention, pure crystalline Empagliflozin prepared according to the present invention are pure having a chemical purity greater than about 98.5%, or greater than about 99.0%, or greater than about 99.5 % by weight as determined using high performance liquid chromatography (HPLC). The pure crystalline Empagliflozin produced by a method of present invention are chemically pure Empagliflozin having purity greater than about 99.5% and contain no single impurity in amounts greater than about 0.15%, by HPLC.

More preferably the pure crystalline Empagliflozin produced by the methods of present invention are chemically pure Empagliflozin having purity greater than about 99.8% and contain no single impurity in amounts greater than about 0.1% by HPLC.

Empagliflozin used as the input material for the preparation of Empagliflozin L-proline complex is obtained by a process known to a person ordinary skilled in the art. In a specific embodiment, the input material is prepared by practicing the chemistry disclosed in US'449 and US' 191 patents or by method illustrated in the present specification.

In one more aspect, the present invention provides a pharmaceutical composition comprising the crystalline Form A of Empagliflozin L-proline complex along with one or more pharmaceutically acceptable carriers, excipients, or diluents.

In yet another aspect, the present invention provides a pharmaceutical composition comprising the pure crystalline Empagliflozin along with one or more pharmaceutically acceptable carriers, excipients, or diluents.

The crystalline Form A of Empagliflozin L-proline complex and the pure crystalline Empagliflozin of the present invention can be used as SGLT2 inhibitor indicated for the treatment of type 2 diabetes mellitus. Such pharmaceutical composition can be prepared by the methods known in the literature.

In yet another aspect the present invention provides crystalline complexes of Empagliflozin with Tryptophan and L-hydroxyproline and processes for preparation thereof. The present invention provides a process for preparation of crystalline Empagliflozin Tryptophan complex comprising:

(a) preparing a mixture of Empagliflozin in isopropanol;

(b) contacting tryptophan to the mixture of step(a);

(c) heating the reaction mass of step(b) to about 50°C to about 60°C;

(d) cooling the reaction mass of step (c) to about 20 °C to about 25 °C to obtain crystalline complex of Empagliflozin with Tryptophan; and

(e) isolating the crystalline complex of Empagliflozin with Tryptophan.

The present invention further provides a process for preparation of crystalline Empagliflozin L-hydroxyproline complex comprising:

(a) preparing a mixture of Empagliflozin in isopropanol;

(b) contacting L-hydroxyproline to the mixture of step(a);

(c) heating the reaction mass of step(b) to about 50°C to about 60°C;

(d) cooling the reaction mass of step (c) to about 20 °C to about 25 °C to form crystalline complex of Empagliflozin with L-hydroxyproline; and

(e) isolating the crystalline complex of Empagliflozin with L-hydroxyproline.

The crystalline complexes of Empagliflozin with tryptophan and L-hydroxyproline are useful intermediate for the preparation of pure crystalline Empagliflozin.

In one more aspect, the present invention provides a pharmaceutical composition comprising the crystalline complexes of Empagliflozin with tryptophan and L-hydroxyproline along with one or more pharmaceutically acceptable carriers, excipients, or diluents.

The crystalline complexes of Empagliflozin with tryptophan and L-hydroxyproline of the present invention can be used as SGLT2 inhibitor indicated for the treatment of type 2 diabetes mellitus. Such pharmaceutical composition can be prepared by the methods known in the literature.

The present invention is further illustrated with the following non-limiting examples.

Example-1: Preparation of crystalline Form A of Empagliflozin L-proline complex

To 1.0 gm of L-Proline, 5 mL of isopropyl alcohol was added and heated to 40 °C. To the obtained slurry was added slurry of lgm Empagliflozin in lOmL of dichloromethane at 30 °C to 40 °C. The reaction mixture was stirred for 2 hrs at 20 °C to 30 °C, filtered and dried under vacuum at 50 °C to yield 1.5 gm of crystalline Form A of Empagliflozin L-proline complex.

Example-2: Preparation of crystalline Form A of Empagliflozin L-proline complex

A solution of 50 gm of (S)-4-bromo-l-chloro-2-(4-tetrahydrofuran-3-yloxy-benzyl)-benzene in tetrahydrofuran 300 mL and toluene 100 mL was cooled to -90 °C to -100 °C, 90 mL of n-hexyl Lithium (33% in tetrahydrofuran) was gradually added and the solution was stirred for 15 to 30 min. Then a solution of 2, 3, 4, 6 -tetrakis-0-(trimethylsilyl)-D-glucopyranone in toluene was added at -90 °C to -100 °C and the reaction mixture was stirred for 2 to 5 hrs. Thereafter 200 mL solution of methanesulphonic acid in methanol was added to the reaction mixture at -70 °C to -90 °C, the temperature of the reaction mixture was raised to 0 °C to 15 °C and the reaction mixture was stirred for 10 to 15 hrs at ambient temperature. The solution was then quenched with 8% aq. sodium bicarbonate solution followed by layer separation. The aqueous layer was extracted with ethylacetate (2 X 250 mL).The combined organic layer was washed with 250 mL 10% brine solution. The combined organic layer was concentrated under vacuum followed by stripping with acetonitrile 50mL to afford 95 gm of crude intermediate compound of formula **(IV)** as an oily mass. 200 mL of dichloromethane and 100 mL of acetonitrile was added to the oily mass at -30 °C to -40 °C followed by addition of trimethylsilane and borontrifluoride etherate. The reaction mixture was stirred for 2 to 3 hrs followed by addition of 550 mL of 8% aq. sodium bicarbonate solution at 5 °C to 20 °C. The organic layer was separated and extracted with dichloromethane (I X 250 mL and 1 X 100 mL). The combined organic layer was concentrated to get an oily mass of compound of formula **(V).** A solution of compound of formula **(V)** in 200 mL dichloromethane was added to slurry of 50 gm L-proline in 200 mL isopropanol and heated at 40 ^{oC} to 50 °C for 7-10 hrs. The

reaction mixture was filtered and washed with 25 mL dichloromethane and dried under vacuum to afford 53 gm of crystalline Form A of Empagliflozin L-proline complex.

