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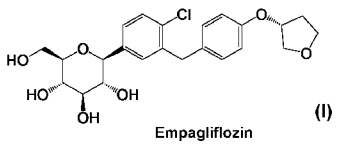
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(54) Title: SOLID STATE FORMS OF EMPAGLIFLOZIN



Empagliflozin (I)

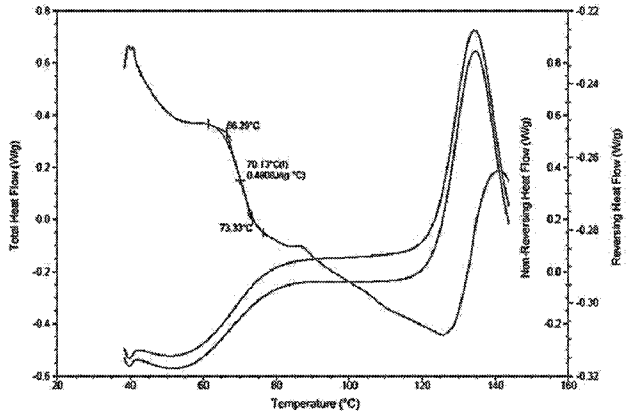


Figure 35

(57) Abstract: The present invention provides solid state forms of empagliflozin, complexes of empagliflozin with amino acids, processes for their preparation and their use in purification of empagliflozin and also provided pharmaceutical compositions comprising them and their use in therapy (Formula I).

[Continued on next page]

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SOLID STATE FORMS OF EMPAGLIFLOZIN

CROSS-REFERENCE TO RELATED APPLICATIONS

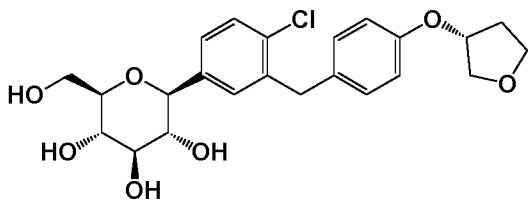
This application claims the benefit of Indian provisional patent application No. 201641018135 filed on 26 May 2016; Indian provisional patent application No. 201641038303 filed on 9 Nov 2016; Indian provisional patent application No. 201741001520 filed on 13 Jan 2017; and Indian provisional patent application No. 201741009875 filed on 21 Mar 2017 which are hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present application relates to solid state forms of empagliflozin and processes for preparation of empagliflozin and intermediates thereof

BACKGROUND OF THE INVENTION

The drug compound having the adopted name Empagliflozin, has a chemical name 1-chloro-4(beta-D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl)-benzene, and is represented by the structure of formula I.



Formula I

Empagliflozin is a sodium-dependent glucose cotransporter 2 (SGLT 2) inhibitor and is used for the treatment of patients with type 2 diabetes mellitus.

Empagliflozin and its synthetic methods are described in US Patent No. 7,579,449 (US '449). Example 3 of US '449 describes isolation of empagliflozin as "the organic phase (ethylacetate phase) is dried over sodium sulphate, the solvent is removed and the residue is purified using silica gel column chromatography (dichloromethane/ methanol 1:0→5:1).

US Patent No. 7,713,938 (US '938) discloses a crystalline form of empagliflozin and a pharmaceutical composition comprising the crystalline form. The US '938 also

discloses that “the method of manufacturing empagliflozin as described in product patent process does not yield a crystalline form”.

Indian patent application (IN1985MUM2013A), PCT applications (WO2016051368A1, WO2016131431A1, WO2016169534A1 and WO2017046730A1), and Chinese patent applications (CN104788438A, CN105384730A1, CN105481843A, CN105496966A, CN106188021A and CN106317035A) describe various solid state forms and co-crystals of empagliflozin and processes for preparation thereof.

Polymorphism, the occurrence of different crystal forms, is a phenomenon of some molecules and molecular complexes. A single molecule may give rise to a variety of polymorphs having distinct crystal structures and physical properties. Polymorphs in general will have different melting points, thermal behaviors (e.g. measured by thermogravimetric analysis - "TGA", or differential scanning calorimetry - "DSC"), X-ray powder diffraction (XRPD or powder XRD) pattern, infrared absorption fingerprint, and solid state nuclear magnetic resonance (NMR) spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

Discovering new polymorphic forms, hydrates and solvates of a pharmaceutical product can provide materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification or as desirable intermediate crystal forms that facilitate conversion to other polymorphic forms. New polymorphic forms and solvates of a pharmaceutically useful compound or salts thereof can also provide an opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for formulation optimization, for example by providing a product with different properties, e.g., better processing or handling characteristics, improved dissolution profile, or improved shelf-life. For at least these reasons, there is a need for additional solid forms of Empagliflozin.

SUMMARY OF THE INVENTION

Aspects of the present application relate to amorphous empagliflozin, amorphous solid dispersion of empagliflozin, and complexes of empagliflozin with amino acids,

crystalline forms of empagliflozin, their preparative processes and pharmaceutical compositions thereof.

In the first aspect, the present application provides stable amorphous empagliflozin.

In the second aspect, the present application provides amorphous empagliflozin having a glass transition onset temperature of at least 60 °C or above.

In the third aspect, the present application provides a process for preparing amorphous empagliflozin having a glass transition onset temperature of at least 60 °C or above, comprising;

a) providing a solution of empagliflozin in a solvent or a mixture solvents;
b) removing solvent from the solution obtained in step (a); and
c) recovering amorphous form of empagliflozin.

In the fourth aspect, the present application provides amorphous solid dispersion of empaglilflozin having a glass transition onset temperature of at least 55 °C or above comprising empagliflozin and one or more pharmaceutically acceptable carriers.

In the fifth aspect, the present application provides a process for preparing amorphous solid dispersion having a glass transition onset temperature of at least 55 °C or above comprising empagliflozin and one or more pharmaceutically acceptable carriers, comprising;

a) providing a solution comprising empagliflozin and one or more pharmaceutically acceptable carriers,
b) removing solvent from the solution obtained in step (a), and
c) recovering an amorphous solid dispersion comprising empagliflozin and one or more pharmaceutically acceptable carriers.

In the sixth aspect, the present application provides a process for preparing crystalline form of empagliflozin characterized by PXRD peaks at 18.84°, 20.36°, and 25.21° 2 theta, which comprises;

a) providing a solution of empagliflozin in a solvent or a mixture of solvents;
b) heating the solution to a temperature higher than the temperature at which the solution is prepared;
c) adding an anti-solvent to the hot solution; and

d) isolating crystalline form of empagliflozin characterized by PXRD peaks at 18.84°, 20.36°, and 25.21° 2 theta.

In the seventh aspect, the present application provides a process for purification of empagliflozin, comprising:

a) providing a solution of empagliflozin L-proline complex characterized, by an X-Ray Powder Diffraction (XRPD) pattern having peaks at about 4.36 ± 0.2, 12.97 ± 0.2, 15.67 ± 0.2 and 18.80 ± 0.2 °2θ, in a mixture of an organic solvent and water;

b) optionally, heating the solution obtained in step (a);

c) separating the organic layer from the mixture obtained in step (b); and

d) isolating pure empagliflozin from the organic layer of step (c).

In the ninth aspect, the present application provides a crystalline Form N of Empagliflozin, characterized by a PXRD pattern comprising the peaks at about 4.13, 7.79, 11.55, 16.74, 23.20 and 27.87 ± 0.2° 2θ.

In the tenth aspect, the present application provides a complex of empagliflozin with phenylalanine.

In the eleventh aspect, the present application provides a process for the preparation of the complex of empagliflozin with phenylalanine, comprising

(a) dissolving empagliflozin and phenylalanine in a solvent,

(b) storing the solution to precipitate the empagliflozin phenylalanine complex, and

(c) isolating the empagliflozin phenylalanine complex.

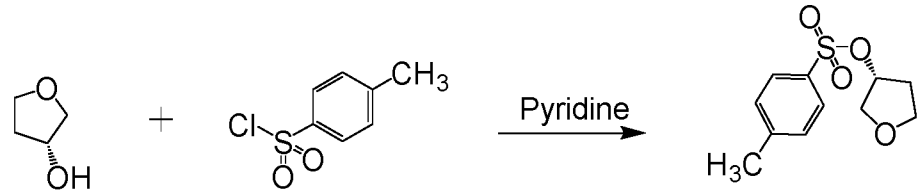
In the twelfth aspect, the present application provides a crystalline Form-Alpha (Form α) of Empagliflozin, characterized by a PXRD pattern as shown in Figure 32.

In the thirteenth aspect, the present application provides a crystalline Form-Beta (Form β) of Empagliflozin, characterized by a PXRD pattern comprising the peaks at about 3.44, 4.04, 9.35, 10.20 and 14.11 ± 0.2° 2θ.

In the fourteenth aspect, the present application provides a crystalline Form-Gamma (Form γ) of Empagliflozin, characterized by a PXRD pattern comprising the peaks at about 4.82, 7.19, 10.17 and 11.20 ± 0.2° 2θ.

In the fifteenth aspect, the present application provides a process for preparation of (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate having greater than about 99.8% of chiral purity, comprising

(a) reacting (R)-tetrahydrofuran-3-ol with 4-methylbenzene-1-sulfonyl chloride in presence of pyridine



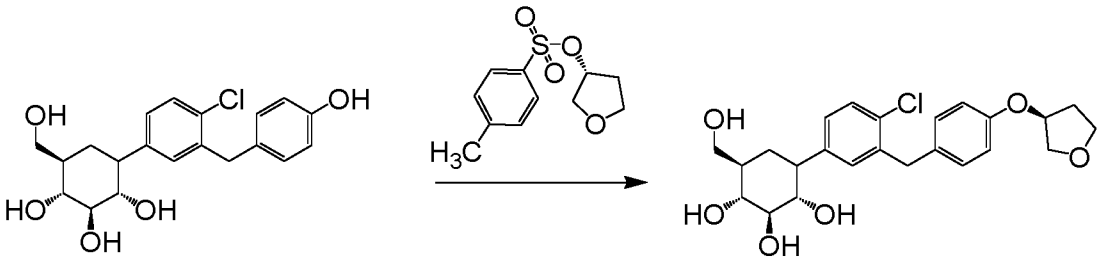
(b) slurrying the crude compound (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate with a mixture of ethylacetate and cyclohexane, and

(c) isolating the (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate having chiral purity of greater than about 99.8%.

In the sixteenth aspect, the present application provides a process for preparation of empagliflozin having greater than about 99.8% of chiral purity, comprising:

(a) slurrying the crude (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate with a mixture of ethylacetate and cyclohexane to get (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate having chiral purity of greater than about 99.8%. and

(b) reacting (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate having greater than about 99.8% of chiral purity with (1R,2R,3S,6R)-4-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl)cyclohexane-1,2,3-triol in presence of a base.



In the seventeenth aspect, the present application provides use of the crystalline forms of empagliflozin of the present invention and the empagliflozin phenylalanine complex and empagliflozin L-proline complex of the present invention to improve the purity of empagliflozin.

In the eighteenth aspect, the present application provides a pharmaceutical composition comprising any of amorphous empagliflozin or empagliflozin solid dispersion or empagliflozin L-proline complex or empagliflozin phenylalanine complex of the present invention or any of the crystalline forms of empagliflozin of the present invention and at least one pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is powder X-ray power diffraction pattern of an amorphous form of empagliflozin prepared according to Example 1.

Figure 2 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and HPMC Phthalate prepared according to Example 6.

Figure 3 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and methyl cellulose prepared according to Example 7.

Figure 4 is powder X-ray power diffraction pattern of crystalline form of empagliflozin prepared according to Example 8.

Figure 5 is powder X-ray power diffraction pattern of empagliflozin L-proline complex prepared according to Example 13.

Figure 6 is powder X-ray power diffraction pattern of an amorphous form of empagliflozin prepared according to Example 15.

Figure 7 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and L-HPC prepared according to Example 17.

Figure 8 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and ethyl cellulose prepared according to Example 18.

Figure 9 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and ethyl cellulose (at 40% RH) prepared according to Example 18.

Figure 10 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and Eudragit RLPO prepared according to Example 19.

Figure 11 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and Eudragit RLPO (at 40% RH) prepared according to Example 19.

Figure 12 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and hydroxypropyl methyl cellulose (HPMC) prepared according to Example 20.

Figure 13 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and hydroxypropyl methyl cellulose (at 40% RH) prepared according to Example 20.

Figure 14 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and hydroxypropyl methyl cellulose acetate succinate (HPMC-AS) prepared according to Example 21.

Figure 15 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and hydroxypropyl methyl cellulose acetate succinate (HPMC-AS) (at 40% RH) prepared according to Example 21.

Figure 16 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and Soluplus prepared according to Example 22.

Figure 17 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and Soluplus (at 40% RH) prepared according to Example 22.

Figure 18 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and Eudragit-E100 prepared according to Example 23.

Figure 19 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and Eudragit-E100 (at 40% RH) prepared according to Example 23.

Figure 20 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and hydroxypropyl methyl cellulose phthalate (HPMC-Phthalate) prepared according to Example 25.

Figure 21 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and hydroxypropyl methyl cellulose phthalate (HPMC-Phthalate) (at 40% RH) prepared according to Example 25.

Figure 22 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and methyl cellulose prepared according to Example 26.

Figure 23 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin and methyl cellulose (at 40% RH) prepared according to Example 26.

Figure 24 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin, hydroxypropyl methyl cellulose (HPMC) and Syloid (1:1:0.5) prepared according to Example 27.

Figure 25 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin, hydroxypropyl methyl cellulose (HPMC) and Lactose monohydrate (1:1:0.5) prepared according to Example 27.

Figure 26 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin, hydroxypropyl methyl cellulose (HPMC) and croscarmellose sodium (1:1:0.5) prepared according to Example 27.

Figure 27 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin, hydroxypropyl cellulose (HPC) and Syloid (1:1:0.5) prepared according to Example 28.

Figure 28 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin, hydroxypropyl cellulose (HPC) and Lactose monohydrate (1:1:0.5) prepared according to Example 28.

Figure 29 is powder X-ray power diffraction pattern of an amorphous solid dispersion comprising empagliflozin, hydroxypropyl cellulose (HPC) and croscarmellose sodium (1:1:0.5) prepared according to Example 28.

Figure 30 is an illustrative X-ray powder diffraction pattern of crystalline Form N of Empagliflozin prepared by the method of Example No 31.

Figure 31 is an illustrative X-ray powder diffraction pattern of crystalline Form of the complex of Empagliflozin with L-phenylalanine prepared by the method of Example No 32.

Figure 32 is an illustrative X-ray powder diffraction pattern of crystalline Form-Alpha (α) of Empagliflozin prepared by the method of Example No 33.

Figure 33 is an illustrative X-ray powder diffraction pattern of crystalline Form-Beta (β) of Empagliflozin prepared by the method of Example No 34.

Figure 34 is an illustrative X-ray powder diffraction pattern of crystalline Form-Gamma (γ) of Empagliflozin prepared by the method of Example No 35.

Figure 35 is DSC thermogram of amorphous Empagliflozin prepared by the method of Example No 15.

DETAILED DESCRIPTION

Empagliflozin used as the input in the process for preparation of stable amorphous empagliflozin and amorphous solid dispersion of the present invention can be prepared by any process known in the art.

In the first aspect, the present application provides stable amorphous empagliflozin.

In the second aspect, the present application provides amorphous empagliflozin having a glass transition onset temperature of at least 60 °C or above.

In the third aspect, the present application provides a process for preparing amorphous empagliflozin having a glass transition onset temperature of at least 60 °C or above, comprising;

a) providing a solution of empagliflozin in a solvent or a mixture solvents;
b) removing solvent from the solution obtained in step (a); and
c) recovering amorphous empagliflozin having a glass transition onset temperature of at least 60 °C or above.

Providing a solution in step (a) includes direct use of a reaction mixture containing empagliflozin that is obtained in the course of its synthesis or dissolving empagliflozin in a solvent or a mixture of solvents.

Any physical form of empagliflozin may be utilized for providing the solution of empagliflozin in step (a). Suitable solvents which can be used for dissolving empagliflozin include but are not limited to: alcohol solvents such as methanol, ethanol, isopropyl alcohol, n-propanol, isoamyl alcohol n-butanol, 2-butanol and the like; halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; dimethylformamide, dimethylacetamide and dimethylsulfoxide; and any mixtures of two or more thereof.

After dissolution in step (a), the obtained solution may be optionally filtered to remove any insoluble particles. Suitable techniques to remove insoluble particles are filtration, centrifugation, decantation, and any other known techniques in the art. The solution can be filtered by passing through paper, glass fiber, or other membrane material, or a clarifying agent such as Celite. Depending upon the equipment used and the concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid premature precipitation of solid.

Step (b) involves removing solvent from the solution of empagliflozin. Suitable techniques which can be used for the removal of solvent include but not limited to evaporation, flash evaporation, simple evaporation, rotational drying, spray drying, agitated thin-film drying, agitated nutsche filter drying, pressure nutsche filter drying, freeze-drying or any other suitable technique known in the art.

Step (c) involves recovering an amorphous form of empagliflozin. The said recovery can be achieved by using the processes known in the art.

The resulting compound in step (c) may optionally be further dried. Drying can be carried out in a tray dryer, vacuum oven, air oven, cone vacuum dryer, rotary vacuum dryer, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying can be carried out at temperatures of less than about 60°C, less than about 50°C, less than about 40°C, less than about 30°C, less than about 20°C, or any other suitable temperatures; at atmospheric pressure or under a reduced pressure; as long as the empagliflozin is not degraded in its quality. The drying can be carried out for any desired times until the required product quality is achieved. Suitable time for drying can vary from few minutes to several hours for example from about 30 minutes to about 24 or more hours.

In another aspect, the present application provides amorphous Empagliflozin having a chemical purity of at least 99% by HPLC or at least 99.5% by HPLC or at least 99.9% by HPLC.

The amorphous empagliflozin is stable for 3 months in ICH storage conditions i.e. (i) 25°C ± 2°C and 60%RH ± 5RH, (ii) 40°C±2°C and 75%RH ± 5RH, (iii) 30 °C ± 2 °C and 75%RH ± 5RH and (iv) 2°C - 8°C. Packing conditions used for amorphous empagliflozin are incorporated below.

Packing method-1: Take the sample in a clear anti-static polyethylene bag and tie it with plastic strip by twisting after removing air. Keep the above in a black polythene bag along with Molecular sieve pouch, fill it with nitrogen gas and tie it with plastic strip. Keep the bag in triple laminated bag and seal it with VNS Sealer, keep the above triple laminated bag in another triple laminated bag and seal it with VNS Sealer. Finally keep the packet in HDPE container and store in the stability chamber.

Packing method-2: Take the sample in a clear anti-static polyethylene bag and tie it with plastic strip by twisting after removing air. Keep the above in a black polythene bag fill it with nitrogen gas and tie it with plastic strip. Keep the bag in triple laminated bag and seal it with VNS Sealer, keep the above triple laminated bag in another triple laminated bag and seal it with VNS Sealer. Finally keep the packet in HDPE container and store in the stability chamber.

Amorphous empagliflozin of the present application was found to be stable under mechanical stress such as grinding and milling and stable under hygroscopic conditions such as higher relative humidity conditions of more than 60% RH.

In another aspect, the amorphous empagliflozin of the present invention is showing glass transition onset temperature of 66.29 °C, and glass transition temperature of 70.13 °C. The DSC thermogram is shown in Figure 35.

In the fourth aspect, the present application provides amorphous solid dispersion of empagliflozin having a glass transition onset temperature of at least 55 °C or above, comprising empagliflozin and one or more pharmaceutically acceptable carriers.

In the fifth aspect, the present application provides a process for preparing amorphous solid dispersion of empagliflozin having a glass transition onset temperature of at least 55 °C or above, comprising empagliflozin and one or more pharmaceutically acceptable carriers, comprising;

a) providing a solution comprising empagliflozin and one or more pharmaceutically acceptable carriers,
b) removing solvent from the solution obtained in step (a), and
c) recovering an amorphous solid dispersion having a glass transition onset temperature of at least 60 °C or above, comprising empagliflozin and one or more pharmaceutically acceptable carriers.

Providing a solution in step (a) includes direct use of a reaction mixture containing empagliflozin that is obtained in the course of its synthesis or dissolving empagliflozin and pharmaceutically acceptable carrier in a solvent.

Any physical form of empagliflozin may be utilized for providing the solution of empagliflozin in step (a).

Suitable pharmaceutically acceptable carriers which can be used in step (a) include, but are not limited to: diluents such as starches, pregelatinized starches, lactose, powdered celluloses, microcrystalline celluloses, dicalcium phosphate, tricalcium phosphate, Polyethylene glycol, Copovidone, Soluplus, Silicified microcrystalline cellulose mannitol, sorbitol, sugar and the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinylpyrrolidones, hydroxypropyl celluloses, hydroxypropyl methylcelluloses such as HPMC-Phthalate, HPMC-AS, HPMC-15 CPS; pregelatinized starches and the like; disintegrants such as starches, sodium starch glycolate, pregelatinized starches, crospovidones, 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 or cationic or neutral surfactants; complex forming agents such as various grades of cyclodextrins and resins; 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 of use include but are not limited to film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants, and the like.