Example-3: Preparation of crystalline Form A of Empagliflozin L-proline complex

A solution of 100 gm of (S)-4-bromo-l-chloro-2-(4-tetrahydrofuran-3-yloxy-benzyl)-benzene in tetrahydrofuran 300 mL and toluene 100 mL was cooled to -90 °C to -100 °C, 90 mL of n-hexyl Lithium (33% hexane) was gradually added and the solution was stirred for 15 to 30 min. Then a solution of 84 gm of 2, 3, 4, 6 -tetrakis-0-(trimethylsilyl)-D-glucopyranone in toluene was added at -90 °C to -100 °C and the reaction mixture was stirred for 2 to 5 hrs. Thereafter 78 gm of methanesulphonic acid in 300 ml methanol was added to the reaction mixture at -70 °C to -90 °C, the temperature of the reaction mixture was raised to 20 °C to 30 °C and the reaction mixture was stirred for 3 to 4 hrs at ambient temperature. The reaction mixture was cooled to 0 °C to 10 °C and then the reaction mixture was quenched with 30% aq. sodium bicarbonate solution followed by layer separation. The aqueous layer was extracted with ethylacetate (2 X 300 mL).The combined organic layer was washed with 500 mL 10% brine solution. The volume of combined organic layer was reduced to 1.8 volumes followed by addition of dichloromethane 400mL and acetonitrile lOOmL.Thereafter 80 mL Of trimethylsilane and 80mL borontrifluoride etherate was added in succession at -40 °C to -25 °C. The reaction mixture was stirred for 15 to 30 min. followed by addition of 300 mL dichloromethane and lOOOmL of 8% aq. sodium bicarbonate solution at 0°C to 10 °C. The temperature was raised to 25 °C to 30 °C followed by addition of 200 mL of isopropyl alcohol. Thereafter the organic layer was separated. To the organic layer 79 gm of L-proline and 100 mL of isopropanol was added and stirred at 40 °C to 45 °C for 1 to 2 hrs. Thereafter the reaction mixture was cooled to 0°C to 10 °C, stirred for 1 to 2 hrs and filtered. The wet cake was slurry washed with isopropanol and dried under vacuum to afford 110 gm of crystalline Form A of Empagliflozin L-proline complex.

Example-4: Preparation of pure crystalline Empagliflozin

A mixture of 20 gm of crystalline Form A of Empagliflozin L-proline complex in 120 mL ethylacetate and 100 mL water was stirred at 25°C to 50°C for 45 to 60 min. Thereafter the layers were separated and the aqueous layer was extracted with 25 mL ethylacetate.

The combined organic layer was washed with 25 mL water and concentrated to afford 10.2 gm solid. The solid thus obtained was mixed with 70 mL ethylacetate and 10 mL water and was heated to 60°C to 70°C to obtain a clear solution. Thereafter the solution was cooled to 20°C to 30°C, followed by filtration and drying under vacuum to afford 9 gm of pure crystalline Empagliflozin.

Example-5: Preparation of pure crystalline Empagliflozin

A mixture of 100 gm of crystalline Form A of Empagliflozin L-proline complex in 800 mL ethylacetate and 400 mL water was heated 45°C to 50°C for 30 to 45 min. Thereafter the reaction mixture was allowed to settle and the layers were separated. The organic layer was passed through micron filtered, the filtrate obtained was heated to 55°C to 60°C, stirred for 30 to 45 min. and cooled to 30°C to 40°C, optionally seeded with Empagliflozin and stirred for 45 to 60 min. The reaction mass was further cooled to 20°C to 25°C and stirred for 2 to 3 hrs. Thereafter, the reaction mass was further cooled to 0°C to 5°C, stirred for 1 to 2 hrs, filtered and dried under vacuum to afford 35 gm of pure crystalline Empagliflozin.

Example-6: Preparation of crystalline Empagliflozin Tryptophan complex

To 10.0 gm of Empagliflozin in 60 mL of isopropyl alcohol was added 9gm of tryptophan. The obtained slurry was heated to 50 °C to 55 °C and stirred for lhr. Thereafter the reaction mixture was cooled to 20 °C to 30 °C, filtered and dried under vacuum at 45 °C to yield 19.6 gm of crystalline Empagliflozin tryptophan complex.

Example-7: Preparation of crystalline Empagliflozin L-hydroxyproline complex

To 10.0 gm of Empagliflozin in 50 mL of isopropyl alcohol was added 4.5gm of L-hydroxyproline. The obtained slurry was heated to 50 °C to 55 °C and stirred for lhr. Thereafter the reaction mixture was cooled to 20 °C to 30 °C, filtered and dried under vacuum at 45 °C to yield 13.9 gm of crystalline Empagliflozin L-hydroxyproline complex.

CLAIMS

1. Crystalline Form-A of Empagliflozin L-proline complex.

2. The crystalline Form-A of Empagliflozin L-Proline complex according to claim 1 characterized by powder X-ray diffraction (PXRD) diffractogram substantially as illustrated by Figure-1.

3. The crystalline Form-A of Empagliflozin L-proline complex of claim 1, characterized by X-ray diffraction peaks at 2Θ values of 4.32, 6.24, 8.62, 11.77, 12.94, 14.12, 15.17, 15.64, 18.06, 18.78, 19.58, 21.63, 22.30 and 24.74 (2Θ± 0.2) degree.

4. The crystalline Form-A of Empagliflozin L-proline complex of claim 1, further characterized by X-ray diffraction peaks at 2Θ values of 4.32, 6.24, 8.62, 11.77, 12.94, 14.12, 15.17, 15.64, 18.06, 18.78, 19.58 and 21.63 (2Θ± 0.2) degree.

5. The crystalline Form-A of Empagliflozin L-proline complex of claim 1, characterized by a differential scanning calorimetry thermogram having endothermic onsets at 47.57°C, 60.83°C and 155.54 °C ± 3°C.

6. The crystalline Form-A of Empagliflozin L-proline complex of claim 1, characterized by a differential scanning calorimetry thermogram substantially as illustrated by Figure-2.

7. A process for preparing pure crystalline Empagliflozin comprising the steps:
   (a) preparing a mixture of crystalline Form-A of Empagliflozin L-proline complex in water and a water immiscible organic solvent;
   (b) heating the mixture of step (a) to obtain a reaction mass;
   (c) separating the layers of the reaction mass of step (b) to obtain an organic layer;
   (d) cooling the organic layer of step (c);
   (e) optionally seeding the organic layer of step (c);
   (f) isolating the pure crystalline Empagliflozin.

8. The process according to claim 7 wherein the water immiscible solvent is an ester or a chlorinated hydrocarbon.

9. The process according to claim 7 wherein the water immiscible organic solvent is an ester and the ester is ethyl acetate.

10. The process for preparing crystalline Form A of Empagliflozin L-proline complex as defined in any of the claims 1 to 6, comprising the steps:

(a) preparing a mixture of L-proline in a solvent A;

(b) contacting Empagliflozin in a solvent B and the mixture of step (a);

(c) heating the reaction mass of step (b);

(d) cooling the reaction mass of step (c) to obtain crystalline Form-A of Empagliflozin L-proline complex ;and

(e) isolating the crystalline Form-A of Empagliflozin L-Proline complex.

11. The process according to claim 10 wherein the solvent A is selected from methanol, ethanol, propanol, isopropanol, butanol, 2-butanol andl-pentanol.

12. The process according to claim 10 wherein the solvent B is selected from methanol, ethanol, propanol, isopropanol, butanol, 2-butanol and 1-pentanol, chlorinated hydrocarbon and a combination thereof.