In a preferred aspect, the pharmaceutically acceptable carriers are hydroxypropyl methylcellulose phthalate (HPMC-Phthalate) and methyl cellulose.

Suitable solvents which can be used for dissolving the empagliflozin include but are not limited to: alcohol solvents such as methanol, ethanol, isopropyl alcohol, n-propanol, isoamyl alcohol n-butanol, 2-butanol and the like; halogenated hydrocarbons such as dichloromethane, 1 ,2-dichloroethane, chloroform, carbon tetrachloride and the like; ketones such as acetone, ethyl methyl ketone and the like; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; nitriles such as

acetonitrile, propionitrile and the like; dimethylformamide, dimethylacetamide and dimethylsulfoxide, and any mixtures of two or more thereof.

After dissolution in step (a), optionally undissolved particles, if any, may be removed suitably by filtration, centrifugation, decantation, and any other known techniques. The solution can be filtered by passing through paper, glass fiber, or other membrane material, or a clarifying agent such as celite. Depending upon the equipment used and the concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid premature crystallization.

Step (b) involves removing solvent from the solution obtained in step (a);

Suitable techniques which can be used for the removal of solvent include but not limited to evaporation, flash evaporation, simple evaporation, rotational drying, spray drying, agitated thin-film drying, agitated nutsche filter drying, pressure nutsche filter drying, freeze-drying, filtration or any other technique known in the art.

Step (c) involves recovering an amorphous solid dispersion comprising empagliflozin and one or more pharmaceutically acceptable carriers. The said recovery can be achieved by using the processes known in the art.

The resulting compound obtained in step (c) may optionally be further dried. Drying can be carried out in a tray dryer, vacuum oven, air oven, cone vacuum dryer, rotary vacuum dryer, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying can be carried out at temperatures of less than about 60°C, less than about 50°C, less than about 40°C, less than about 30°C, less than about 20°C, or any other suitable temperatures; at atmospheric pressure or under a reduced pressure; as long as the empagliflozin is not degraded in its quality. The drying can be carried out for any desired time until the required product quality is achieved. Suitable time for drying can vary from few minutes to several hours for example from about 30 minutes to about 24 or more hours.

When the active ingredient is hygroscopic or the formulation contains a hygroscopic ingredient, and to increase the stability of the amorphous form or a solid dispersion comprising amorphous empagliflozin, addition of other carriers such as syloid, methyl cellulose, colloidal silicon dioxide, Eudragit, amorphous silica, micro crystalline cellulose, and the like, in the formulation has been found to be of particular

value. Therefore these ingredients may be combined during the preparation of solid dispersion or after the preparation of amorphous empagliflozin or solid dispersion to control hygroscopicity and to improve stability.

In the sixth aspect, the present application provides a process for preparing crystalline form of empagliflozin characterized by PXRD peaks at 18.84°, 20.36°, and 25.21° 2 theta, which comprises;

a) providing a solution of empagliflozin in a solvent or a mixture of solvents;
b) heating the solution to a temperature higher than the temperature at which the solution is prepared;
c) adding an anti-solvent to the hot solution; and
d) isolating crystalline form of empagliflozin characterized by PXRD peaks at 18.84°, 20.36°, and 25.21° 2 theta.

Providing a solution in step (a) includes direct use of a reaction mixture containing empagliflozin that is obtained in the course of its synthesis or dissolving empagliflozin in a solvent or a mixture of solvents.

Any physical form of empagliflozin may be utilized for providing the solution of empagliflozin in step (a). Suitable solvents which can be used for dissolving empagliflozin include but are not limited to: alcohol solvents such as methanol, ethanol, isopropyl alcohol, n-propanol, isoamyl alcohol n-butanol, 2-butanol and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like and the like; halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; dimethylformamide, dimethylacetamide and dimethylsulfoxide; and any mixtures of two or more thereof.

If the empagliflozin is not dissolved in the solvent the mixture may be heated to get the complete dissolution.

After dissolution in step (a), the obtained solution may optionally be filtered to remove any insoluble particles. Suitable techniques to remove insoluble particles are filtration, centrifugation, decantation, and any other known techniques in the art. The solution can be filtered by passing through paper, glass fiber, or other membrane material, or a clarifying agent such as Celite. Depending upon the equipment used and

the concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid premature precipitation of solid.

Step (b) involves heating the solution obtained in step (a) to a temperature higher than the temperature at which the solution is prepared.

If the solution of step (a) is prepared at 30°C, the solution is heated to above 30°C, or If the solution of step (a) is prepared at 45°C, the solution is heated to above 45°C.

Step (c) involves adding an anti-solvent to the hot solution obtained step (c). The suitable anti-solvents may include, but not limited to water, pentane, n-hexane, cyclohexane, cylcoheptane, n-heptane, diethyl ether, methyl ter. butyl ether, di isopropyl ether, cyclopentyl methyl ether, pet ether and the like. Preferably suitable anti- solvents are water, n-heptane and pet ether.

The anti-solvent may be added to precipitate the crystalline form of empagliflozin or a reverse mode of addition may also be employed.

In an aspect, the mixture may be stirred for sufficient time i.e. 15 minutes to 10 hours or more.

In an aspect, anti-solvent addition may be carried out at suitable temperatures, such as at about 30°C to 100°C. Preferably suitable temperature may be at about 40 to 80°C.

In an aspect, anti-solvent addition may be carried out for sufficient time to complete precipitation of crystalline form of empagliflozin. In an aspect, anti-solvent addition may be carried out in sufficient volume to complete precipitation of crystalline form of empagliflozin.

Step (d) involves isolation of crystalline form of empagliflozin. Isolation of crystalline form of empagliflozin may be carried out by any known methods such as filtration of precipitated solid.

In one aspect, the isolation of crystalline form of empagliflozin is carried out at a temperature at which the precipitation is formed.

The crystalline form of empagliflozin obtained in step (d) may optionally be washed with the anti-solvent with sufficient volume to remove traces solvent from wet solid. The crystalline form of empagliflozin obtained as above may be dried, if desired,

at suitable temperatures at about 50°C, or above. The drying may be performed at atmospheric or reduced pressures, for about 1 – 20 hours, or longer by using the drying equipment known in the art.

In another aspect, the crystalline form of empagliflozin characterized by PXRD peaks at 18.84°, 20.36°, and 25.21° ± 0.2 degrees 2 theta can be prepared by slurrying amorphous empagliflozin in water or on a similar solvent and isolating the crystalline form of empagliflozin by the known methods.

In another aspect, the present application provides the crystalline form of empagliflozin characterized by PXRD peaks at 18.84°, 20.36°, and 25.21° ± 0.2 degrees 2 theta prepared by the process described above having a chemical purity of at least 99% by HPLC or at least 99.5% by HPLC or at least 99.9% by HPLC.

In the seventh aspect, the present application provides an empagliflozin L-proline complex characterized by PXRD peaks at about 4.36 ± 0.2, 12.97 ± 0.2, 15.67 ± 0.2 and 18.80 ± 0.2 degrees 2-theta.

In the eighth aspect, the present application provides a process for preparation of the empagliflozin L-proline complex characterized by PXRD peaks at about 4.36 ± 0.2, 12.97 ± 0.2, 15.67 ± 0.2 and 18.80 ± 0.2 degrees 2-theta, comprising:

(a) mixing empagliflozin and L-proline in a solvent or a mixture of solvents;

(b) optionally, heating the mixture obtained in step (a);

(c) isolating the empagliflozin L-proline complex.

Step (a) of the process involves mixing empagliflozin and L-proline in a solvent or a mixture of solvents.

Preferred solvents are alcoholic solvents such as methanol, ethanol, isopropyl alcohol, n-propanol, isoamyl alcohol and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like. Any physical form of empagliflozin can be used as the starting material of the present invention.

The mixture of empagliflozin and L-proline is prepared in any method such as first the L-proline is added to the solvent and then empagliflozin is added or first empagliflozin is added to a solvent and then L-proline is added. In a specific aspect empagliflozin and L-proline are added at a time.

In certain aspects, about 1 equivalent of L-proline is used to prepare empagliflozin L-proline complex. In other aspects, about 2 equivalents of L-proline is used to prepare empagliflozin L-proline complex. In yet other aspects, greater than 2 equivalents of L-proline is used to prepare empagliflozin L-proline complex. In still other aspects, about 0.9 to about 1.1 equivalents of L-proline is used to prepare empagliflozin L-proline complex. In further aspects, about 1.8 to about 2.2 equivalents, such as about 1.98 to 2.02 equivalents, of L-proline is used to prepare empagliflozin L-proline complex.

Step (b) involves optionally heating the mixture obtained in step (a). The mixture obtained step (a) may be heated to a temperature of about 40°C to about 150°C. Preferably the mixture is heated to a temperature of about 60°C to about 80°C. The mixture may be stirred for about 10 minutes to about 10 hours or longer.

Step (c) involves isolation of empagliflozin L-proline complex from the mixture of step (b). The isolation of empagliflozin L-proline complex may be carried out by any known methods such as filtration of precipitated solid.

The empagliflozin L-proline complex obtained as above may be dried, if desired, at suitable temperatures at about 50°C, or above. The drying may be performed at atmospheric or reduced pressures, for about 1 – 20 hours, or longer by using the drying equipment known in the art.

Powder X-ray diffraction pattern (PXRD) the empagliflozin L-proline complex obtained by the process of the present application is depicted in Figure 5.

Similar process can be adopted to produce other amino acid complexes of empagliflozin. The amino acids which can be used to produce empagliflozin complexes include, but not limited to, glycine, alanine, serine, threonine, cysteine, valine, leucine, isoleucine, methionine, phenylalanine, tyrosine, tryptophan, aspartic acid, glutamic acid, asparagine, glutamine, histidine, lysine, arginine.

The amino acid complexes of empagliflozin may be useful as intermediate. During the formation of the complex, the empagliflozin crude may get purified as the impurities are removed during the complex formation. This intermediate can sufficiently be purified to produce the final empagliflozin in the desired form. The purification involves slurrying, recrystallization, crystallization etc.

In the eighth aspect, the present application provides a process for purification of empagliflozin, comprising:

(a) providing a solution of empagliflozin L-proline complex characterized by PXRD peaks at about 4.36 ± 0.2, 12.97 ± 0.2, 15.67 ± 0.2 and 18.80 ± 0.2 ° 2θ in a mixture of an organic solvent and water;

(b) optionally, heating the solution obtained in step (a);

(c) separating the organic layer from the mixture obtained in step (b); and

(d) isolating pure empagliflozin from the organic layer of step (c).

Step (a) of the process involves providing a solution of empagliflozin L-proline complex in a mixture of an organic solvent and water. Any type of organic solvent can be used in this process. Preferred solvents are esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; alcoholic solvents such as methanol, ethanol, isopropyl alcohol, n-propanol, isoamyl alcohol and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; halogenated hydrocarbon solvents such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like. Most preferably the organic solvent is ethylacetate. The step (a) solution is prepared by any means such as first the complex is added to an organic solvent and then water is added or first the complex is added to water and then an organic solvent is added. The organic solvent and water are taken in a ratio of about 1:0.2 to about 1:5.

The solution obtained in step (a) may be heated to about 50°C and the solution may be stirred for about 10 minutes to about 5 hours.

Step (c) of the process involves separating the organic layer form the mixture. The organic layer containing empagliflozin is separated from the mixture and the organic layer may be washed with water.

Step (d) involves isolation of pure empagliflozin from the organic layer. Empagliflozin can be isolated by removal of the solvent. The solvent can be removed using a rotational distillation device such as a Buchi rotavapor, spray drying, agitated thin film drying, freeze drying (lyophilization), and the like, or other techniques specific to the equipment used. Small quantity of solvent or anti solvent may be added to the

reaction flask or the reactor to make the slurry or suspension when the solvent is completely removed, which will be useful for easy filtration.

The solvent may be removed, optionally under reduced pressures, at temperatures less than reflux temperature of the solvent, less than about 100°C, less than about 60°C, less than about 40°C, less than about 20°C, or any other suitable temperatures.

The product thus isolated may be optionally further dried to afford pure empagliflozin. Drying may suitably be carried out in a tray dryer, vacuum oven, Buchi rotavapor, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying may be carried out at atmospheric pressure or under reduced pressures at temperatures of less than about 100°C, less than about 60°C, less than about 40°C or any other suitable temperatures. The drying may be carried out for any time period required for obtaining a desired quality, such as from about 15 minutes to several hours.

In one aspect, the present application provides empagliflozin prepared by the purification process described above is having a chemical purity of at least 99% by HPLC or at least 99.5% by HPLC or at least 99.9% by HPLC.

In the ninth aspect, the present application provides a crystalline Form N of Empagliflozin, characterized by a PXRD pattern comprising the peaks at about 4.13, 7.79, 11.55, 16.74, 23.20 and 27.87 ± 0.2° 2θ. In an aspect, the present application provides a crystalline Form N of Empagliflozin, characterized by a PXRD pattern having one or more additional peaks at about 7.16, 15.51, 15.86, 16.36, 22.08, 23.65, 24.47 and 26.65 ±0.2° 2θ. In an aspect, the application provides crystalline Form N of Empagliflozin, characterized by a PXRD pattern of figure 30.

In one aspect, the present application provides a process for the preparation of crystalline Form N of Empagliflozin, comprising the step of treating Empagliflozin with N-methyl pyrrolidine or a mixture thereof.

In an aspect, crystalline Form N of Empagliflozin may be obtained by treating Empagliflozin with N-methyl pyrrolidine.

In an aspect, crystalline Form N of Empagliflozin may be obtained by treating Empagliflozin with a mixture of N-methyl pyrrolidine and atleast one additional solvent. In an aspect, additional solvent may be selected from the group comprising

of diethyl ether, di isopropyl ether, methyl tert. butyl ether, methanol, ethanol, 2-propanol, acetone, methyl isobutyl ketone, water or mixtures thereof.

In an aspect, treating Empagliflozin with N-methyl pyrrolidine or a mixture thereof may be carried out by combining Empagliflozin and N-methyl pyrrolidine or a mixture thereof.

In an aspect, the mixture of Empagliflozin and N-methyl pyrrolidine or a mixture thereof may form a homogeneous mixture in the form of a solution.

In an aspect, the mixture of Empagliflozin and N-methyl pyrrolidine or a mixture thereof is a heterogeneous mixture in the form a suspension.

In an aspect, combining Empagliflozin with N-methyl pyrrolidine or a mixture thereof may be carried out optionally by heating a mixture of Empagliflozin and N-methyl pyrrolidine or a mixture thereof at about 0°C to reflux temperature.

In an aspect, when the mixture of Empagliflozin and N-methyl pyrrolidine or a mixture forms a homogenous solution, it may be filtered to make it particle free and optionally treated with decolorizing agents such as charcoal, prior to filtration.

In an aspect, optionally seeds of crystalline Form N of Empagliflozin may be added to the mixture of Empagliflozin and N-methyl pyrrolidine or a mixture thereof, when the mixture forms a homogenous solution. In an aspect, seeds may be added at a suitable temperature and sufficient quantity such that the seeds are not dissolved.

In an aspect, optionally the mixture of Empagliflozin and N-methyl pyrrolidine or a mixture thereof may be contacted with an anti-solvent, when the mixture forms a homogenous solution. The anti-solvent may be a solvent in which Empagliflozin has low solubility or is insoluble. Anti-solvent may include, but not limited to water, diethyl ether, di isopropyl ether, methyl tert. butyl ether, n-propanol, 2-propanol, ethyl acetate, toluene, acetonitrile or mixtures thereof.

In an aspect, anti-solvent may be contacted at a temperature and duration, suitable for the formation of crystalline form III of Empagliflozin. In an aspect, anti-solvent may be contacted either by adding the anti-solvent to the mixture of Empagliflozin and N-methyl pyrrolidine or by adding the mixture to anti-solvent. In an aspect, anti-solvent may be contacted in single lot or multiple lots.

In an aspect, the mixture of Empagliflozin and N-methyl pyrrolidine or a mixture thereof may be stirred for sufficient time to complete the formation of Form N and at suitable temperature where crystalline Form N is stable and do not convert to any other form of Empagliflozin.

In an aspect, the mixture of Empagliflozin and N-methyl pyrrolidine or a mixture thereof may be stirred for at least 1 hour or more. In an aspect, the mixture of Empagliflozin and N-methyl pyrrolidine or a mixture thereof may be stirred at a temperature of about 0°C to reflux temperature.

In an optional aspect, the mixture of Empagliflozin and N-methyl pyrrolidine or a mixture thereof may be cooled to a relatively lower temperature. In an aspect, the mixture may be cooled to a suitable temperature before or after addition of seeds and / or contacting with anti-solvent. In an aspect, the mixture comprising Empagliflozin and N-methyl pyrrolidine or a mixture thereof may be further stirred at the same temperature for time sufficient, after cooling, to obtain crystalline Form N of Empagliflozin.

Isolation of crystalline Form N of Empagliflozin may be carried out by any methods known in the art or procedures described in the present application. In an aspect, crystalline Form N may be isolated by employing any of the techniques, but not limited to: decantation, filtration by gravity or suction, centrifugation, adding solvent to make slurry followed by filtration, or other techniques specific to the equipment used and the like, and optionally washing with a solvent.

In an aspect, the crystalline Form N of Empagliflozin may be optionally dried under suitable drying conditions, at which the Form N is stable. In an alternate aspect, the crystalline Form N of Empagliflozin may be directly converted to any other solid form of Empagliflozin, without drying.

In one aspect, the present application provides a pharmaceutical composition comprising the crystalline Form N of Empagliflozin and at least pharmaceutically acceptable carrier.

In another aspect, the present application provides crystalline Form N of Empagliflozin or their pharmaceutical compositions comprising Empagliflozin having a

chemical purity of at least 99% by HPLC or at least 99.5% by HPLC or at least 99.9% by HPLC.

In another aspect, the present application provides crystalline Form N of Empagliflozin or their pharmaceutical composition, wherein particle size (D90) of Empagliflozin may be less than 100 microns or less than 50 microns or less than 20 microns.

In the tenth aspect, the present application provides a complex of empagliflozin with phenylalanine.

Empagliflozin forms a stable complex with L-phenylalanine. The empagliflozin phenylalanine complex can be prepared by the following process. The process comprising:

(a) dissolving empagliflozin and phenylalanine in a solvent,

(b) storing the solution to precipitate the empagliflozin phenylalanine complex, and

(c) isolating the empagliflozin phenylalanine complex.

The step (a) involves dissolving empagliflozin and phenylalanine in a suitable solvent to form a solution. The solution containing empagliflozin and phenylalanine may prepared by adding phenylalanine into a solution containing empagliflozin.

The solvent may be selected form the group comprising methanol, ethanol, isopropanol, tetrahydrofuran, acetone, acetonitrile and water or a mixture thereof. Preferably a mixture of ethanol and water is used.

To get the complete dissolution the mixture containing empagliflozin, phenylalanine and the solvent may be heated to elevated temperatures.

The step (b) involves storing the solution to precipitate empagliflozin phenylalanine complex. Storing the solution means keeping the solution or stirring the solution at below the temperature at which the solution is formed. Storing may be carried till the precipitation occurs. Storing may be continued for additional time to precipitate maximum product. Storing may be carried out at about 35 °C to about -10 °C. A precipitate will be formed upon storing the solution.

The step (c) involves isolation of empagliflozin phenylalanine complex. The suspension formed in the step (b) may be isolated by known techniques such as decantation, filtration by gravity or suction, centrifugation, adding solvent to make slurry

followed by filtration, or other techniques specific to the equipment used and the like, and optionally washing with a solvent.

In an aspect, the empagliflozin Phenylalanine complex may optionally be dried under suitable drying conditions, at which the complex is stable.

In another aspect, the empagliflozin Phenylalanine complex may be directly converted to any other solid form of empagliflozin, without drying.

The empagliflozin Phenylalanine complex is confirmed with the use of X-ray powder diffraction (XRPD), differential scanning calorimetry. The XRPD pattern is shown in Figure 31. The empagliflozin phenylalanine complex exhibits a crystalline character. The characteristic diffraction peaks are 8.28 and 16.45 ±0.2 °2θ. Other characteristic diffraction peaks are 4.24, 24.67 and 25.32 ±0.2 °2θ.

In the eleventh aspect, the present application provides a crystalline Form-Alpha (α) of Empagliflozin, characterized by a PXRD pattern as shown in Figure 32.

In an alternate aspect, the crystalline Form-Alpha of Empagliflozin may be directly converted to any other solid form of Empagliflozin, without drying.

In the twelfth aspect, the present application provides a crystalline Form-Beta (Form β) of Empagliflozin, characterized by a PXRD pattern comprising the peaks at about 3.44, 4.04, 9.35, 10.20 and 14.11 ± 0.2° 2θ.

The XRPD pattern of crystalline Form-Beta of Empagliflozin is shown in Figure 33. The characteristic diffraction peaks are 3.44, 4.04, 9.35, 10.20 and 14.11 ±0.2 °2θ. Other characteristic diffraction peaks are 18.21, 19.13 and 24.20 ±0.2 °2θ.

In the thirteenth aspect, the present application provides a crystalline Form-Gamma (Form γ) of Empagliflozin, characterized by a PXRD pattern comprising the peaks at about 4.82, 7.19, 10.17 and 11.20 ± 0.2° 2θ.