13. The process according to claim 10 wherein the solvent B is isopropanol, dichloromethane or a combination thereof.

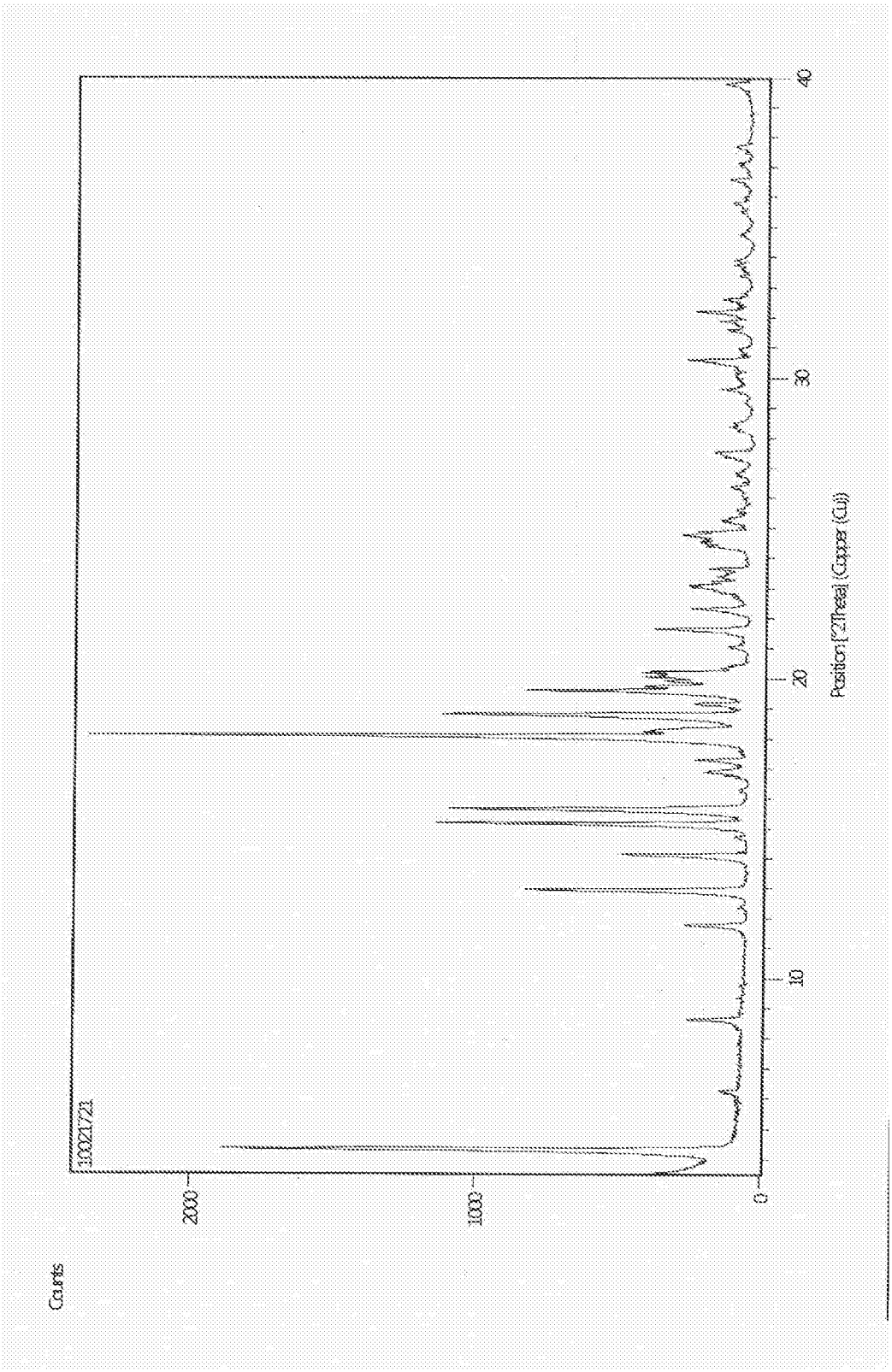


Figure-1: The PXRD pattern of crystalline Form A of Empagliflozin-L-Proline Complex

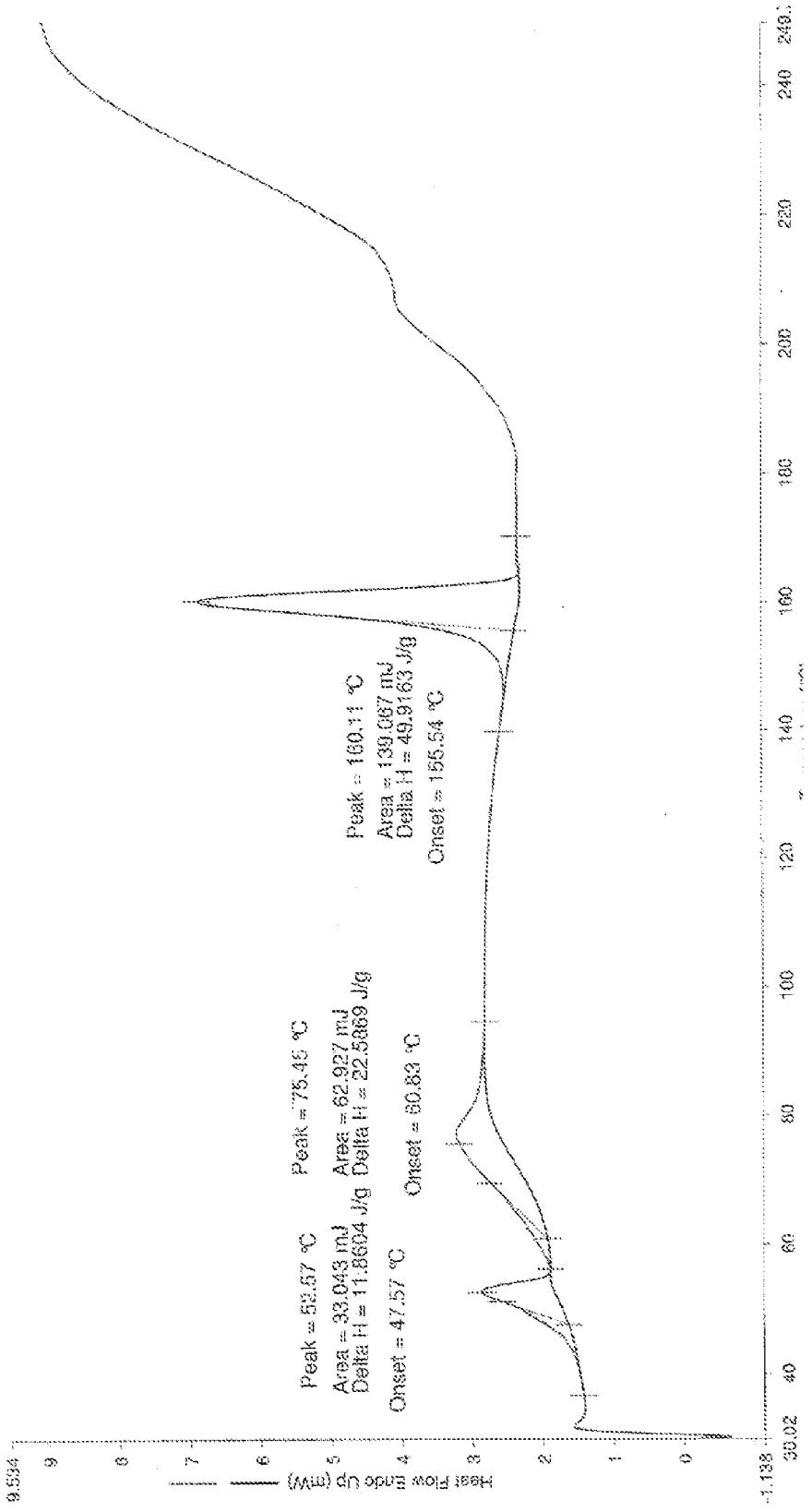


Figure-2: The DSC thermogram of crystalline Form A of Empagliflozin-L-Proline

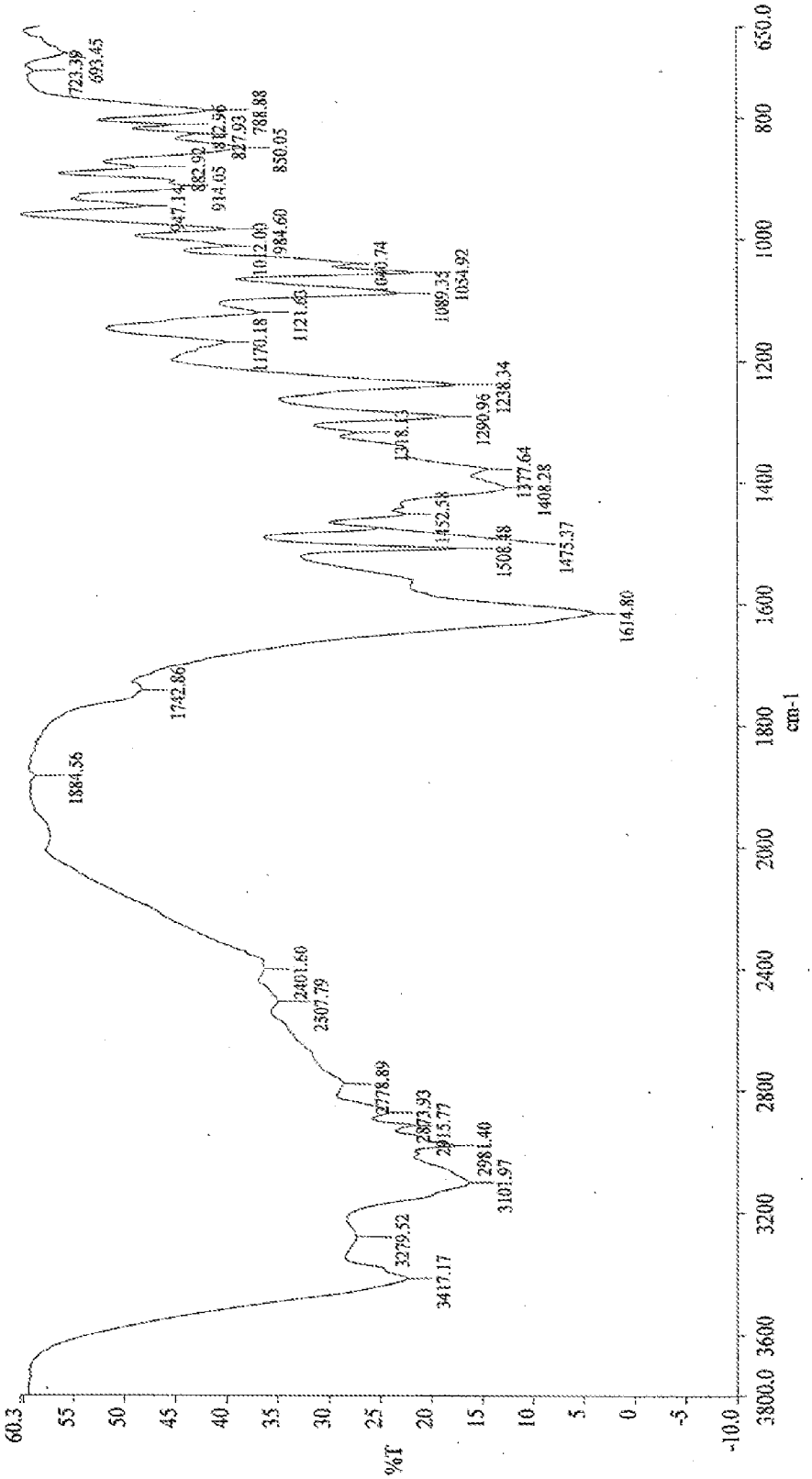


Figure-3: The IR spectrum of crystalline Form A of Empagliflozin-L-Proline Complex