The XRPD pattern of crystalline Form-Gamma of Empagliflozin is shown in Figure 34. The characteristic diffraction peaks are 4.82, 7.19, 10.17 and 11.20 ±0.2 °2θ. Other characteristic diffraction peaks are 4.18, 18.15, 23.55 and 23.90 ±0.2 °2θ.

The crystalline Form-Alpha, Form-Beta and Form-Gamma of empagliflozin can be prepared by the processes described in this application or by the processes described in the art.

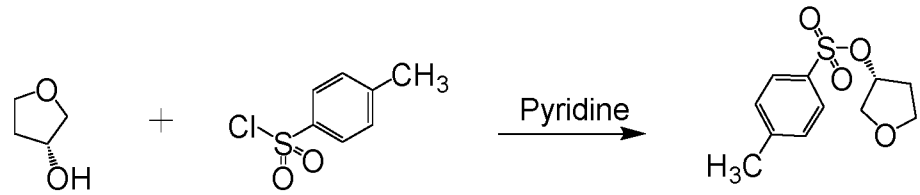
In another aspect, the present application provides crystalline forms of Empagliflozin described in this application having a chemical purity of at least 99% by HPLC or at least 99.5% by HPLC.

In another aspect, the present application provides crystalline forms of Empagliflozin described in this application or their pharmaceutical composition, wherein particle size (D90) of Empagliflozin may be less than 200 microns or less than 100 microns or less than 50 microns or less than 20 microns.

In the fourteenth aspect, the present application provides a pharmaceutical composition comprising any of amorphous empagliflozin or empagliflozin solid dispersion or empagliflozin L-proline complex or empagliflozin phenylalanine complex of the present invention or any of the crystalline forms of empagliflozin of the present invention and at least pharmaceutically acceptable carrier.

In the fifteenth aspect, the present application provides a process for preparation of (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate having greater than about 99.8% of chiral purity, comprising

(a) reacting (R)-tetrahydrofuran-3-ol with 4-methylbenzene-1-sulfonyl chloride in presence of pyridine



(b) slurrying the crude compound (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate with a mixture of ethylacetate and cyclohexane, and

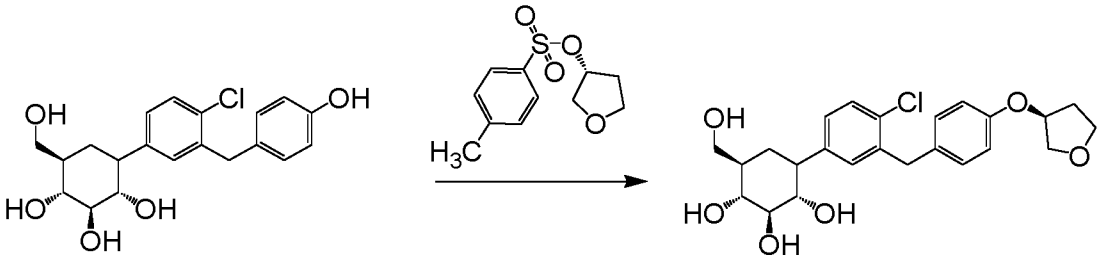
(c) isolating the (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate having chiral purity of greater than about 99.8%.

The step (a) is carried out using a suitable solvent such as dichloromethane, chlorobenzene or acetonitrile and the like. After completion of the reaction the crude product is slurried in a solvent or a mixture of solvents such as a mixture of ethylacetate and cyclohexane or a mixture of ethylacetate and n-hexane. The specific process of the reaction and purification are described in the examples section.

In the sixteenth aspect, the present application provides a process for preparation of empagliflozin having greater than about 99.8% of chiral purity, comprising:

(a) slurrying crude (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate with a mixture of ethylacetate and cyclohexane to get (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate having chiral purity of greater than about 99.8%, and

(b) reacting the (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate having greater than about 99.8% of chiral purity with (1R,2R,3S,6R)-4-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl)cyclohexane-1,2,3-triol in presence of a base.



The specific process of the reaction and purification are described in the examples section.

In the seventeenth aspect, the present application provides a method of treating or preventing type 2 diabetes, comprising administering to a subject in need thereof an effective amount of any of amorphous empagliflozin or empagliflozin solid dispersion or empagliflozin L-proline complex or empagliflozin phenylalanine complex of the present invention or any of the crystalline forms of empagliflozin of the present invention or a pharmaceutical composition thereof.

Empagliflozin and its impurities can be analyzed using HPLC, such as with a liquid chromatography equipped with a UV detector and the parameters described below:

Column	Poroshell 120 EC C-18 150mm X 4.6mm, 2.7µm
Flow	0.8mL/min
Load	10.0µL

<table>
<tr><td>Column oven temp</td><td>40°C</td></tr>
<tr><td>Detection</td><td>225nm</td></tr>
<tr><td>Diluent</td><td>Methanol: Water 800: 200 v/v</td></tr>
<tr><td>Preparation of Mobile phase-A</td><td>Mix separately MQ water: Methanol: Acetonitrile: Ortho phosphoric acid in the ratio of 650: 140: 210: 0.1 v/v/v/v.</td></tr>
<tr><td>Preparation of Mobile phase-B</td><td>Mix separately Acetonitrile: Water in the ratio of 900: 100 v/v.</td></tr>
<tr><td>Gradient programme</td><td>
<table>
<tr><td>Time (min)</td><td>0</td><td>35</td><td>70</td><td>78</td><td>80</td><td>90</td></tr>
<tr><td>% M.P-A</td><td>100</td><td>85</td><td>20</td><td>20</td><td>100</td><td>100</td></tr>
<tr><td>% M.P-B</td><td>0</td><td>15</td><td>80</td><td>80</td><td>0</td><td>0</td></tr>
</table>
</td></tr>
</table>

Certain specific aspects and aspects 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 application in any manner. Variations of the described procedures, as will be apparent to those skilled in the art, are intended to be within the scope of the present application.

DEFINITIONS

The following definitions are used in connection with the present invention unless the context indicates otherwise. The term “amorphous” refers to a solid lacking any long-range translational orientation symmetry that characterizes crystalline structures although; it may have short range molecular order similar to a crystalline solid.

As used herein, the term "complex" refers to a molecular entity formed by association involving two or more component molecular entities (ionic or uncharged), or by association involving two or more chemical species. The bonding between the components is non-covalent and is normally weaker than covalent bonding. Accordingly, the empagliflozin L-proline complex described herein is a molecular entity formed by the association between empagliflozin and L-proline. The empagliflozin- L-proline complex may in some aspects exist as a solid state form that is referred to

herein as a co crystal form of an empagliflozin-L-proline complex, or as an empalgiflozin L-proline co-crystal, or as a crystalline empagliflozin- L-proline complex.

The term “anti-solvent” refers to a liquid that, when combined with a solution of empagliflozin, reduces solubility of the empagliflozin in the solution, causing crystallization or precipitation in some instances spontaneously, and in other instances with additional steps, such as seeding, cooling, scratching and/or concentrating.

Celite is flux-calcined diatomaceous earth. Hyflo is flux-calcined diatomaceous earth treated with sodium carbonate.

An “alcohol solvent” is an organic solvent containing a carbon bound to a hydroxyl group. “Alcoholic solvents” include, but are not limited to, methanol, ethanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, hexafluoroisopropyl alcohol, ethylene glycol, 1-propanol, 2-propanol (isopropyl alcohol), 2- methoxyethanol, 1-butanol, 2-butanol, i-butyl alcohol, t-butyl alcohol, 2- ethoxyethanol, diethylene glycol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, glycerol, or the like.

A “hydrocarbon solvent” refers to a liquid, non-aromatic, hydrocarbon, which may be linear, branched, or cyclic. It is capable of dissolving a solute to form a uniformly dispersed solution. Examples of a hydrocarbon solvent include, but are not limited to, n-pentane, isopentane, neopentane, n-hexane, isohexane, 3-methylpentane, 2,3-dimethylbutane, neohexane, n-heptane, isoheptane, 3-methylhexane, neoheptane, 2,3-dimethylpentane, 2,4-dimethylpentane, 3,3-dimethylpentane, 3-ethylpentane, 2,2,3-trimethylbutane, n-octane, isooctane, 3-methylheptane, neooctane, cyclohexane, methylcyclohexane, cycloheptane, Examples of aromatic hydrocarbon solvents include, but are not limited to benzene, toluene, ethylbenzene, m-xylene, o xylene, p-xylene, indane, naphthalene, tetralin, trimethylbenzene, chlorobenzene, fluorobenzene, trifluorotoluene, anisole, C6-C10 aromatic hydrocarbons, or mixtures thereof.

An “ester solvent” is an organic solvent containing a carboxyl group -(C=O)-O bonded to two other carbon atoms. “Ester solvents” include, but are not limited to, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, t-butyl

acetate, ethyl formate, methyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, C3-6 esters, or the like.

A “halogenated hydrocarbon solvent” is an organic solvent containing a carbon bound to a halogen. “Halogenated hydrocarbon solvents” include, but are not limited to, dichloromethane, 1,2-dichloroethane, trichloroethylene, perchloroethylene, 1,1,1-trichloroethane, 1,1,2-trichloroethane, chloroform, carbon tetrachloride, or the like.

A “ketone solvent” is an organic solvent containing a carbonyl group -(C=O)- bonded to two other carbon atoms. “Ketone solvents” include, but are not limited to, acetone, ethyl methyl ketone, diethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone, C3-6ketones, 4- methyl-pentane-2-one or the like.

A “nitrile solvent” is an organic solvent containing a cyano -(C≡N) bonded to another carbon atom. “Nitrile solvents” include, but are not limited to, acetonitrile, propionitrile, C2-6nitriles, or the like.

A “polar aprotic solvent” has a dielectric constant greater than 15 and is at least one selected from the group consisting of amide-based organic solvents, such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), Nmethylpyrrolidone (NMP), formamide, acetamide, propanamide, hexamethyl phosphoramide (HMPA), and hexamethyl phosphorus triamide (HMPT); nitro-based organic solvents, such as nitromethane, nitroethane, nitropropane, and nitrobenzene; pyridine-based organic solvents, such as pyridine and picoline; sulfone-based solvents, such as dimethylsulfone, diethylsulfone, diisopropylsulfone, 2-methylsulfolane, 3-methylsulfolane, 2,4-dimethylsulfolane, 3,4-dimethy sulfolane, 3-sulfolene, and sulfolane; and sulfoxide-based solvents such as dimethylsulfoxide (DMSO).

An “ether solvent” is an organic solvent containing an oxygen atom –O bonded to two other carbon atoms. “Ether solvents” include, but are not limited to, diethyl ether, diisopropyl ether, methyl t-butyl ether, glyme, diglyme, tetrahydrofuran (THF), 2-methyltetrahydrofuran, 1,4-dioxane, dibutyl ether, dimethylfuran, 2-methoxyethanol, 2-ethoxyethanol, anisole, C2-6 ethers, or the like.

As used herein, the term "co-crystal" refers to a crystal complex composed of at least two neutral molecules bound together in a crystal lattice by non-covalent interactions. The term “co-crystal” also can be referred as adduct.

"A therapeutically effective amount" as used herein refers to an amount of an agent which is effective, upon single or multiple dose administration to the subject in providing a therapeutic benefit to the subject. In one aspect, the therapeutic benefit is maintaining glucose homeostasis, or regulating blood glucose levels. In additional aspects, the empagliflozin amino acid complex of the present invention is used for the preparation of a medicament for treating conditions mediated by SLGT2, preferably type 2 diabetes.

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

EXAMPLES

Example 1: **Preparation of amorphous form of empagliflozin**.

Empagliflozin (2 gm) and n-Propanol (120 mL) were charged into a 250 mL round bottom flask at 27°C. The mixture was heated to 70°C and stirred for 15 min. The solution was filtered to remove the un-dissolved particles and the filtrate was evaporated by spray drying, using a Büchi® MINI Spray Dryer B-290 with Büchi® Inert Loop B-295 at 95°C to afford 880 mg of amorphous empagliflozin.

PXRD pattern: Fig. 1.

Parameters for the spray drier of the above experiment: Aspirator: 70 %; Feed rate: 20 mL/ min; Inlet temperature: 95°C; Outlet temperature: 60°C.

Example 2: **Preparation of amorphous form of empagliflozin**.

Empagliflozin (500 mg) and methanol (35 mL) were charged into a Buchi flask at 27°C. The mixture was heated to 55°C and stirred for 10 min. The solution was filtered to remove the un-dissolved particles and the filtrate was distilled under reduced pressure at 60°C. After distillation the solid was dried under vacuum at 25°C to get 260 mg of amorphous empagliflozin. PXRD pattern: amorphous

Example 3: **Preparation of amorphous form of empagliflozin**.

Empagliflozin (500 mg), dichloromethane (10 mL) and n-Propanol (10 mL) were added to a test tube at 27°C. The mixture was heated to 65°C and stirred for 15 min. The

solution was filtered to remove the un-dissolved particles and the filtrate was distilled under reduced pressure at 60°C to get 180 mg of amorphous empagliflozin. PXRD pattern: amorphous.

Example 4: **Preparation of amorphous form of empagliflozin**.

Empagliflozin (500 mg) and acetone (40 mL) were charged into a round bottom flask at 27°C. The mixture was heated to 60°C and stirred for 15 min. The solution was filtered to remove the un-dissolved particles and the filtrate was distilled under reduced pressure at 60°C to get amorphous empagliflozin. PXRD pattern: amorphous.

Example 5: **Preparation of amorphous form of empagliflozin**.

Empagliflozin (2 gm) and 2-Butanol (170 mL) were charged into a 250 mL round bottom flask at 27°C. The mixture was heated to 75°C and stirred for 15 min. The solution was filtered to remove the un-dissolved particles and the filtrate was evaporated by spray drying, using a Büchi® MINI Spray Dryer B-290 with Büchi® Inert Loop B-295 at 95°C to afford 830 mg of amorphous empagliflozin. PXRD pattern: amorphous.

Parameters for the spray drier of the above experiment: Aspirator: 70%; Feed rate: 20 mL/min; Inlet temperature: 95°C; Outlet temperature: 60°C.

Example 6: Preparation of amorphous solid dispersion of empagliflozin and hydroxy propyl methyl cellulose phthalate (Hypromellose Phthalate; HPMC-Phthalate).

Empagliflozin (250 mg), Hypromellose Phthalate (250 mg) and methanol (30 mL) were charged into a round bottom flask at 27°C. The resulted mixture was heated to 60°C and stirred for 15 min. at 60°C. The clear solution was filtered to remove the un-dissolved particles and the filtrate was completely evaporated under reduced pressure at 60°C to get 180 mg of amorphous solid dispersion of empagliflozin and Hypromellose Phthalate. PXRD pattern: Fig. 2.

Glass transition onset temperature is 75.99 °C

Glass transition temperature is 81.61 °C

Example 7: Preparation of amorphous solid dispersion of empagliflozin and Methyl cellulose.

Empagliflozin (250 mg), Methyl cellulose (250 mg), methanol (25 mL) and water (25 mL) were charged into a round bottom flask at 27°C. The resulted mixture was heated to

50°C and stirred for 15 min. at 50°C. The clear solution was filtered to remove the un-dissolved particles and the filtrate was completely evaporated under reduced pressure at 70°C to get 432 mg of amorphous solid dispersion of empagliflozin and Methyl cellulose. PXRD pattern: Fig. 3.

Glass transition onset temperature is 90.87 °C

Glass transition temperature is 92.40.13 °C

Example 8: Preparation of crystalline form of empagliflozin.

Empagliflozin (500 mg) and methanol (10 mL) were charged into a round bottom flask at 27°C. The mixture was heated to 40°C and stirred for 10 min. The solution was filtered to remove the un-dissolved particles and the hot filtrate was taken into another round bottom flask. Water (30 mL) was added to the flask at 50°C and the mixture was stirred at 50°C for 2 hours. The precipitate was filtered at 50°C and the solid was dried under vacuum at 50°C to get 254 mg of crystalline empagliflozin. PXRD pattern: Fig. 4.

Example 9: Preparation of crystalline form of empagliflozin.

Empagliflozin (500 mg) and methanol (10 mL) were charged into a round bottom flask at 27°C. The mixture was heated to 40°C and stirred for 10 min. The solution was filtered to remove the un-dissolved particles and the hot filtrate was added to water (25 mL) at 60°C. The mixture was stirred at 50°C for 2 hours. The precipitate was filtered at 60°C to get 320 mg of crystalline empagliflozin. PXRD pattern matches with Fig. 4.

Example 10: Preparation of crystalline form of empagliflozin.

Empagliflozin (500 mg) and DMSO (2 mL) were charged into a test tube at 27°C and stirred for 10 min. The solution was filtered to remove the un-dissolved particles. The clear solution was added to water (10 mL) at 50°C and the mixture was stirred at 50°C for 2 hours. The precipitate was filtered at 50°C to get 340 mg of crystalline empagliflozin. PXRD pattern matches with Fig. 4.

Example 11: Preparation of crystalline form of empagliflozin.

Empagliflozin (500 mg) and acetone (15 mL) were charged into an easymax reactor at 27°C. The mixture was heated to 55°C and stirred for 10 min. The solution was filtered to remove the un-dissolved particles and the hot filtrate was taken into another round bottom flask. The clear solution was added to Heptane (25 mL) at 70°C and stirred for 1 hour at 70°C. Pet ether (25 mL) was added the mixture at 70°C and the mixture was

stirred at 70°C for 2 hours. The precipitate was filtered at 70°C to get 374 mg of crystalline empagliflozin. PXRD pattern matches with Fig. 4.

Example 12: Purification of empagliflozin

(a) Preparation of empagliflozin and L-proline complex

Isopropanol (4 mL) and L-proline (0.459 g) were charged into 50 mL 2 neck round bottom flask. Water (0.5 mL) was added to the mass at 26°C. The mixture was heated to 80°C and stirred for 30 minutes at 80°C. A solution of empagliflozin (purity: 91.6%) (1 g of empagliflozin in 4 mL of isopropanol) was added to the reaction mixture at 80°C and resulted mixture was stirred for 1 hour at 80°C. Reaction mixture was cooled to 27°C and MTBE (16 mL) was added to the mixture and the reaction mixture was stirred for 2 hours at 27°C. The precipitation was filtered and the wet cake was washed with MTBE (4 mL) and suck dried for 1 hour to get the title complex.

(b) Conversion of empagliflozin L-proline complex to empagliflozin

Empagliflozin and L-proline complex prepared in example 12 was dissolved in water (10 mL) and ethylacetate (10 mL) and the resulted solution was stirred for 20 minutes at 27°C. Separated the layers and the aqueous layer was extracted with ethylacetate (10 mL). The ethylacetate layers were combined and washed with saturated NaCl solution (5 mL). The organic layer was dried over sodium sulphate and was concentrated under vacuum at 40°C to yield 0.470 g of empagliflozin. Purity: 98.15 by HPLC.

Example 13: Preparation of empagliflozin L-proline complex

Isopropanol (4 mL) and L-proline (0.459 g) were charged into 50 mL 2 neck round bottom flask. Water (0.5 mL) was added to the mass at 30°C. The mixture was heated to 82°C and stirred for 30 minutes at 82°C. A solution of empagliflozin (purity: 95%) (1 g of empagliflozin in 4 mL of isopropanol) was added to the reaction mixture at 82°C and resulted mixture was stirred for 1 hour at 82°C. Reaction mixture was cooled to 30°C and MTBE (16 mL) was added to the mixture and the reaction mixture was stirred for 2 hours at 33°C. The precipitation was filtered and the wet cake was washed with MTBE (4 mL) and suck dried under vacuum for 1 hour to get the 1.12 gm of title complex as white solid. Purity: 98.57% by HPLC.

PXRD pattern: Fig. 5.

Example 14: **Preparation of amorphous form of empagliflozin**.

Empagliflozin (40 g) and methanol (800 mL) were charged into a 2000 mL round bottom flask at 30 °C. The mixture was heated to 50 °C and stirred for 15 min. The solution was filtered to remove the un-dissolved particles and the filtrate was evaporated by spray drying, using a Büchi® MINI Spray Dryer B-290 with Büchi® Inert Loop B-295 at 75°C to afford 26 g of amorphous empagliflozin. The solid was dried for 4 hours at 30 °C under reduced pressure to get 22 grams of amorphous empagliflozin. Purity by HPLC: 99.85%. Methanol content by GC: 1919 ppm

Parameters for the spray drier of the above experiment: Aspirator: 70 %; Feed rate: 9 mL/ min; Inlet temperature: 75°C; Outlet temperature: 60°C.

Example 15: **Preparation of amorphous form of empagliflozin**.

Empagliflozin (45 g) and methanol (900 mL) were charged into a 2000 mL round bottom flask at 30 °C. The mixture was heated to 50 °C and stirred for 10 min. The solution was filtered to remove the un-dissolved particles and the filtrate was evaporated by spray drying, using a Büchi® MINI Spray Dryer B-290 with Büchi® Inert Loop B-295 at 75°C to afford 28 g of amorphous empagliflozin. The solid was dried for 4 hours at 30 °C under reduced pressure to get 28 grams of amorphous empagliflozin. Purity by HPLC: 99.9%. Methanol content by GC: 1189 ppm.