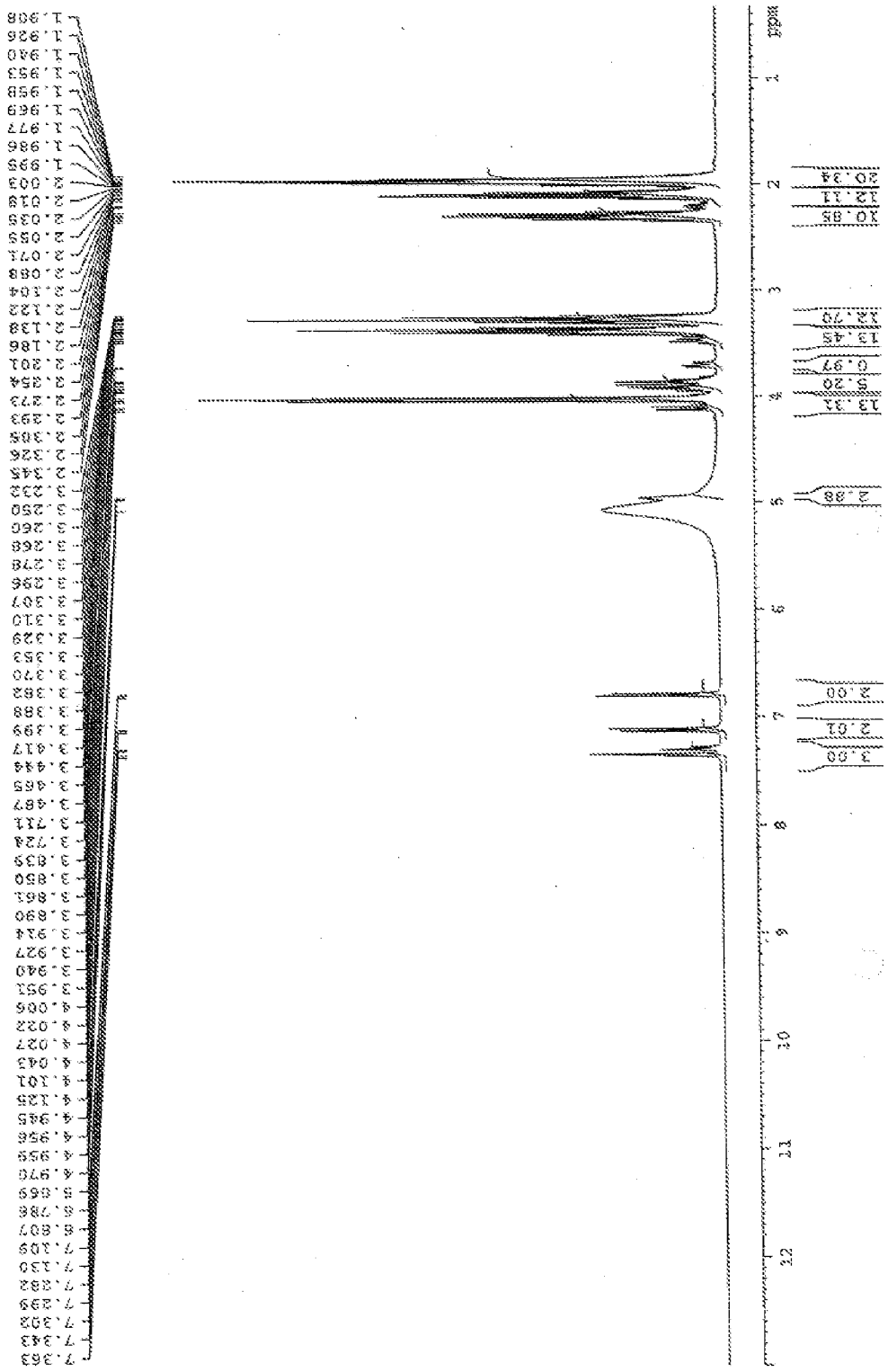


Figure-4: ^{1}H NMR of Crystalline Form A of Empagliflozin L-proline complex

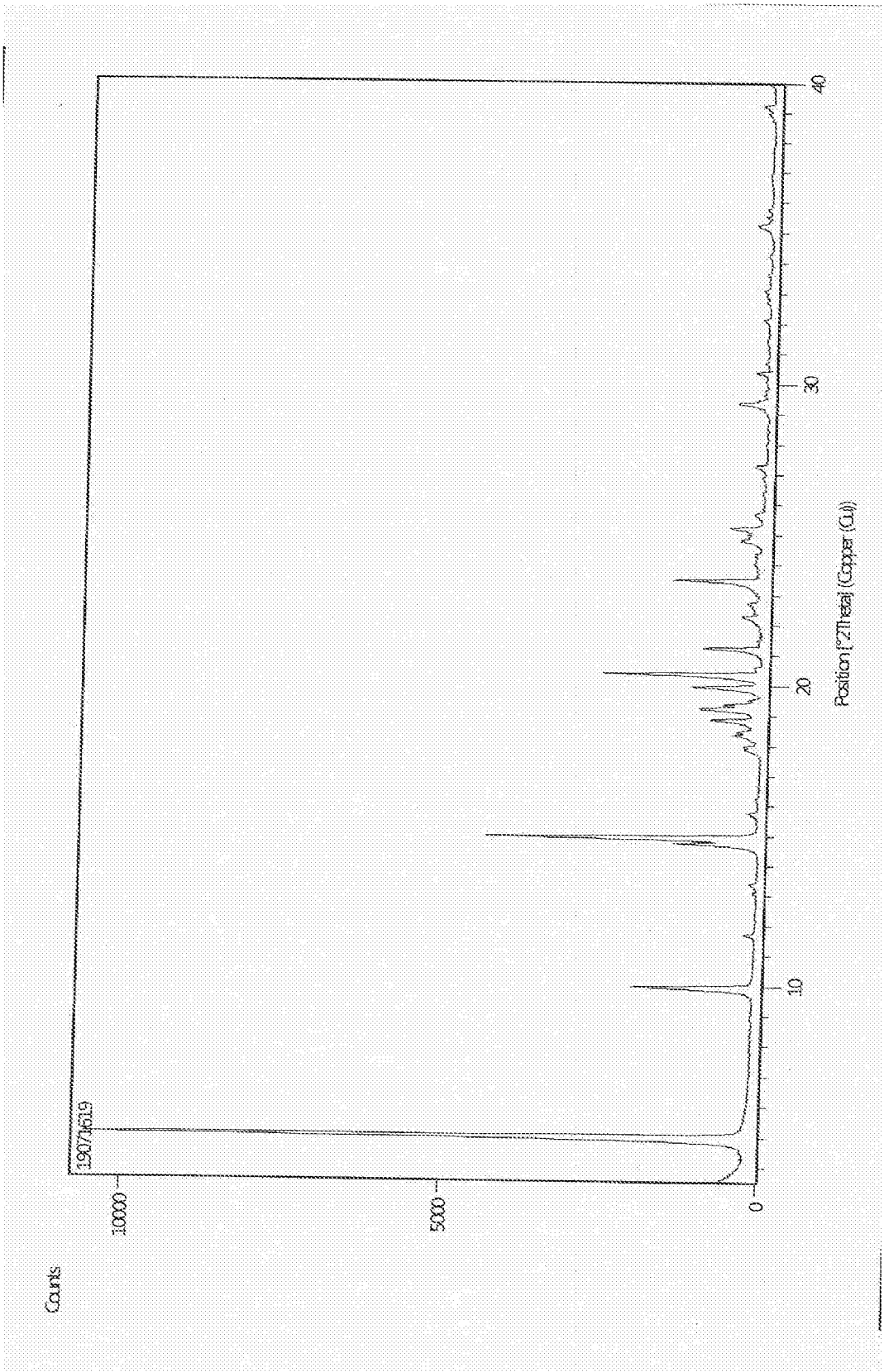