Glass transition onset temperature is 66.29 °C

Glass transition temperature is 70.13 °C

PXRD pattern: Fig. 6.

DSC thermogram: Fig. 35.

Parameters for the spray drier of the above experiment: Aspirator: 75 %; Feed rate: 9 mL/ min; Inlet temperature: 75°C; Outlet temperature: 60°C.

Example 16: **Preparation of amorphous form of empagliflozin**.

Empagliflozin (60 g) and methanol (1200 mL) were charged into a 2000 mL round bottom flask at 25 °C. The mixture was heated to 50 °C and stirred for 10 min. The solution was cooled to 30 °C and filtered to remove the un-dissolved particles and the filtrate was evaporated by spray drying, using a Büchi® MINI Spray Dryer B-290 with Büchi® Inert Loop B-295 at 70 °C to afford 37 g of amorphous empagliflozin. The solid was dried for 4 hours at 30 °C under reduced pressure to get 31 grams of amorphous empagliflozin. Purity by HPLC: 99.81%. PXRD pattern: Fig. 1.

Parameters for the spray drier of the above experiment: Aspirator: 70 %; Feed rate: 9 mL/ min; Inlet temperature: 75°C; Outlet temperature: 60°C.

Example 17: Preparation of amorphous solid dispersion of empagliflozin and Low-Substituted Hydroxypropyl Cellulose (L-HPC).

Low-Substituted Hydroxypropyl Cellulose (L-HPC) (2 g) and methanol (50 mL) were charged into a Buchi rotavapor flask at 25 °C and the mixture was heated to 55 °C. In another flask Empagliflozin (2 g) and methanol (50 mL) were charged at 25 °C and stirred for 15 min. Both the clear solutions were combined and the solution was charged into a rotavapor and completely evaporated under reduced pressure at 55 °C to get 3 g of amorphous solid dispersion of empagliflozin and L-HPC. PXRD pattern: Fig. 7.

The solid amorphous material (1 g) was humidified at 30 °C and 40% RH for 10 hours. Flowable solid lumps obtained.

Example 18: Preparation of amorphous solid dispersion of empagliflozin and Ethyl Cellulose.

Empagliflozin (2 g) and methanol (50 mL) were charged into a Buchi rotavapor flask at 25 °C and stirred for 15 minutes. In another flask Ethyl Cellulose (2 g) and methanol (60 mL) were charged at 25 °C and heated to 58 °C to get clear solution. Both the clear solutions were combined and the solution was charged into a rotavapor and completely evaporated under reduced pressure at 60 °C to get 2.8 g of amorphous solid dispersion of empagliflozin and Ethyl Cellulose. PXRD pattern: Fig. 8.

The solid amorphous material (1 g) was humidified at 30 °C and 40% RH for 10 hours. Freely flowable amorphous solid obtained. PXRD pattern: 9

Glass transition onset temperature is 66.79 °C

Glass transition temperature is 70.48 °C

Example 19: Preparation of amorphous solid dispersion of empagliflozin and Eudragit RLPO.

Empagliflozin (2 g) and methanol (50 mL) were charged into a Buchi rotavapor flask at 25 °C and stirred for 15 minutes. In another flask Eudragit RLPO (2 g) and methanol (36 mL) were charged at 25 °C and heated to 55 °C to get clear solution. Both the clear solutions were combined and the solution was charged into a rotavapor and completely

evaporated under reduced pressure at 60 °C to get 3.2 g of amorphous solid dispersion of empagliflozin and Eudragit RLPO. PXRD pattern: Fig. 10.

The solid amorphous material (1 g) was humidified at 30 °C and 40% RH for 10 hours. Amorphous solid (flowable upon disturbing) obtained. PXRD pattern: Fig. 11.

Glass transition onset temperature is 67.17 °C

Glass transition temperature is 70.87 °C

Example 20: Preparation of amorphous solid dispersion of empagliflozin and HPMC.

Empagliflozin (2 g) and methanol (50 mL) were charged into a Buchi rotavapor flask at 25 °C and stirred for 15 minutes and heated to 55 °C to get clear solution. In another flask hydroxy propyl methyl cellulose (HPMC) (2 g) and methanol (50 mL) were charged at 25 °C and stirred for 15 minutes. Both the clear solutions were combined and the solution was charged into a rotavapor and completely evaporated under reduced pressure at 60 °C to get 2.4 g of amorphous solid dispersion of empagliflozin and HPMC. PXRD pattern: Fig. 12.

The solid amorphous material (1 g) was humidified at 30 °C and 40% RH for 10 hours. Amorphous solid (flowable upon disturbing) obtained. PXRD pattern: Fig. 13.

Example 21: Preparation of amorphous solid dispersion of empagliflozin and HPMC-AS.

Empagliflozin (2 g) and methanol (50 mL) were charged into a Buchi rotavapor flask at 25 °C and stirred for 15 minutes and heated to 55 °C to get clear solution. In another flask hydroxy propyl methyl cellulose acetate succinate (HPMC-AS MG) (2 g) and methanol (50 mL) were charged at 25 °C and stirred for 15 minutes. Both the clear solutions were combined and the solution was charged into a rotavapor and completely evaporated under reduced pressure at 60 °C to get 2.8 g of amorphous solid dispersion of empagliflozin and HPMC-AS. PXRD pattern: Fig. 14.

The solid amorphous material (1 g) was humidified at 30 °C and 40% RH for 10 hours. Amorphous solid (flowable) obtained. PXRD pattern: Fig.15.

Example 22: Preparation of amorphous solid dispersion of empagliflozin and Soluplus.

Empagliflozin (2 g) and methanol (50 mL) were charged into a Buchi rotavapor flask at 25 °C and stirred for 15 minutes and heated to 55 °C to get clear solution. In another flask hydroxy propyl methyl cellulose acetate succinate (HPMC-AS MG) (2 g) and methanol (50 mL) were charged at 25 °C and stirred for 15 minutes. Both the clear solutions were combined and the solution was charged into a rotavapor and completely evaporated under reduced pressure at 60 °C to get 3.4 g of amorphous solid dispersion of empagliflozin and Soluplus. PXRD pattern: Fig. 16.

The solid amorphous material (1 g) was humidified at 30 °C and 40% RH for 10 hours. Amorphous solid (sticky solid lumps) obtained. PXRD pattern: Fig.17.

Glass transition onset temperature is 74.42 °C

Glass transition temperature is 76.30 °C

Example 23: Preparation of amorphous solid dispersion of empagliflozin and Eudragit-E100.

Eudragit-E100 (2 g) and methanol (80 mL) were charged into a Buchi rotavapor flask at 25 °C and stirred for 15 minutes and heated to 65 °C to get clear solution. In another flask Empagliflozin (2 g) and methanol (50 mL) were charged at 25 °C and stirred for 15 minutes. Both the clear solutions were combined and the solution was charged into a rotavapor and completely evaporated under reduced pressure at 60 °C to get 3 g of amorphous solid dispersion of empagliflozin and Eudragit-E100. PXRD pattern: Fig. 18.

The solid amorphous material (1 g) was humidified at 30 °C and 40% RH for 10 hours. Amorphous solid (sticky solid lumps) obtained. PXRD pattern: Fig.19.

Glass transition onset temperature is 96.08 °C

Glass transition temperature is 99.22 °C

Example 24: Preparation of amorphous solid dispersion of empagliflozin and Microcrystalline Cellulose.

Empagliflozin (2 g) and methanol (80 mL) were charged into a Buchi rotavapor flask at 25 °C and stirred for 15 minutes and heated to 55 °C to get clear solution. Microcrystalline Cellulose (MCC; 2 g) was charged at 55 °C and stirred for 15 minutes. The solution was charged into a rotavapor and completely evaporated under reduced pressure at 65 °C. 2.7 g of crystalline sticky solid dispersion of empagliflozin and MCC was obtained.

Example 25: Preparation of amorphous solid dispersion of empagliflozin and hydroxy propyl methyl cellulose phthalate (Hypromellose Phthalate; HPMC-Phthalate).

Hypromellose Phthalate (2 g) and methanol (60 mL) were charged into a round bottom flask at 27°C. Empagliflozin (2 g) and methanol (50 mL) were charged into another flask and heated to 55 °C. The resulted mixture was heated to 55°C and stirred for 15 min. at 55°C. Both the clear solutions were combined and the solution was charged into a rotavapor and completely evaporated under reduced pressure at 60 °C to get 3 g of amorphous solid dispersion of empagliflozin HPMC-Phthalate. PXRD pattern: Fig. 20.

The solid amorphous material (1 g) was humidified at 30 °C and 40% RH for 10 hours. Amorphous solid obtained. PXRD pattern: Fig.21.

Example 26: Preparation of amorphous solid dispersion of empagliflozin and Methyl cellulose.

Methyl cellulose (2 g) and methanol (60 mL) were charged into a round bottom flask at 27°C. In another flask Empagliflozin (2 g) and methanol (50 mL) were charged at 27°C. Both the API and excipient solutions were combined and the solution was charged into a rotavapor and completely evaporated under reduced pressure at 62 °C to get 3.1 g of amorphous solid dispersion of empagliflozin Methyl Cellulose. PXRD pattern: Fig. 22.

The solid amorphous material (1 g) was humidified at 30 °C and 40% RH for 10 hours. Amorphous solid obtained. PXRD pattern: Fig.23.

Example 27: Preparation of amorphous solid dispersion of empagliflozin, HPMC and adsorbent.

Empagliflozin (5 g) and methanol (175 mL) were charged into a Buchi rotavapor flask at 25 °C and stirred for 15 minutes and heated to 55 °C to get clear solution. In another flask hydroxy propyl methyl cellulose (HPMC) (5 g) and methanol (125 mL) were charged at 25 °C and stirred for 15 minutes and heated to 55 °C to get clear solution. Both the clear solutions were combined and the solution was charged into a rotavapor and completely evaporated under reduced pressure at 60 °C to get 6.2 g of amorphous solid dispersion of empagliflozin and HPMC. PXRD pattern: Fig. 12.

Glass transition onset temperature is 58.77 °C

Glass transition temperature is 73.92 °C

Taken 3 g of the above amorphous solid dispersion and divided into 3 parts (P1, P2 and P3) 1 g each part. Added 500 mg of Syloid to P1, 500 mg of Lactose to P2 and 500 mg of Croscarmellose sodium and kept all the three samples in humidification chamber at 40 % RH and 30 °C for 10 hours.

Good improvement in flowability and stability is found by addition of adsorbents syloid, lactose, and croscarmellose sodium (API : HPMC : Adsorbent = 1:1:0.5) when exposed even for one day at 40% RH and 30 °C remained amorphous.

P1 PXRD pattern: Fig 24; P2 PXRD pattern: Fig 25; P3 PXRD pattern: Fig 26.

P1: Glass transition onset temperature is 54.18 °C; Glass transition temperature is 63.71 °C

P2: Glass transition onset temperature is 71.36 °C; Glass transition temperature is 76.08 °C.

Example 28: Preparation of amorphous solid dispersion of empagliflozin, HPC and adsorbent.

Empagliflozin (5 g) and methanol (175 mL) were charged into a Buchi rotavapor flask at 25 °C and stirred for 15 minutes and heated to 55 °C to get clear solution. In another flask hydroxy propyl cellulose (HPC) (5 g) and methanol (125 mL) were charged at 25 °C and stirred for 15 minutes and heated to 55 °C to get clear solution. Both the clear solutions were combined and the solution was charged into a rotavapor and completely evaporated under reduced pressure at 60 °C to get 6.8 g of amorphous solid dispersion of empagliflozin and HPC. PXRD pattern: Fig. 7.

Glass transition onset temperature is 73.32 °C

Glass transition temperature is 84.59 °C.

Taken 3 g of the above amorphous solid dispersion and divided into 3 parts (P1, P2 and P3) 1 g each part. Added 5oo mg of Syloid to P1, 500 mg of Lactose monohydrate to P2 and 500 mg of Croscarmellose sodium and kept all the three samples in humidification chamber at 40 % RH and 30 °C for 10 hours.

Good improvement in flowability and stability is found by addition of adsorbents syloid, lactose, and croscarmellose sodium (API : HPC : Adsorbent = 1:1:0.5) when exposed even for one day at 40% RH and 30 °C remained amorphous.

P1 PXRD pattern: Fig 27; P2 PXRD pattern: Fig 28; P3 PXRD pattern: Fig 29.

P1: Glass transition onset temperature is 76.67 °C; Glass transition temperature is 90.64 °C

P2: Glass transition onset temperature is 70.89 °C; Glass transition temperature is 82.46 °C

P3: Glass transition onset temperature is 82.62 °C; Glass transition temperature is 84.88 °C

Example 29: **Preparation of crystalline Form N of Empagliflozin**.

Empagliflozin (0.5 g) was dissolved in N-methyl pyrrolidine (0.5 mL) at 25°C and methyl tert. butyl ether (7.5 mL) was added slowly at the same temperature. Stirred the mixture for 15.5 hours at 25°C and the solid was filtered to obtain the title compound.

Example 30: **Preparation of crystalline Form N of Empagliflozin**.

Empagliflozin (0.5 g) was dissolved in N-methyl pyrrolidine (0.5 mL) at 22°C and methyl tert. butyl ether (7.5 mL) was added slowly at the same temperature. Stirred the mixture for 15 hours at 22°C and the solid was filtered to obtain the title compound.

Example 31: **Preparation of crystalline Form N of Empagliflozin**.

Empagliflozin (5 g) was dissolved in N-methyl pyrrolidine (5 mL) at 23°C and methyl tert. butyl ether (75 mL) was added slowly in 8 minutes at the same temperature. Stirred the mixture for 15 hours at 23°C and the solid was filtered to obtain 4.9 g of the title compound. PXRD pattern: Figure 30.

Example 32: **Preparation of Empagliflozin L-phenylalanine complex**.

Empagliflozin (300 mg) and L-phenylalanine (143 mg) were added to water ethanol mixture (1:1, 14 mL) at 25°C and the mixture was heated to 50 °C using a hot air gun to form clear solution. The solution was kept idle for 14 days at 5 ° C. The precipitation was filtered to obtain the title compound. PXRD pattern: Figure 31.

Example 33: Preparation of crystalline Form-Alpha of Empagliflozin.

Empagliflozin (100 mg) and ethanol (4 mL) were charged into a test tube and the mixture was heated to 70 °C to get clear solution and the clears solution was filtered for particle free. Propyl acetate (10 mL) was added to the test tube at 25°C and the mixture was kept at -20 °C for 4 days and the solid was filtered to obtain the title compound. PXRD pattern: Figure 32.

Example 34: Preparation of crystalline Form-Beta of Empagliflozin.

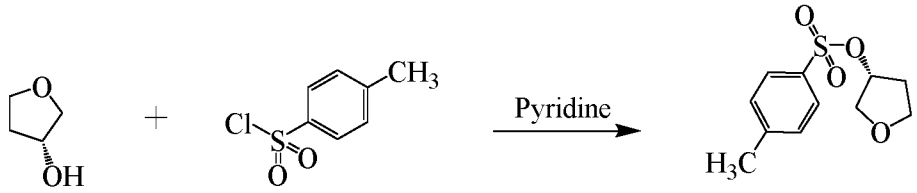
Empagliflozin (500 mg) and ethanol (20 mL) were charged into a round bottom flask and the mixture was heated to 70 °C to get clear solution and the clears solution was filtered for particle free. Butyl acetate (50 mL) was added to the test tube at 25°C and the mixture was kept at -20 °C for 22 days and the solid was filtered and dried in a vacuum tray drier to obtain the title compound. PXRD pattern: Figure 33.

Example 35: Preparation of crystalline Form-Gamma of Empagliflozin.

Empagliflozin (1000 mg) and dimethylacetamide (2 mL) were charged into a round bottom flask. The solid dissolved and isolated immediately. N-Hexane (20 mL) was added to the mixture at 25°C, thick mass was formed. The suspension was filtered and the solid was washed with diethyl ether (10 mL) and the solid was dried in an air tray drier obtain the title compound. PXRD pattern: Figure 34.

Example 36: Preparation of Empagliflozin

(a) Preparation of (R)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate

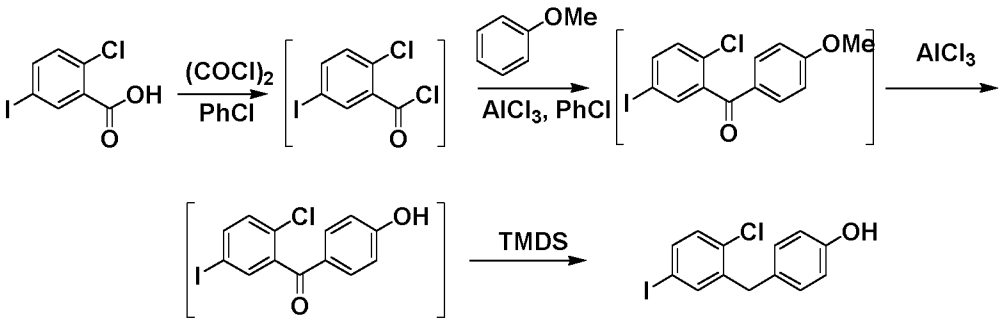


(R)-Hydroxy-THF (20 g), dichloromethane (300 mL) and Pyridine (71.8 g) were charged into a 1000 mL round bottom flask and the mixture was cooled to 5 °C. 4-methylbenzene-1-sulfonyl chloride (47.6 gm) was charged into the flask at 5 °C and the mixture was stirred for 10 hours at 28 °C. Water (500 mL) was charged to the flask and stirred for 15 minutes. Layers separated and the organic layer was washed with dilute hydrochloric acid (50 mL of HCl in 150 mL of water). The organic layer was washed with aqueous sodium bicarbonate solution (200 mL) and water (200 mL). The organic layer was concentrated under vacuum to yield 48 gm of (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate.

The crude compound was taken into another round bottom flask and ethylacetate (30 mL) was added and stirred for 10 minutes. The clear solution was cooled to 15 °C and 50 mg seed compound was added. Cyclohexane (300 mL) was added slowly over a period of 30 minutes at 15 °C. The obtained suspension was stirred for 1 hour at 15 °C. The precipitation was filtered and wet material was washed with chilled cyclohexane (80

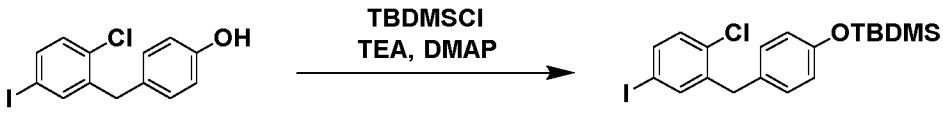
mL). The wet compound was dried under vacuum for 2 hours at 30 °C to yield 42 gm of title compound. Purity by HPLC: 99.87%.

(b) Preparation of 4-(2-chloro-5-iodobenzyl)phenol



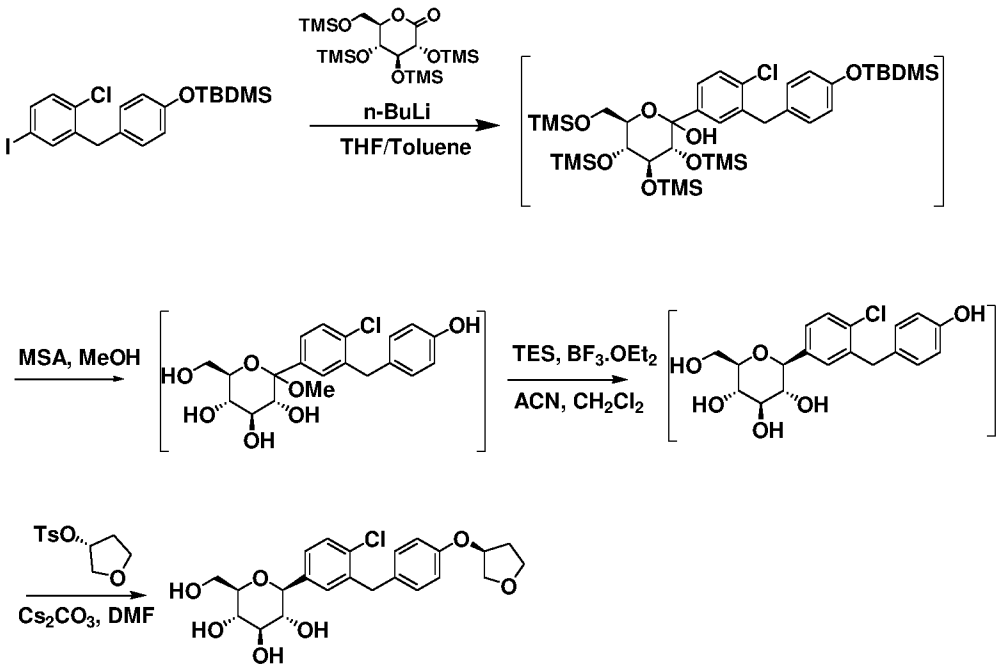
In a clean and dried round bottom flask, 2-chloro-5-iodobenzoic acid (30 g), chlorobenzene (300 mL), and catalytic amount of N,N-dimethylformamide (1.5 mL) were charged. The reaction mixture was cooled to 10 °C and oxalyl chloride (17.52 g) was added drop wise over 15 minutes. At the end of the addition, reaction mixture was warmed to 25 °C and stirred for 3 hours. The reaction mixture was concentrated under vacuum and to this crude material, 300 mL of chlorobenzene was added under nitrogen atmosphere and the mixture was cooled to 5 °C. To this, $AlCl_3$ (15.58 g) was charged. To the reaction mixture, anisole (12.06 g) was added drop wise at 5 °C. The reaction mixture was stirred for 1.5 h at 5 °C. Fresh $AlCl_3$ (28.3 g) was charged at 5 °C and the reaction mixture heated to 60 °C. The reaction mixture was cooled to 5 °C. At this temperature, TMDS (49.9 g) was added drop wise over a period of 0.5 h. The reaction mixture was then warmed to 25 °C and stirred for 5 hours. The reaction mixture was quenched by pouring the RM into 450 mL ice cold water. Ethyl acetate (600 mL) was added to this RM and stirred for 10 minutes at 20 °C. Layers were separated and aqueous layer extracted with ethyl acetate (90 mL). The combined organic layers were washed with 5% aqueous $NaHCO_3$ (600 mL) and saturated brine solution (300 mL). The organic layer was concentrated under vacuum at 50 °C. n-Hexane (150 mL) was added to the crude and stirred for 1h at 60 °C. The heterogeneous mixture was cooled to 10 °C and stirred for further 1h. The solid was filtered and washed with n-Hexane (50 mL). The white solid obtained was dried under vacuum at 40 °C (White solid, 28.8 g, Yield: 78.69 %, HPLC purity 97.7 %.

(c) Preparation of tert-butyl(4-(2-chloro-5-iodobenzyl)phenoxy)dimethylsilane



4-(2-chloro-5-iodobenzyl)phenol (30 g), dichloromethane (300 mL) were charged into a 1000 mL round bottom flask and the clear solution was cooled to 5 °C. A solution of tert-butylchlorodimethylsilane (14.43 g of TBDMSCl in 150 mL of DCM) was added to the flask at 5 °C. N,N-dimethylpyridin-4-amine (1.064 g) and triethylamine (13.21 g) were added to the reaction mass at 5 °C. The reaction mass was stirred at 28 °C for 3 hours. Water (150 mL) was charged to the reaction mass and the mixture was stirred for 30 minutes. Layers separated and the organic layer was washed with 1% aqueous HCl (150 mL) and with saturated sodium bicarbonate solution (150 mL), and with water (150 mL). The organic layer was concentrated under vacuum to yield 40 g crude material. The crude material and methanol (120 mL) were charged into a round bottom flask and 0.5 g of seed material was added. The solution was cooled to 10 °C and stirred for 2 hours. The suspension was filtered and was with 20 mL of methanol and the wet cake was dried under vacuum to yield 30 g of the title compound. Purity 98% by HPLC.

(d) Preparation of Empagliflozin

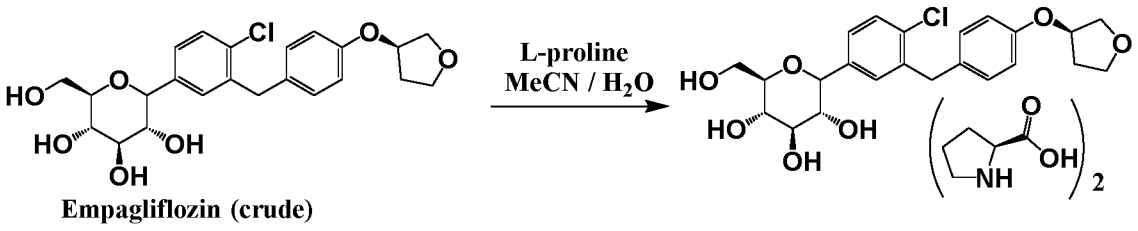


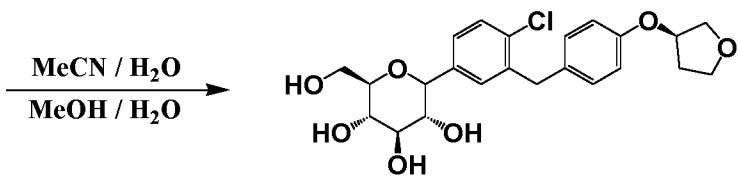
Tert-butyl(4-(2-chloro-5-iodobenzyl)phenoxy)dimethylsilane (1.0 Kg), tetrahydrofuran (6.0 L) and (3R,4S,5R,6R)-3,4,5-tris((trimethylsilyl)oxy)-6-(((trimethylsilyl)oxy)methyl)

tetrahydro-2H-pyran-2-one (1.221 Kg) were charged into a 20 L flask under Nitrogen atmosphere. Toluene (6.0 L) was charged into the flask and the resulted mixture was cooled to -80 °C. n-Butyl Lithium in hexane (1.6M, 2.8 Kg) was added slowly over a period of 3 hours at -80 °C. The reaction mixture was maintained for 1 hour at -80 °C. A solution of methanesulfonic acid (1.46 Kg of methanesulfonic acid in 9.0 L of methanol) was added to the reaction mass at -70 °C. The reaction mass was heated to -10 °C and stirred for 30 minutes and heated to 30 °C and stirred for 12 hours at 30 °C. The reaction mass was cooled to 5 °C and sodium bicarbonate solution (2.0 Kg of sodium bicarbonate in 23 L of water) was added slowly. The reaction mass was stirred for 30 minutes at 30 °C. The reaction mass was washed with Toluene (6.0 L× 3) and the reaction mass was concentrated under vacuum until 20 volumes remains in the flask. The reaction mass was extracted with ethylacetate (10.0 L×5) and the ethylacetate layer was washed with water (3.0 L). The ethylacetate layer was charged into a 100 L reactor and concentrated under vacuum to 3 volumes remained in the reactor. The concentrated ethylacetate layer was stripped off with acetonitrile (3.0 L× 3) then dichloromethane (7.0 L) and acetonitrile (1.2 L) were charged into the reactor and the reaction mass was cooled to -30 °C. Triethylsilane (0.57 Kg) and Borontrifluoride etherate solution (1.307 Kg) were charged into the reactor and the reaction mass was stirred for 3 hours at -30 °C. Temperature was raised to -5 °C and stirred for 6 hours. A solution of sodium carbonate (2.0 Kg of sodium carbonate in 20.0 L of water) was added to the reaction mass over a period of 30 minutes at 5 °C. The reaction mass was heated to 30 °C and stirred for 30 minutes. The reaction mass was concentrated under vacuum until 25 volumes remained in the reactor. The mass was washed with toluene (4.0 L) and extracted with ethylacetate (8.0 L×2 and 4.0 L×4) and the ethylacetate layer washed with water (2.0 L×2) The organic layer was concentrated under vacuum until 2 volumes remained in the reactor then the crude mass was stripped off with ethylacetate (3.0 L×2) and with DMF (1.4 L). Tosyl-THF (0.634 Kg) and DMF (0.20 L) were charged into the reactor and the resulted mass was stirred for 30 minutes at 30 °C. Cesium carbonate lot 1 (0.57 Kg) was added to the reaction mass. Reaction mass was heated to 45 °C and stirred for 2 hours at 45 °C. Cesium carbonate lot 2 (0.57 Kg) was added to the reaction mass and the reaction mass was stirred for 2 hours. Cesium carbonate

lot 3 (0.57 Kg) was added to the reaction mass the reaction mass was stirred for 20 hours at 45 °C. The reaction mass was cooled to 30 °C and water (4.0 L) was added to the mass and stirred for 30 minutes. Layers were separated and the aqueous layer was washed with toluene (4.0 L). The aqueous layer was concentrated at 70 °C under vacuum until 1.0 volume remained in the reactor. The concentrated mass was cooled to 30 °C and water (10.0 L) and acetonitrile 1.0 L) were charged into the reactor at 30 °C and the resulted mixture was heated to 45 °C and the mixture was stirred for 6 hours at 45 °C. The suspension was cooled to 25 °C and stirred for 7 hours at 25 °C. The precipitation was filtered and the wet solid was washed with water (3.0L) and the solid was suck dried. The wet compound and DMF (1.0 L) were charged into another reactor and the solution was heated to 45 °C. Acetonitrile (1.0 L) charged followed by water (10.0 L) into the reactor at 45 °C and stirred for 6 hours. The suspension was cooled to 25 °C and stirred for 6 hours. The precipitation was fileted and the wet cake was washed with water. The wet material was suck dried. The wet material was dried under vacuum at 60 °C for 6 hours to yield 0.55 Kg of crystalline empagliflozin. Purity by HPLC 99%.

Example 37: Purification of Empagliflozin



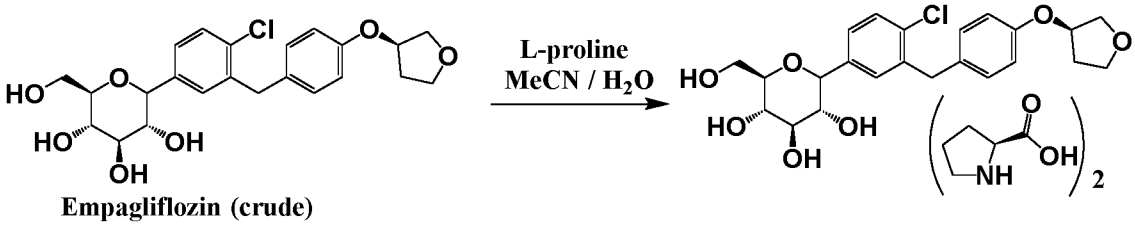


Empaglilfozin (pure)

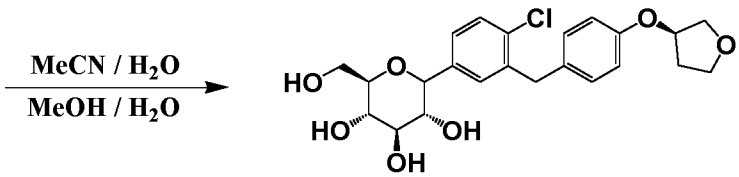
Empagliflozin (75 g), acetonitrile (1500 mL) and water (15 mL) were charged into a round bottom flask and the resulted mixture was heated to 75 °C and stirred for 30 minutes to form clear solution. L-proline lot 1 (19.2 g) was charged into the flask and stirred for 2 hours at 75 °C. L-proline lot 2 (19.2 g) was charged into the flask and stirred

for 6 hours at 75 °C. Reaction mass was cooled to 25 °C and stirred for 6 hours. The precipitation was filtered and suck dried for 30 minutes. The wet solid was washed with acetonitrile (375 mL) and suck dried for 2 hours. The wet compound was dried under vacuum at 65 °C for 4 hours. The dry compound was charged into a round bottom flask and acetonitrile (337 mL) and water (225 mL) were added to the flask and stirred for 20 minutes to get clear solution. The reaction mass was heated to 45 °C and stirred for 1 hour. Water (900 mL) was charged into the flask slowly over a period of 30 minutes. The reaction mass was cooled to 25 °C and stirred for 10 hours. The precipitation was filtered and the wet material suck dried for 30 minutes. The wet material was washed with water (225 mL x 2) and suck dried for 30 minutes. The wet material was charged into a round bottom flask. Methanol (300 ml) and water (45 mL) was added and the mass was heated to 50 °C to form clear solution. Water (1200 mL) was added to the clear solution and stirred the mass at 60 °C for 3 hours. Solid was isolated. The precipitation was cooled to 25 °C and stirred for 8 hours. The precipitation was filtered and suck dried for 30 minutes. The wet material was washed with water (225 mL) and suck dried for 30 minutes. The wet material was dried under vacuum at 65 °C for 6 hours to get 64 g of crystalline empagliflozin. Purity by HPLC: 99.8%.

Example 38: Purification of Empagliflozin



Empagliflozin (crude)



Empaglilfozin (pure)

Empagliflozin (75 g), acetonitrile (1500 mL) and water (15 mL) were charged into a round bottom flask and the resulted mixture was heated to 75 °C and stirred for 30 minutes to form clear solution. L-proline lot 1 (19.2 g) was charged into the flask and

stirred for 2 hours at 75 °C. L-proline lot 2 (19.2 g) was charged into the flask and stirred for 6 hours at 75 °C. Reaction mass was cooled to 25 °C and stirred for 6 hours. The precipitation was filtered and suck dried for 30 minutes. The wet solid was washed with acetonitrile (375 mL) and suck dried for 2 hours. The wet compound was dried under vacuum at 65 °C for 4 hours. The dry compound was charged into a round bottom flask and DMF (200 mL) and water (200 mL) were added to the flask and stirred for 20 minutes to get clear solution. The clear solution was filtered through a micron filter to get a particle free clear solution. The reaction mass was heated to 55 °C and stirred for 1 hour. Water (600 mL) was charged into the flask slowly over a period of 30 minutes. The reaction mass was cooled to 25 °C and stirred for 3 hours. The precipitation was filtered and the wet material suck dried for 30 minutes. The wet material was washed with water (500 mL) and suck dried for 30 minutes. The wet material was charged into a round bottom flask. Methanol (300 ml) and water (45 mL) was added and the mass was heated to 50 °C to form clear solution. Water (1200 mL) was added to the clear solution and stirred the mass at 60 °C for 3 hours. Solid was isolated. The precipitation was cooled to 25 °C and stirred for 8 hours. The precipitation was filtered and suck dried for 30 minutes. The wet material was washed with water (225 mL) and suck dried for 30 minutes. The wet material was dried under vacuum at 65 °C for 6 hours to get 65 g of crystalline empagliflozin. Purity by HPLC: 99.8%.

CLAIMS

1. A process for preparing crystalline form of empagliflozin characterized by PXRD peaks at about 18.84°, 20.36°, and 25.21° 2 theta, comprising;

a) providing a solution of empagliflozin in a solvent or a mixture of solvents;

b) heating the solution to a temperature higher than the temperature at which the solution is prepared;

c) adding an anti-solvent to the hot solution of step (b); and

d) isolating crystalline form of empagliflozin characterized by PXRD peaks at 18.84°, 20.36°, and 25.21° 2 theta.

2. The process of claim 1, wherein the solvent is selected from the group comprising methanol, ethanol, isopropanol, tetrahydrofuran, acetone, acetonitrile, water and mixtures thereof.

3. The process of claim 1, wherein the solvent is methanol.

4. The process of claim 1, wherein the anti-solvent is water.

5. A complex of empagliflozin with L-proline, characterized by an X-Ray Powder Diffraction (XRPD) pattern having peaks at about 4.36 ± 0.2, 12.97 ± 0.2, 15.67 ± 0.2 and 18.80 ± 0.2 °2θ.

6. A process for preparation of empagliflozin L-proline complex, characterized by an X-Ray Powder Diffraction (XRPD) pattern having peaks at about 4.36 ± 0.2, 12.97 ± 0.2, 15.67 ± 0.2 and 18.80 ± 0.2 °2θ, comprising:

(a) mixing empagliflozin, L-proline and a mixture of isopropanol and water;

(b) optionally, heating the mixture obtained in step (a);

(c) adding methyl tertiary butyl ether (MTBE) to the mixture; and

(d) isolating the empagliflozin L-proline complex characterized by an X-Ray Powder Diffraction (XRPD) pattern having peaks at about 4.36 ± 0.2, 12.97 ± 0.2, 15.67 ± 0.2 and 18.80 ± 0.2 °2θ.

7. A process for purification of empagliflozin, comprising:

(a) providing a solution of empagliflozin L-proline complex, characterized by an X-Ray Powder Diffraction (XRPD) pattern having peaks at about 4.36 ± 0.2, 12.97 ± 0.2, 15.67 ± 0.2 and 18.80 ± 0.2 °2θ in a mixture of organic solvent and water;

(b) optionally heating the solution obtained in step (a);

(c) separating the organic layer from the mixture obtained in step (b); and

(d) isolating pure empagliflozin from the organic layer of step (c).

8. Amorphous empagliflozin having a glass transition onset temperature of at least 60 °C or above.

9. A process for preparation of amorphous empagliflozin having a glass transition onset temperature of at least 60 °C or above, comprising:

a) providing a solution of empagliflozin in a solvent or a mixture of solvents;

b) removing solvent from the solution obtained in step (a); and

c) recovering amorphous empagliflozin having a glass transition onset temperature of at least 60 °C or above.

10. The process of claim 9, wherein the solvent is selected from the group comprising methanol, ethanol, isopropanol, n-propanol, tert-butanol, tetrahydrofuran, acetone, acetonitrile, dichloromethane, water and mixtures thereof.

11. Amorphous solid dispersion of empagliflozin, having a glass transition onset temperature of at least 55 °C or above, comprising empagliflozin and one or more pharmaceutically acceptable carriers.

12. The amorphous solid dispersion of empagliflozin of claim 11, wherein the pharmaceutically acceptable carrier is selected from the group comprising pregelatinized starch, lactose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, Copovidone, Soluplus, Silicified microcrystalline cellulose, mannitol, sorbitol, acacia, guar gum, tragacanth, gelatin, polyvinylpyrrolidone, hydroxymethyl celluloses, ethylcellulose, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, HPMC-Phthalate, HPMC-AS, HPMC-15 CPS, sodium starch glycolate, crospovidone, croscarmellose sodium, colloidal silicon dioxide stearic acid, magnesium stearate, zinc stearate, colloidal silicon dioxide and mixtures thereof.

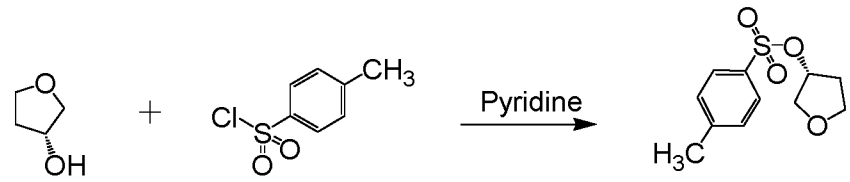
13. The amorphous solid dispersion of empagliflozin of claim 11, wherein the pharmaceutically acceptable carrier is selected from the group comprising hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate (HPMC-Phthalate), methyl cellulose and Copovidone.

14. The amorphous solid dispersion of empagliflozin of claim 11, wherein the pharmaceutically acceptable carrier is Copovidone.

15. The amorphous solid dispersion of empagliflozin of claim 11, wherein the pharmaceutically acceptable carrier is hydroxypropyl methylcellulose phthalate (HPMC-Phthalate).

16. A process for preparation of (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate having greater than about 99.8% of chiral purity, comprising

(a) reacting (R)-tetrahydrofuran-3-ol with 4-methylbenzene-1-sulfonyl chloride in presence of pyridine



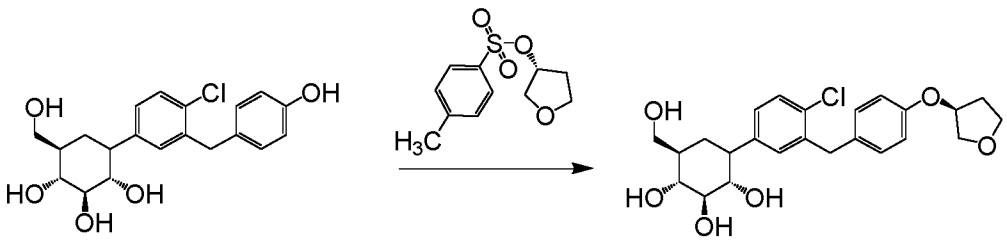
(b) slurrying the crude compound (R)-tetrahydrofuran-3-yl-4-methyl benzenesulfonate with a mixture of ethylacetate and cyclohexane, and

(c) isolating the (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate having chiral purity of greater than about 99.8%.

17. A process for preparation of empagliflozin having greater than about 99.8% of chiral purity, comprising:

(a) slurrying the crude compound (R)-tetrahydrofuran-3-yl-4-methyl benzenesulfonate with a mixture of ethylacetate and cyclohexane to get (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate having chiral purity of greater than about 99.8%, and

(b) reacting the (R)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate having greater than about 99.8% of chiral purity with (1R,2R,3S,6R)-4-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl)cyclohexane-1,2,3-triol in presence of a base.