Figure-5: The PXRD diffractogram of crystalline Empagliflozin Tryptophan Complex

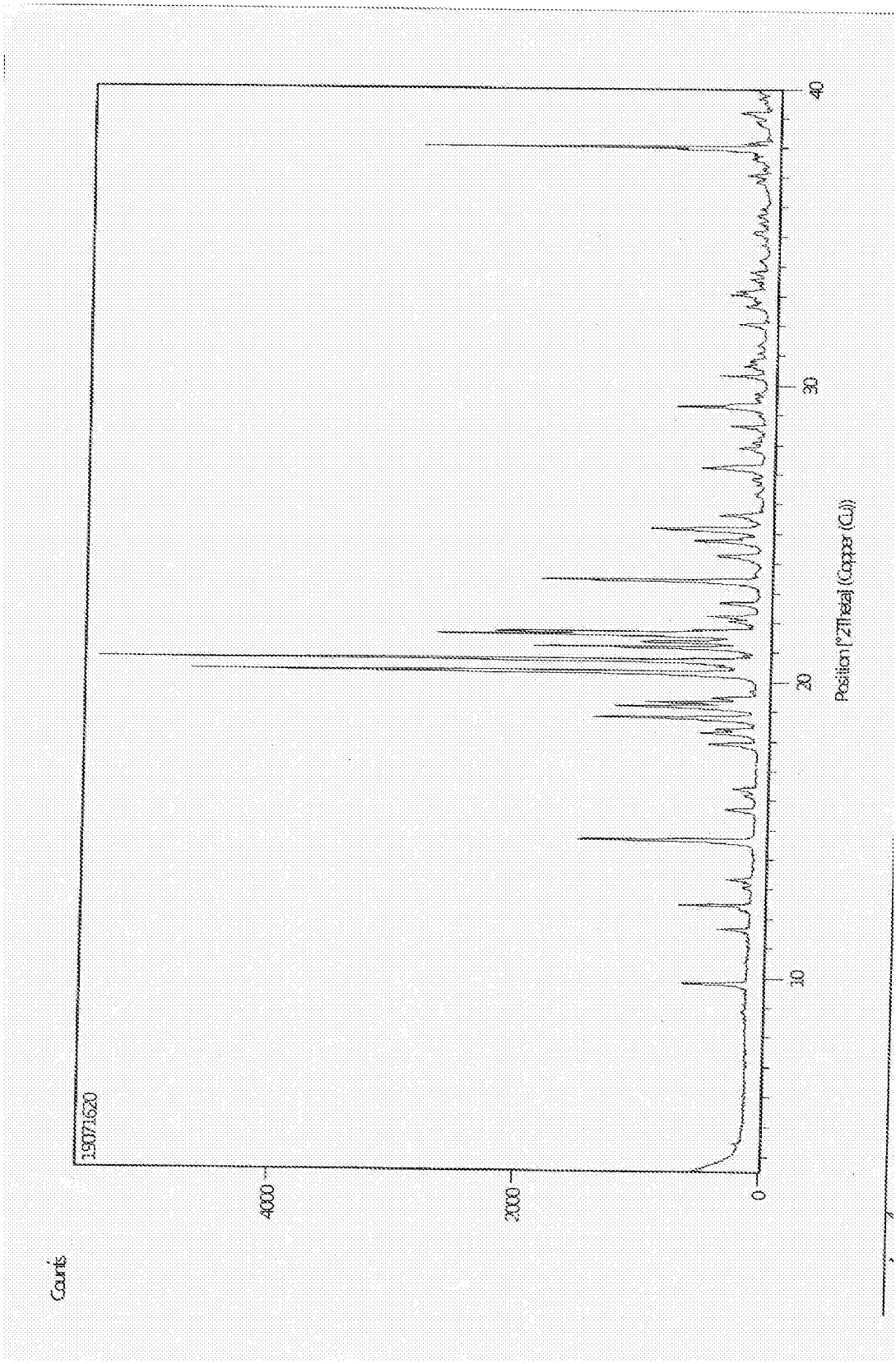


Figure-6: The PXRD diffractogram of crystalline Empagliflozin L-hydroxyproline Complex