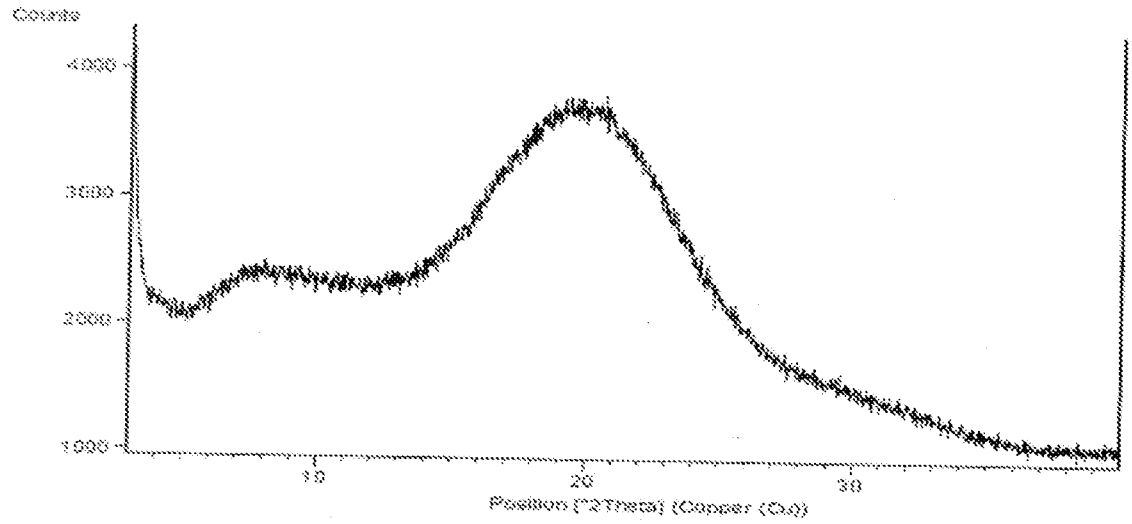


Figure 1

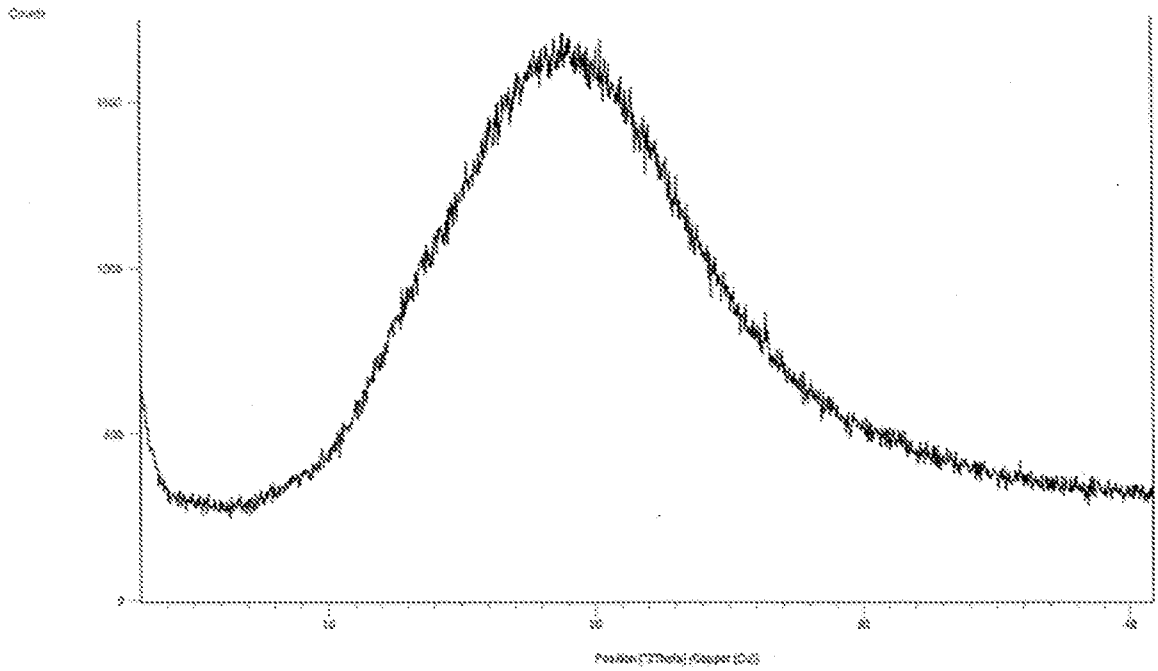


Figure 2

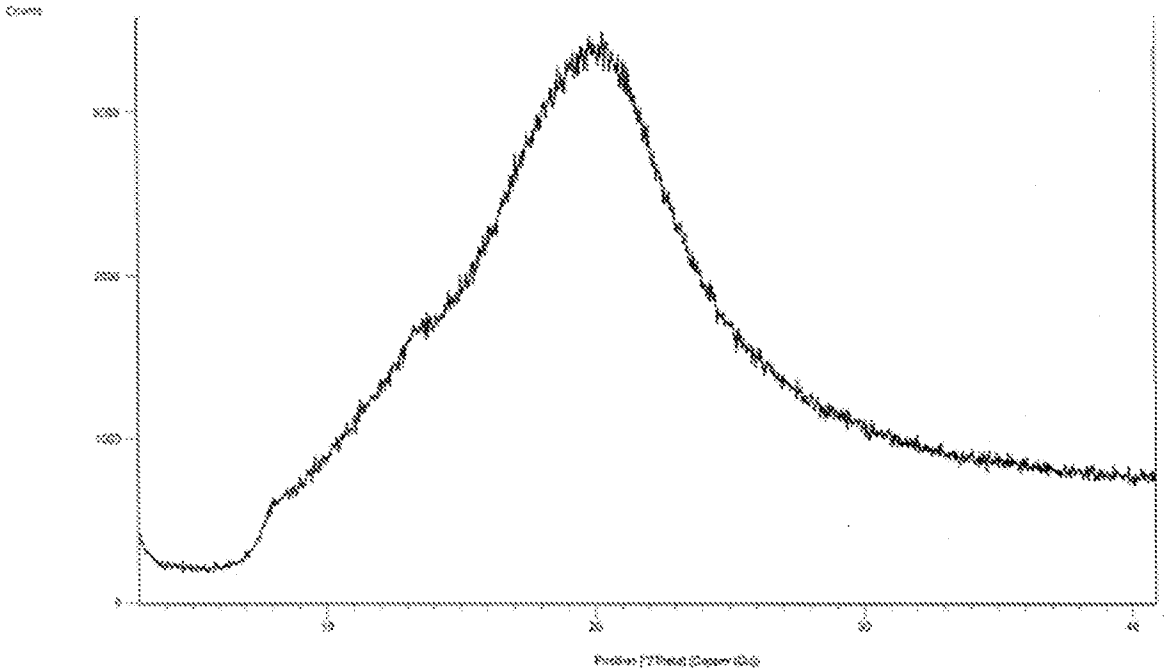


Figure 3

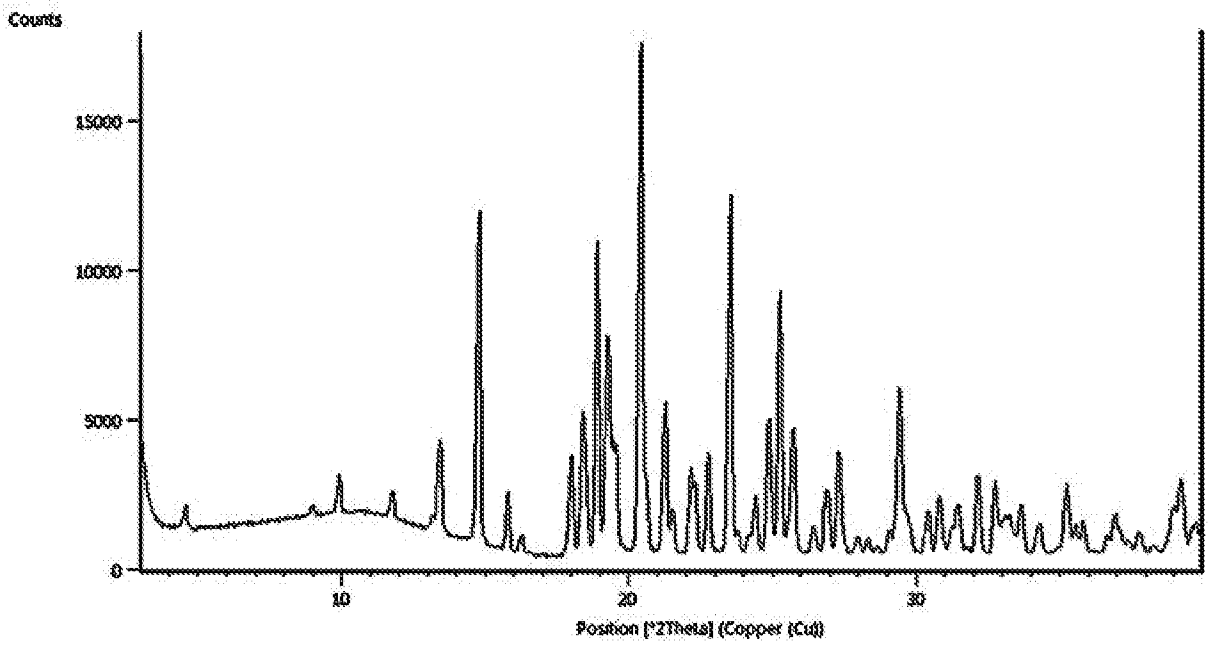


Figure 4

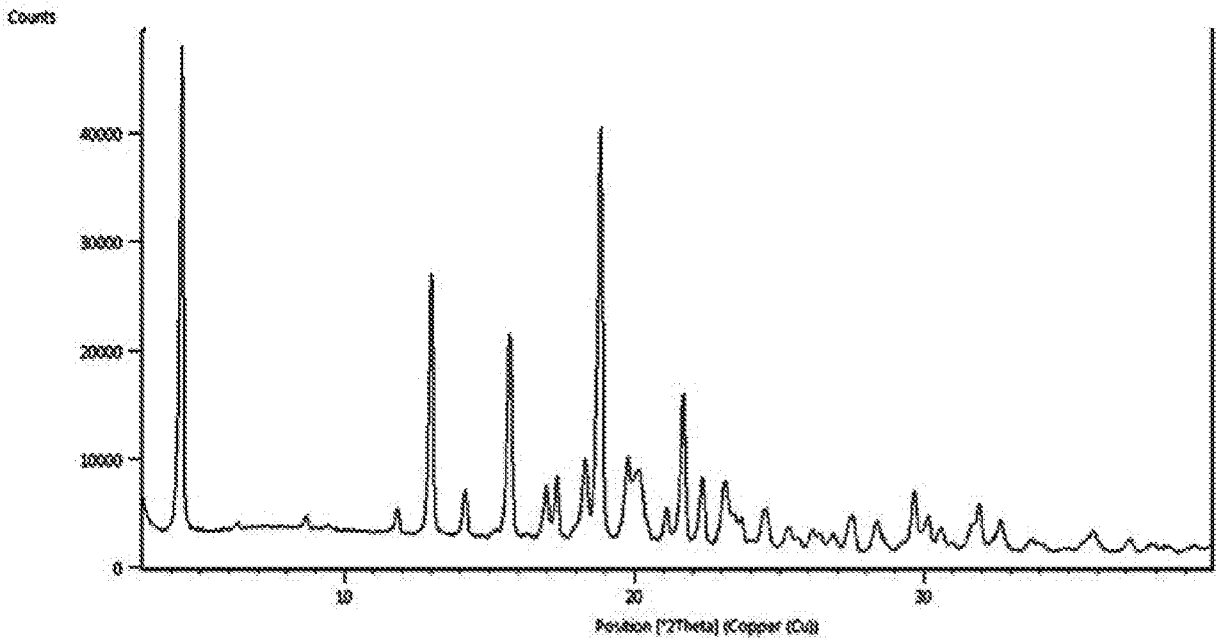


Figure 5

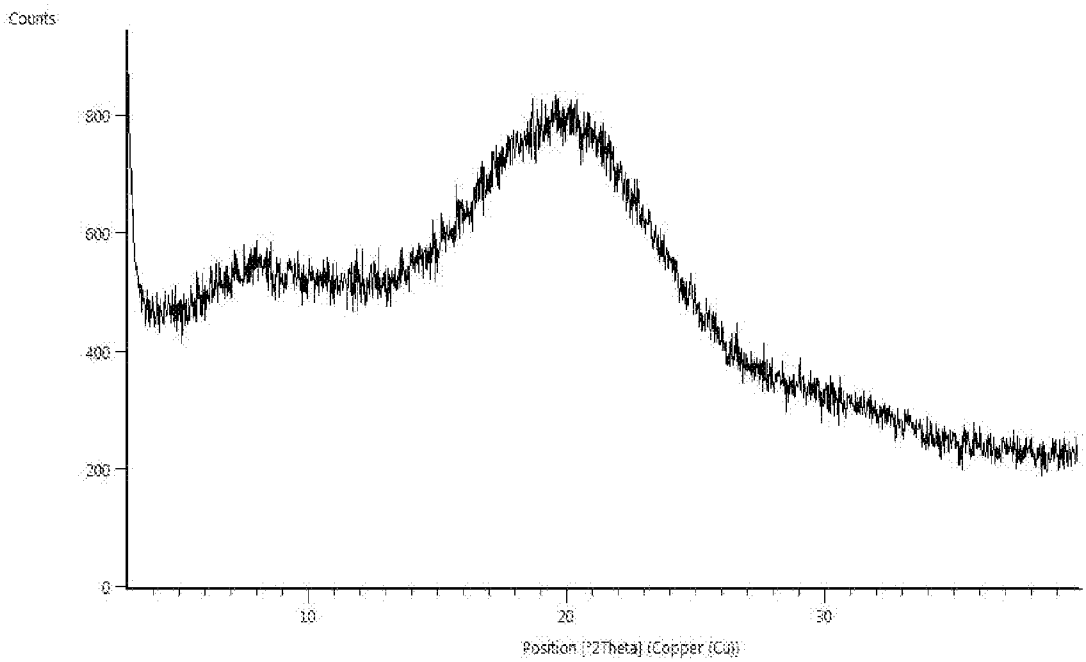


Figure 6

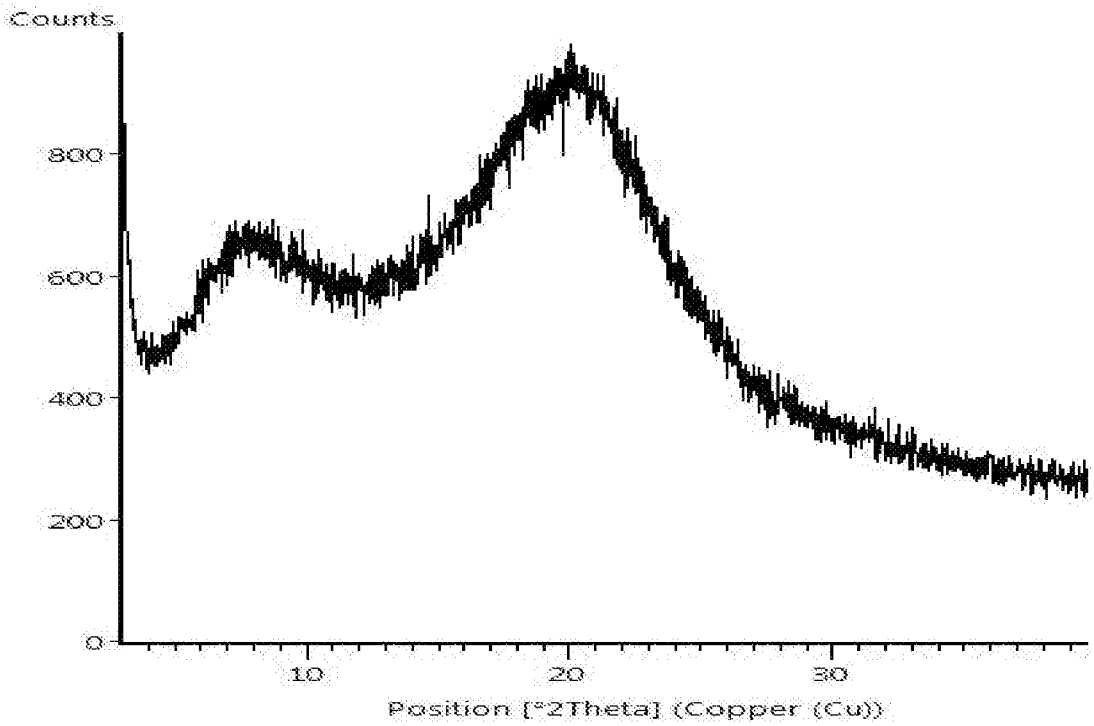


Figure 7

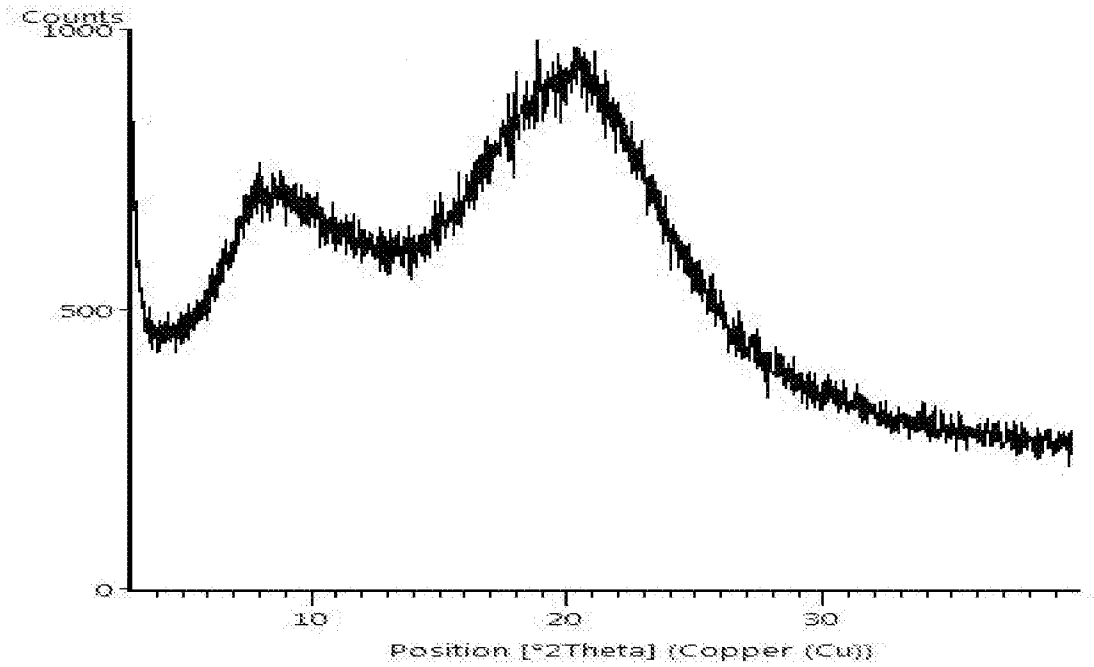


Figure 8

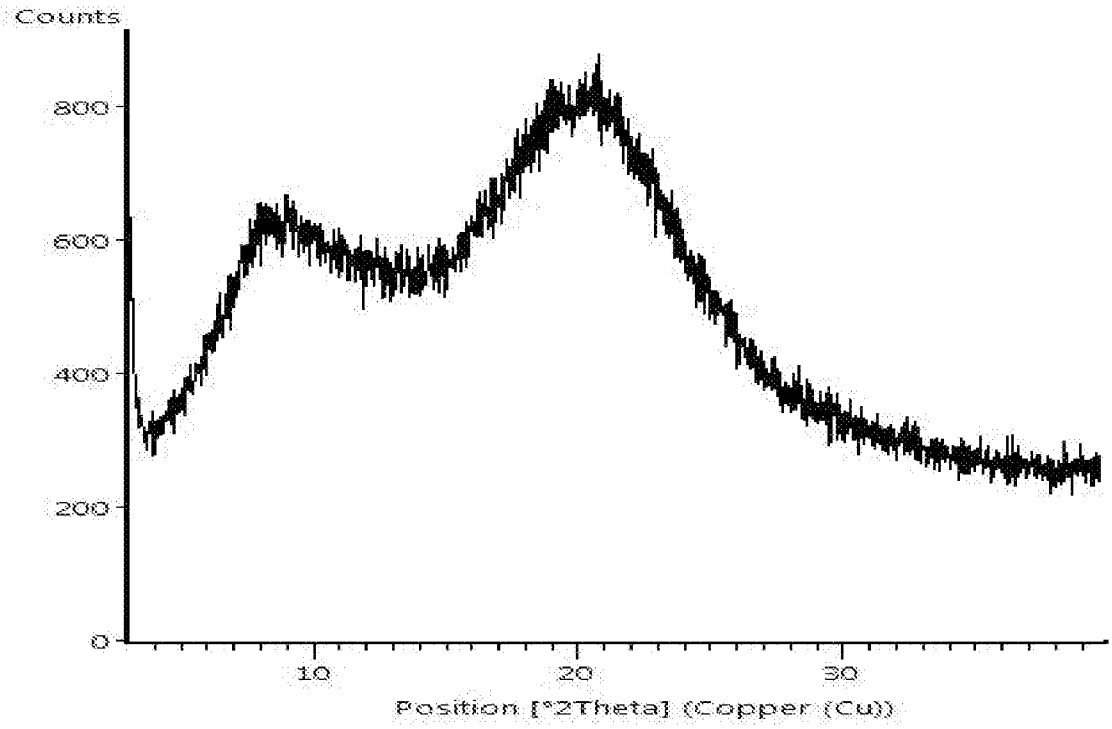


Figure 9

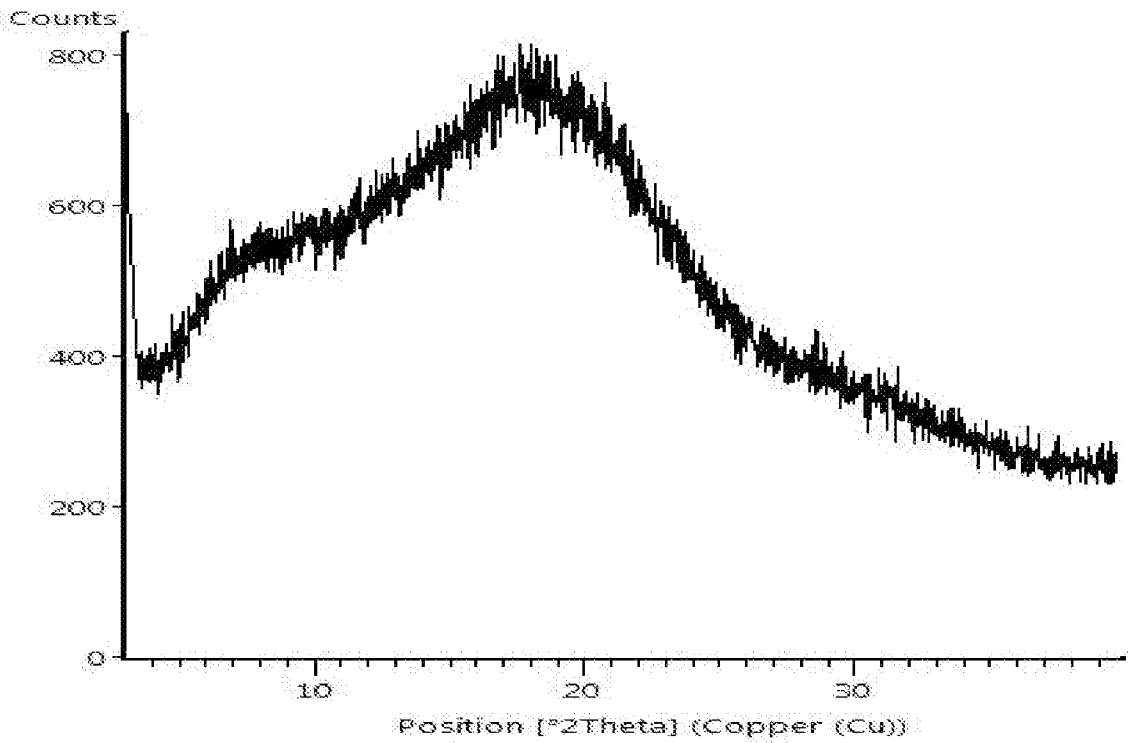


Figure 10

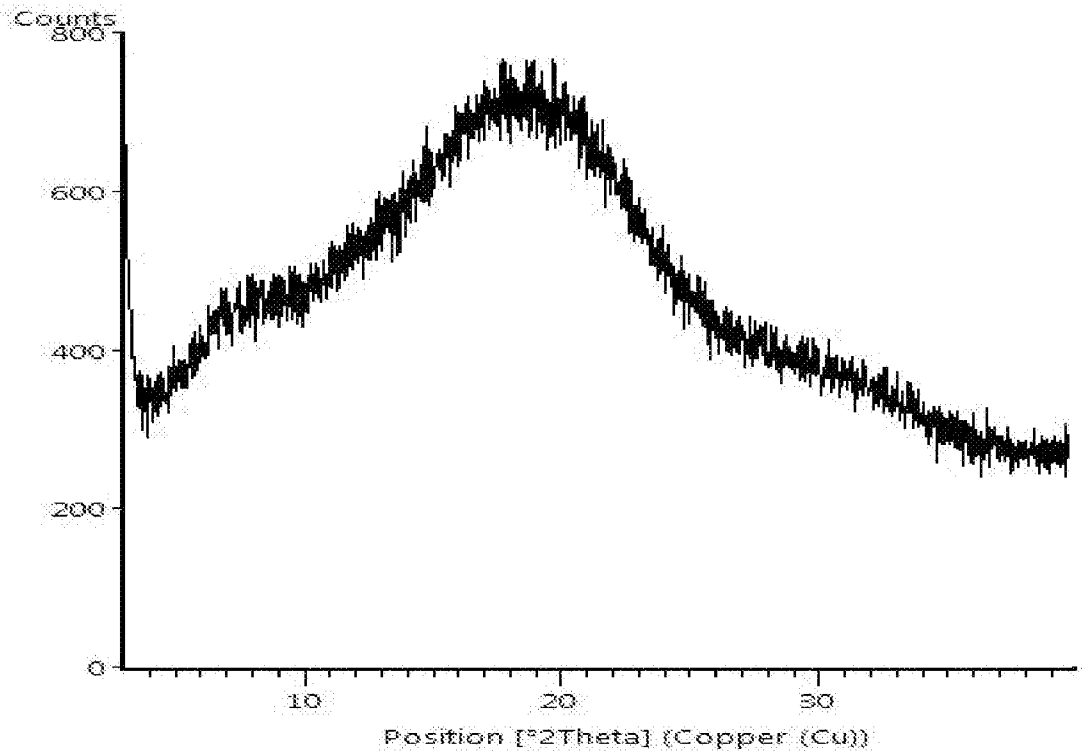


Figure 11

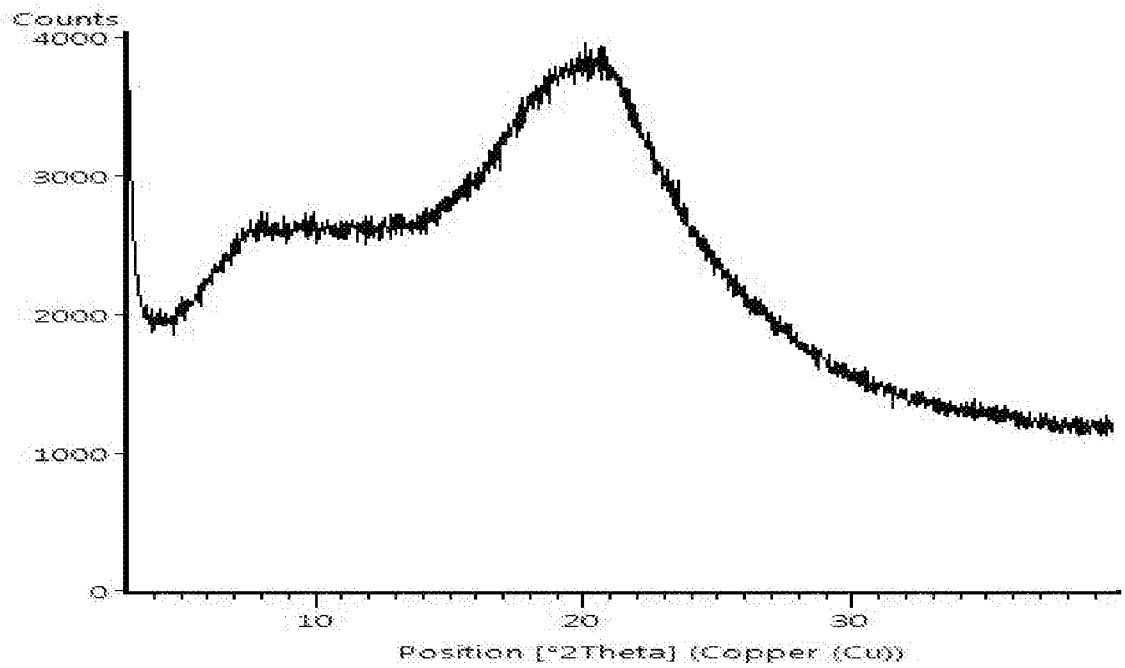


Figure 12

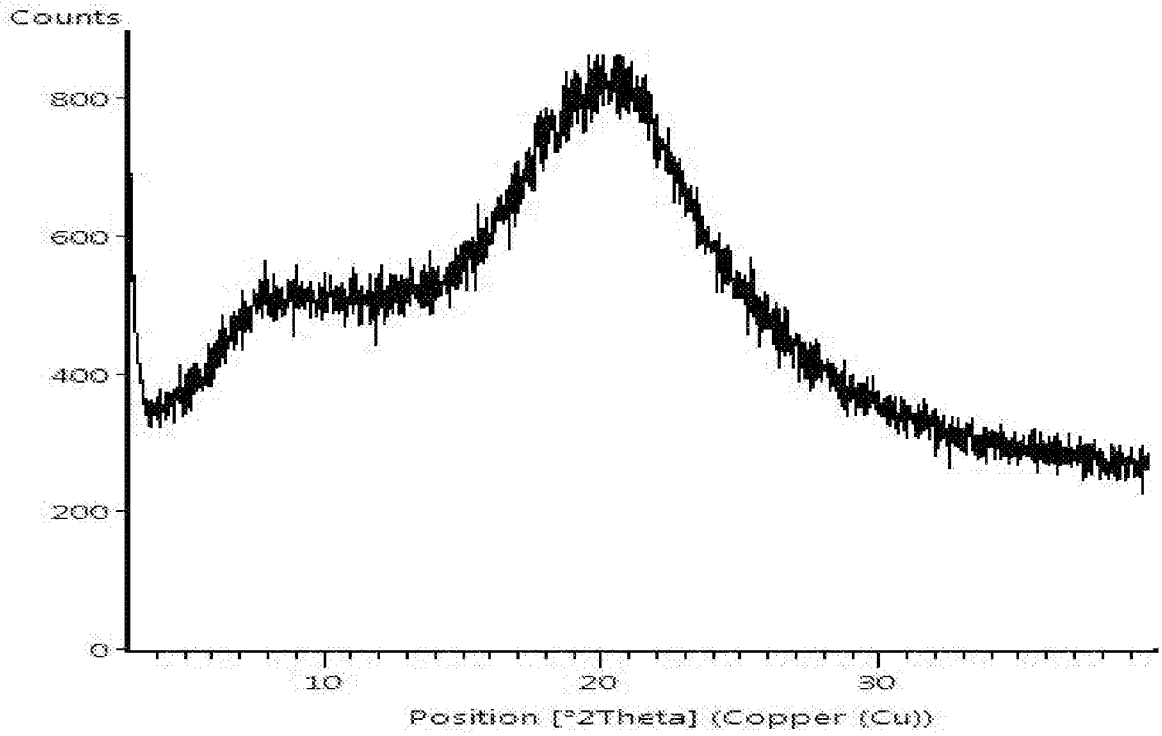


Figure 13

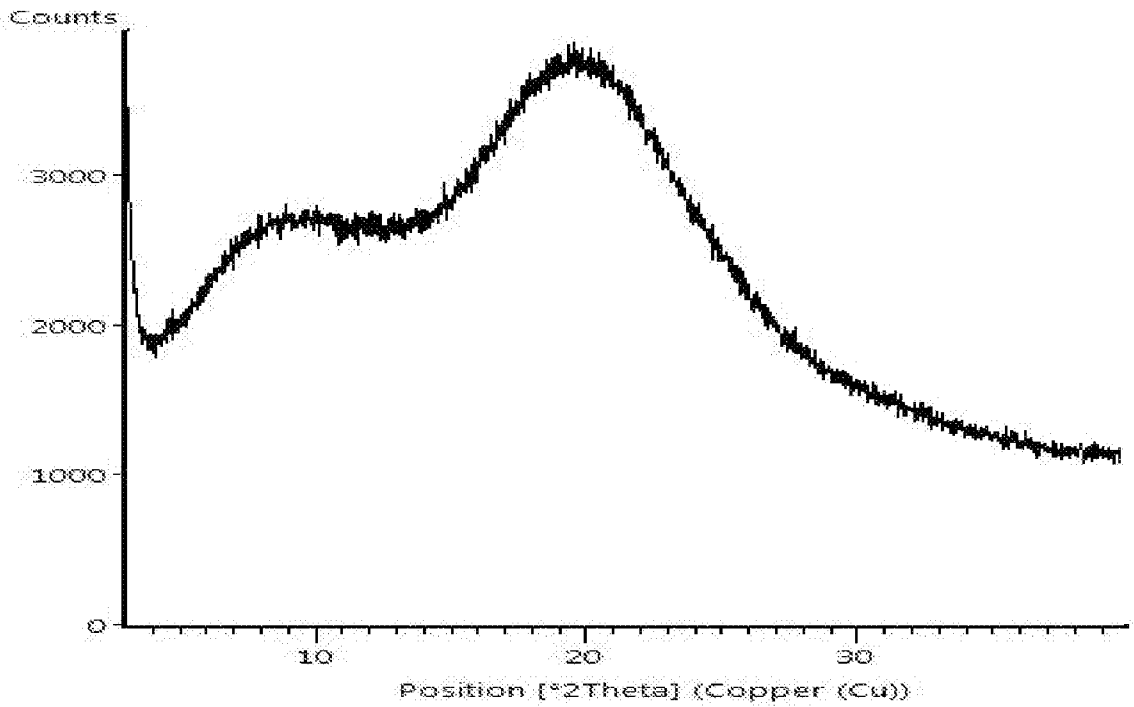


Figure 14

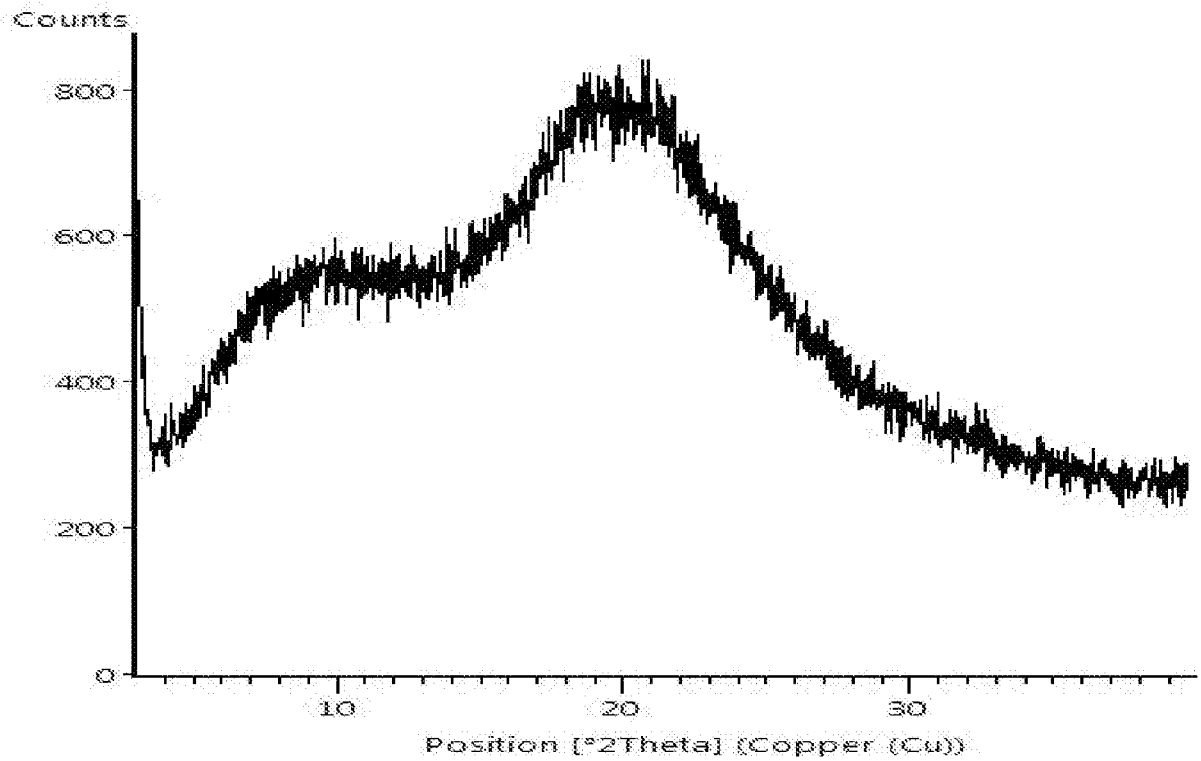


Figure 15

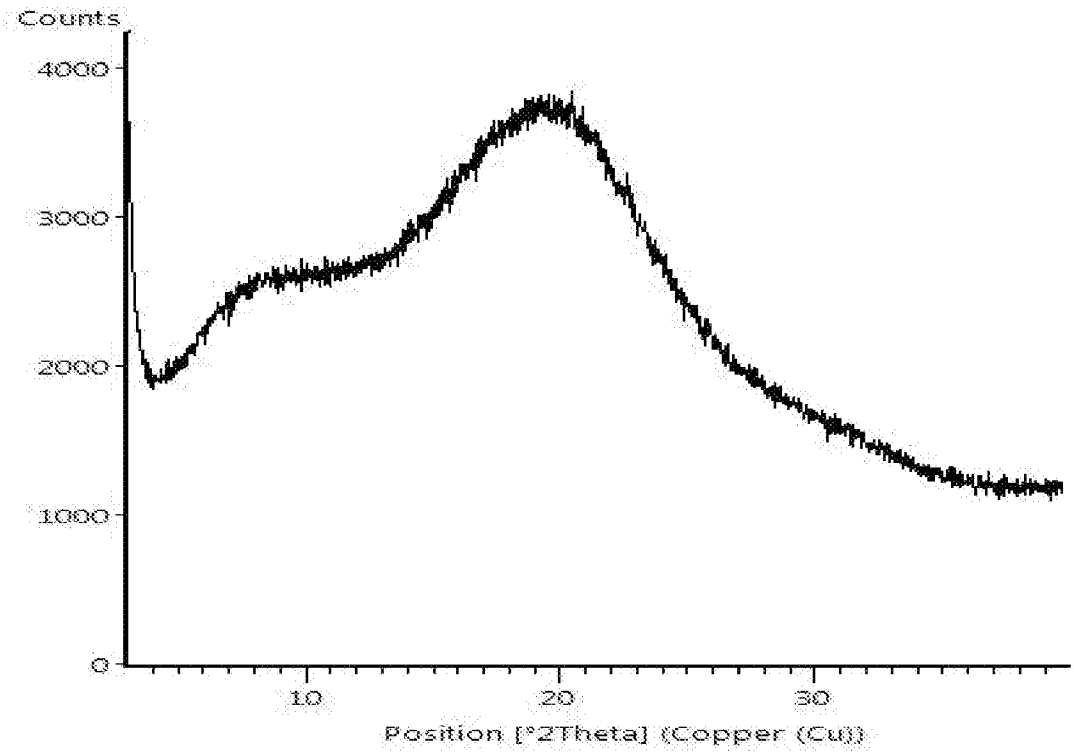


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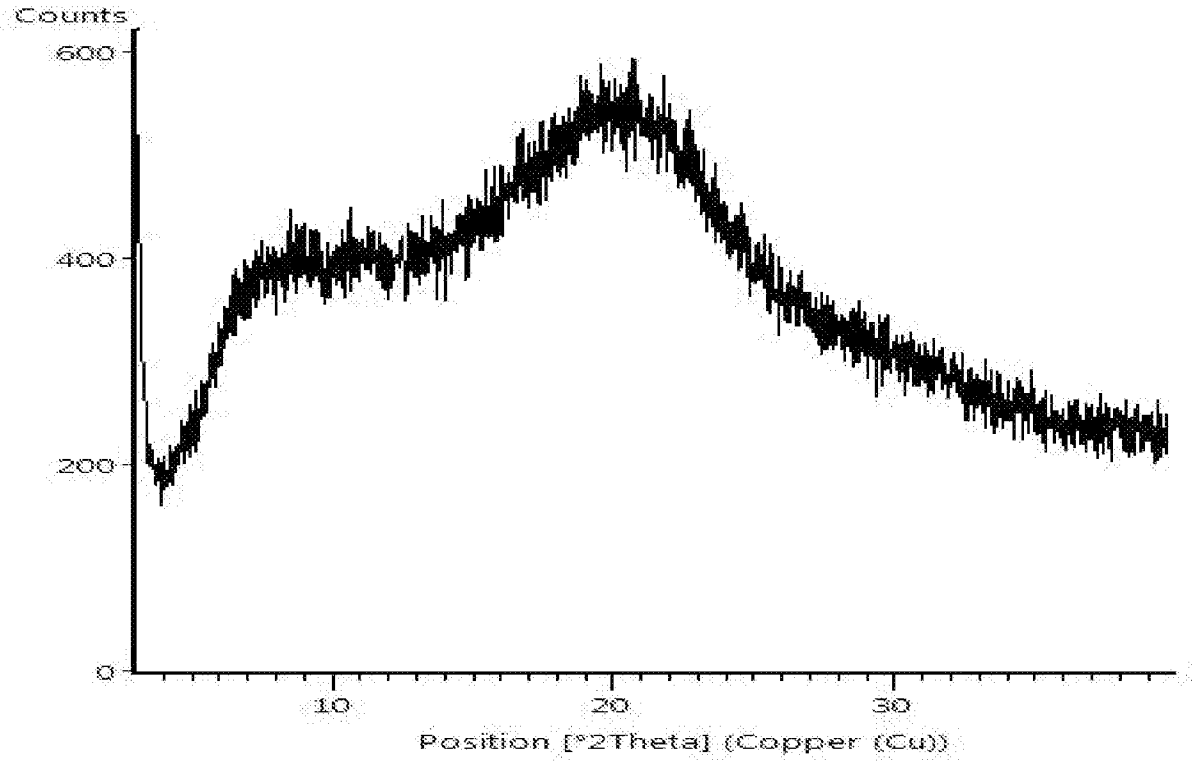