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/050904

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D407/12 A61K31/351 A61P3/00
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/117359 A1 (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; ECKHA) 9 November 2006 (2006-11-09) claims	1-13
X	WO 2005/092877 A1 (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; HIMME) 6 October 2005 (2005-10-06) page 68, second compound	1-13
X,P	WO 2016/131431 A1 (ZENTIVA K S [CZ]) 25 August 2016 (2016-08-25) cited in the application claims; examples	1,10

-/-

[X] Further documents are listed in the continuation of Box C.

[X] 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

"E" earlier application or patent but published on or after the international filing date

"L" documentwhich may throw doubts on priority claim(s) orwhich is cited to establish the publication date of another citation or other special reason (as specified)

"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

"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
20 April 2017	28/04/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Beyss-Kahana, Ellen

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CAI RA: "Crystal l i ne Polymorphi sm of Organi c Compounds" , TOPICS I N CURRENT CHEMISTRY, SPRINGER, BERLIN , DE, vol . 198, 1 January 1998 (1998-01-01) , pages 163-208, XP008166276, ISSN : 0340-1022 paragraph bri dgi ng pages 165-166; chapter 3 . 1 . ; the whol e document -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2017/050904

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006117359 Al	09-11-2006	AR 053720 Al	16-05-2007
		AR 087208 A2	26-02-2014
		AT 452883 T	15-01-2010
		AU 2006243859 Al	09-11-2006
		BR PI0610994 A2	10-08-2010
		CA 2606650 Al	09-11-2006
		CY 1109870 TI	10-09-2014
		DK 1888552 T3	12-04-2010
		EA 200702346 Al	28-04-2008
		EP 1888552 Al	20-02-2008
		EP 2166007 Al	24-03-2010
		ES 2337498 T3	26-04-2010
		HK 1115133 Al	23-12-2011
		HR P20100033 TI	31-03-2010
		IL 187087 A	30-06-2011
		JP 4226070 B2	18-02-2009
		JP 2008540373 A	20-11-2008
		JP 2009046513 A	05-03-2009
		KR 20080015424 A	19-02-2008
		MY 142108 A	15-09-2010
		NO 339073 Bl	07-11-2016
		NZ 563563 A	26-11-2010
		PE 10632009 Al	19-08-2009
		PE 13742006 Al	09-01-2007
		PT 1888552 E	02-03-2010
		SI 1888552 TI	30-04-2010
		TW 1344465 B	01-07-2011
		US 2007249544 Al	25-10-2007
		US 2010099641 Al	22-04-2010
		UY 29505 Al	30-11-2006
		Wo 2006117359 Al	09-11-2006
WO 2005092877 Al	06-10-2005	AR 048041 Al	22-03-2006
		AR 077512 A2	31-08-2011
		AR 077513 A2	31-08-2011
		AT 557013 T	15-05-2012
		AU 2005225511 Al	06-10-2005
		BR PI0508830 A	14-08-2007
		CA 2557801 Al	06-10-2005
		CN 103030617 A	10-04-2013
		CN 103435581 A	11-12-2013
		CN 103450129 A	18-12-2013
		CN 103467423 A	25-12-2013
		CY 1112948 TI	09-12-2015
		DK 1730131 T3	13-08-2012
		EA 200601584 Al	27-04-2007
		EC SP066855 A	24-11-2006
		EP 1730131 Al	13-12-2006
		EP 2295422 A2	16-03-2011
		EP 2360164 A2	24-08-2011
		EP 2360165 A2	24-08-2011
		ES 2387881 T3	03-10-2012
		HK 1188775 Al	16-12-2016
		HK 1188776 Al	08-04-2016
		HK 1188777 Al	08-04-2016
		HR P20120627 TI	31-08-2012
		IL 177043 A	24-03-2013
		IL 218714 A	28-02-2013

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2017/050904

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		JP 4181605 B2	19-11-2008
		JP 5147314 B2	20-02-2013
		JP 5147469 B2	20-02-2013
		JP 2007246544 A	27-09-2007
		JP 2007522143 A	09-08-2007
		JP 2008208127 A	11-09-2008
		KR 20060133021 A	22-12-2006
		KR 20120007088 A	19-01-2012
		LU 92555 12	24-11-2014
		MY 151336 A	15-05-2014
		NO 335264 Bl	27-10-2014
		NO 2014028 11	17-11-2014
		NZ 550464 A	29-10-2010
		PT 1730131 E	15-06-2012
		RS 52365 B	31-12-2012
		SG 151271 Al	30-04-2009
		SI 1730131 TI	31-08-2012
		TW 1323264 B	11-04-2010
		US 2005209166 Al	22-09-2005
		US 2009023913 Al	22-01-2009
		US 2009326215 Al	31-12-2009
		US 2011178033 Al	21-07-2011
		US 2012296080 Al	22-11-2012
		US 2014046046 Al	13-02-2014
		Wo 2005092877 Al	06-10-2005
W0 2016131431 Al	25-08-2016	NONE	