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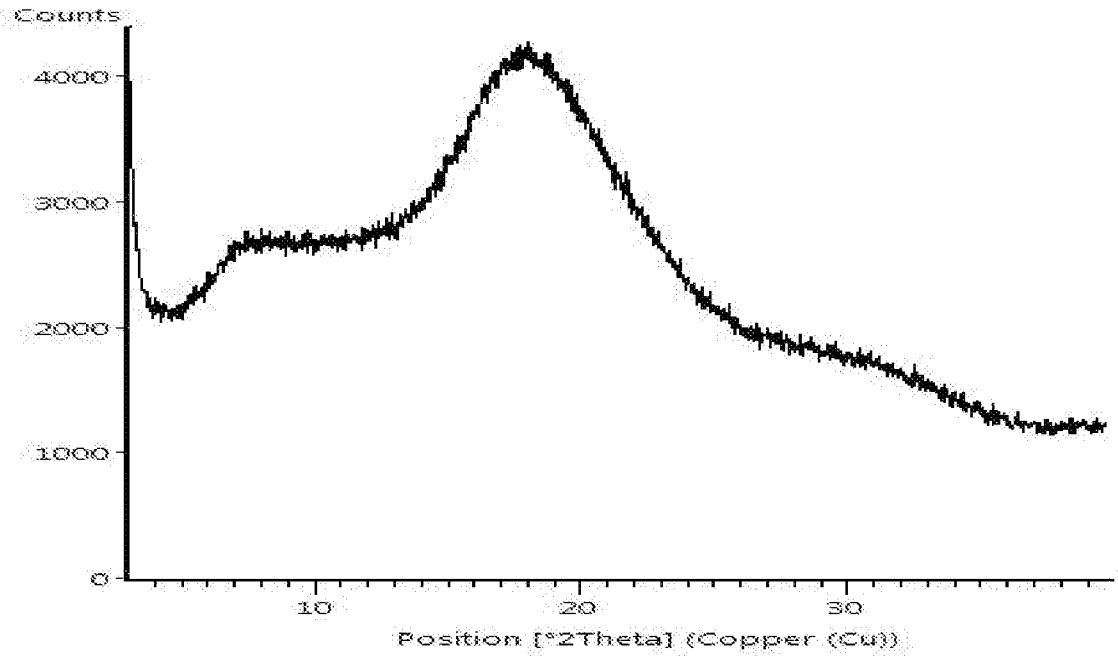


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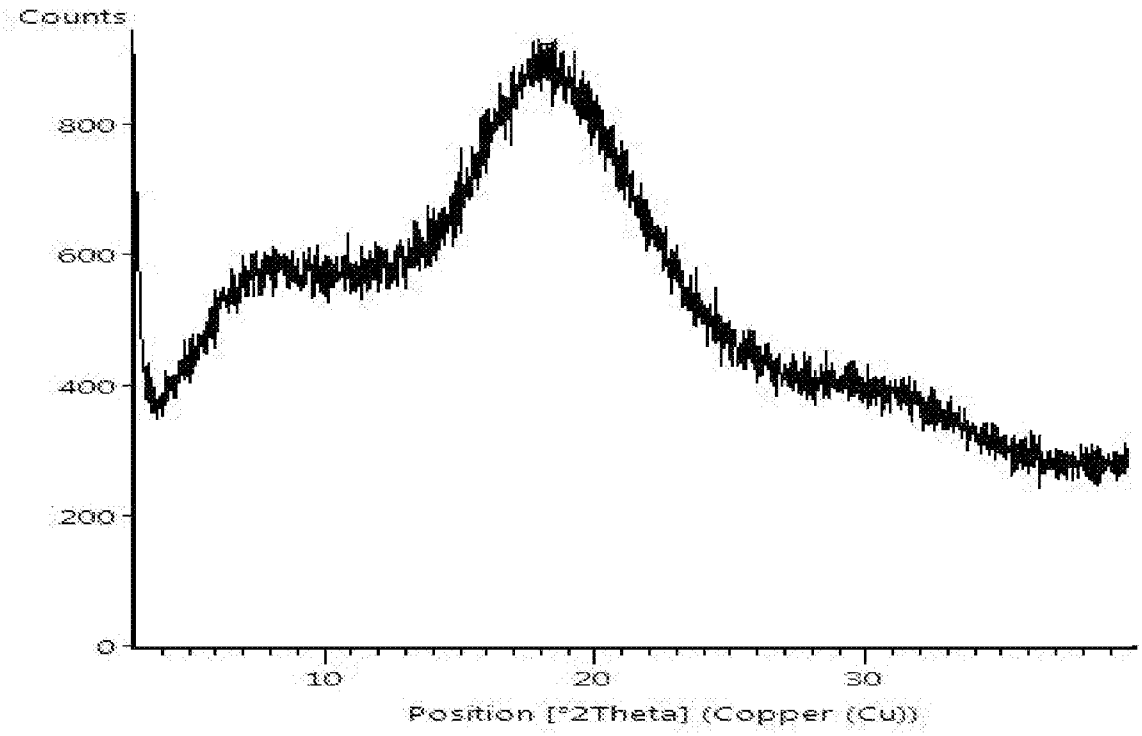


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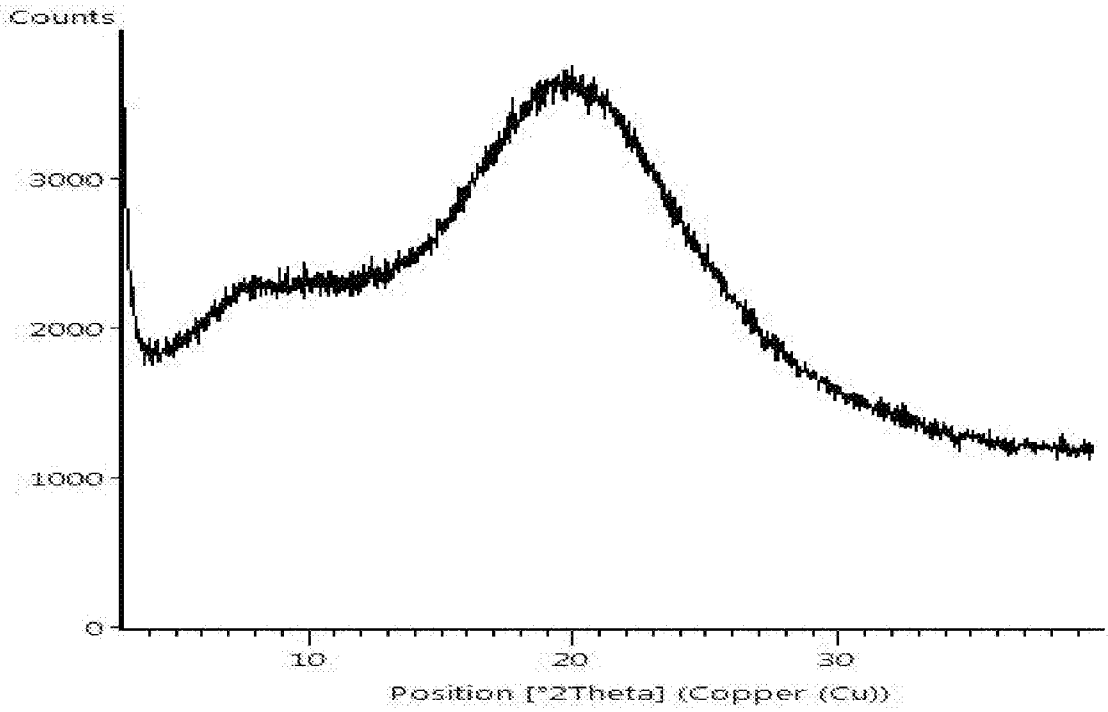


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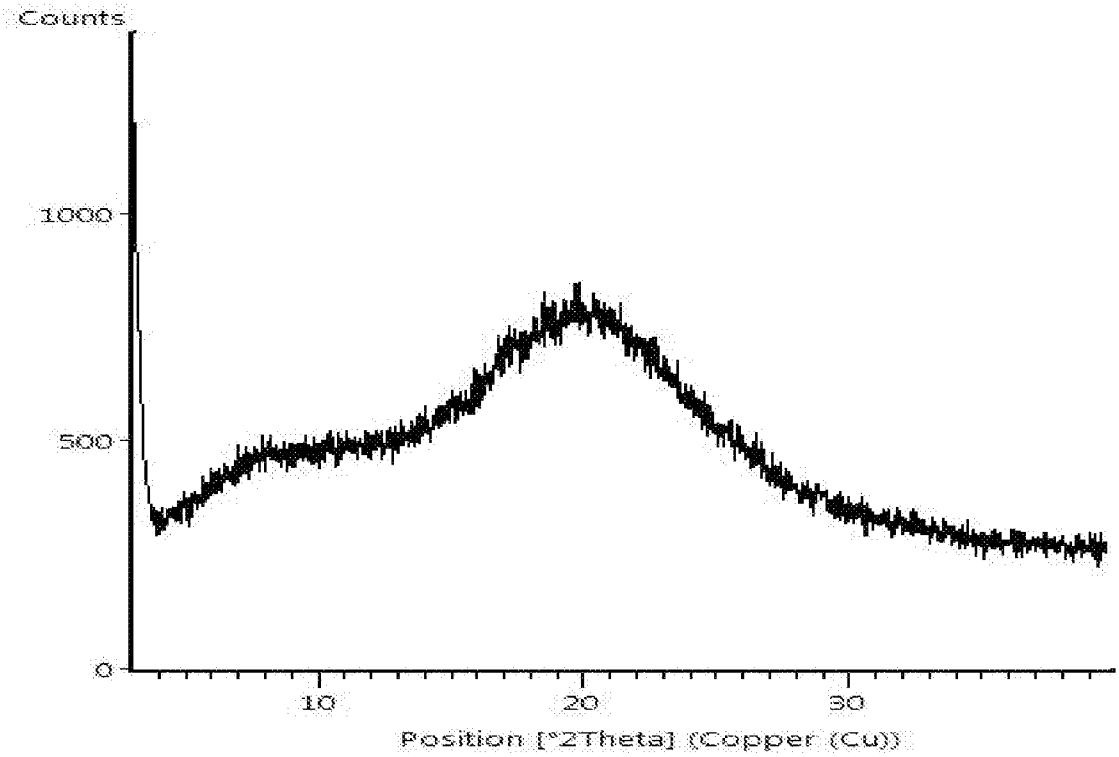


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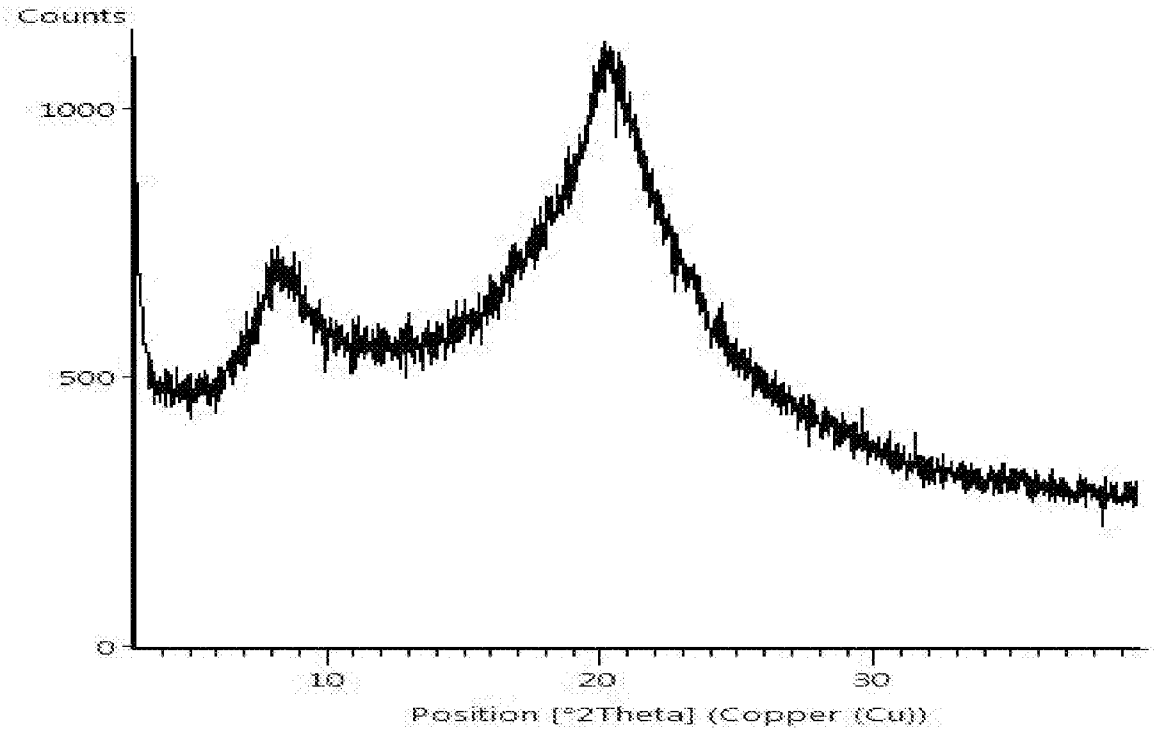


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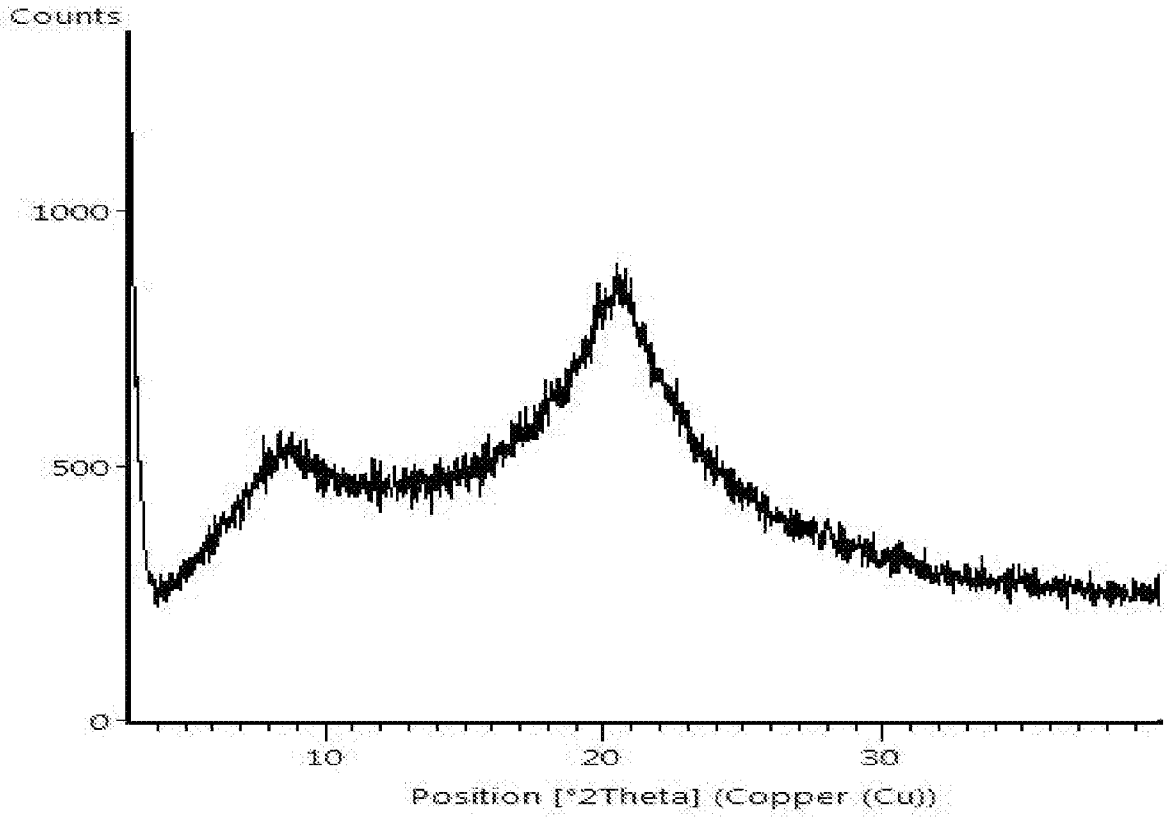


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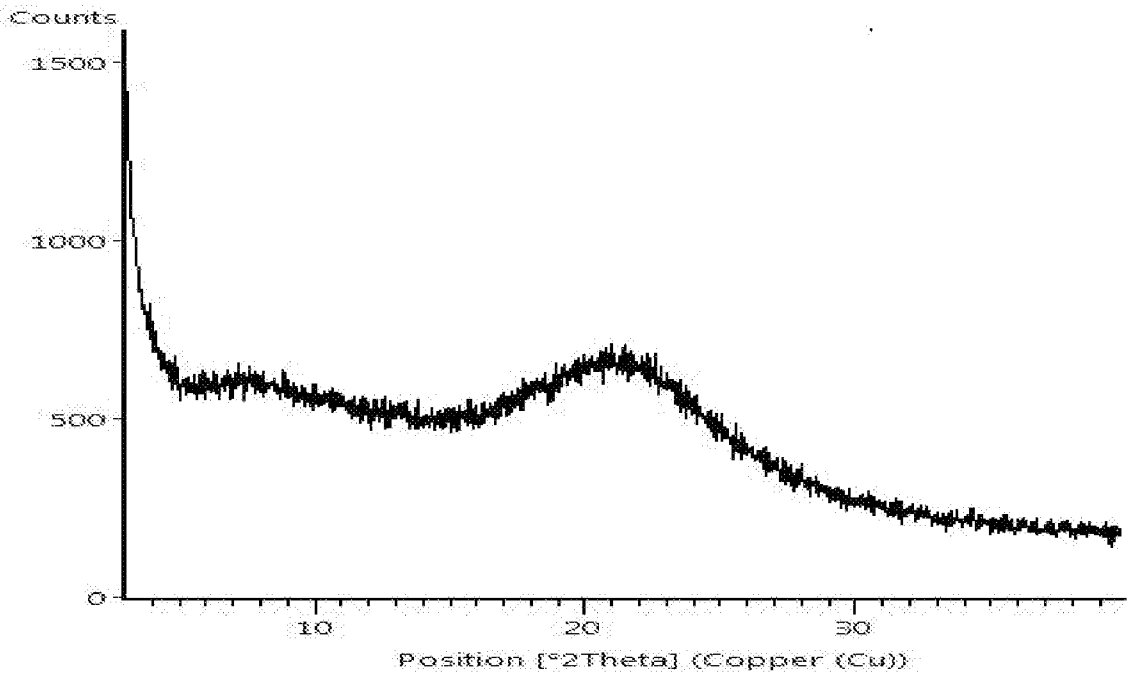


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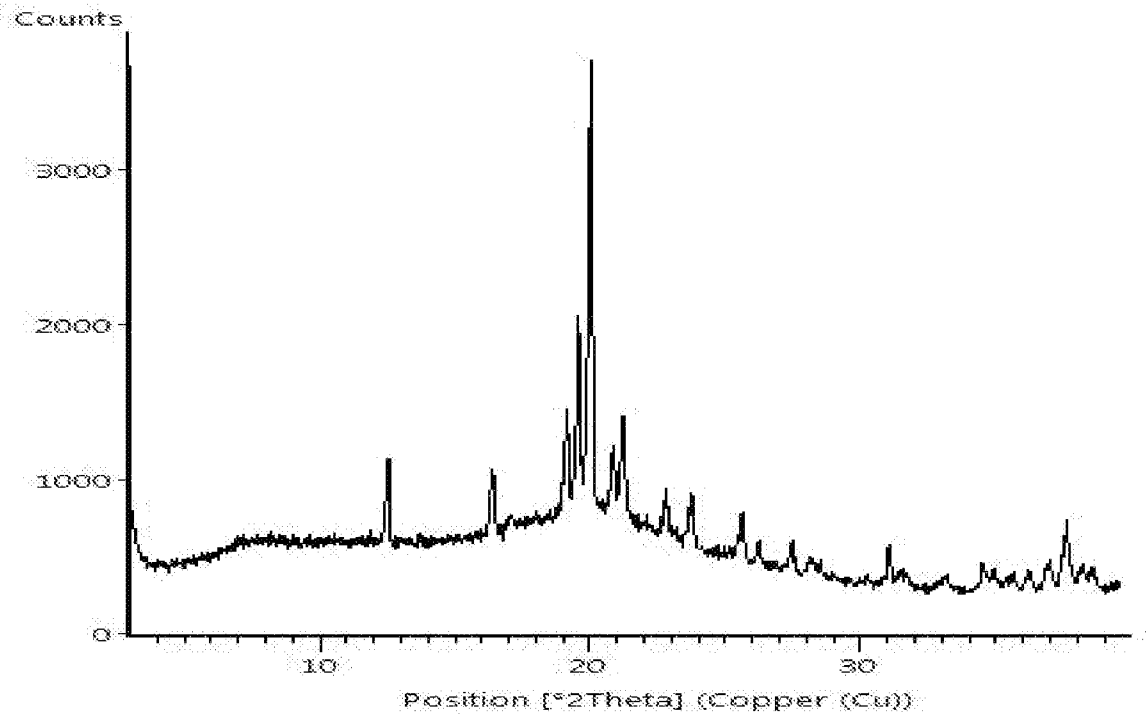


Figure 25

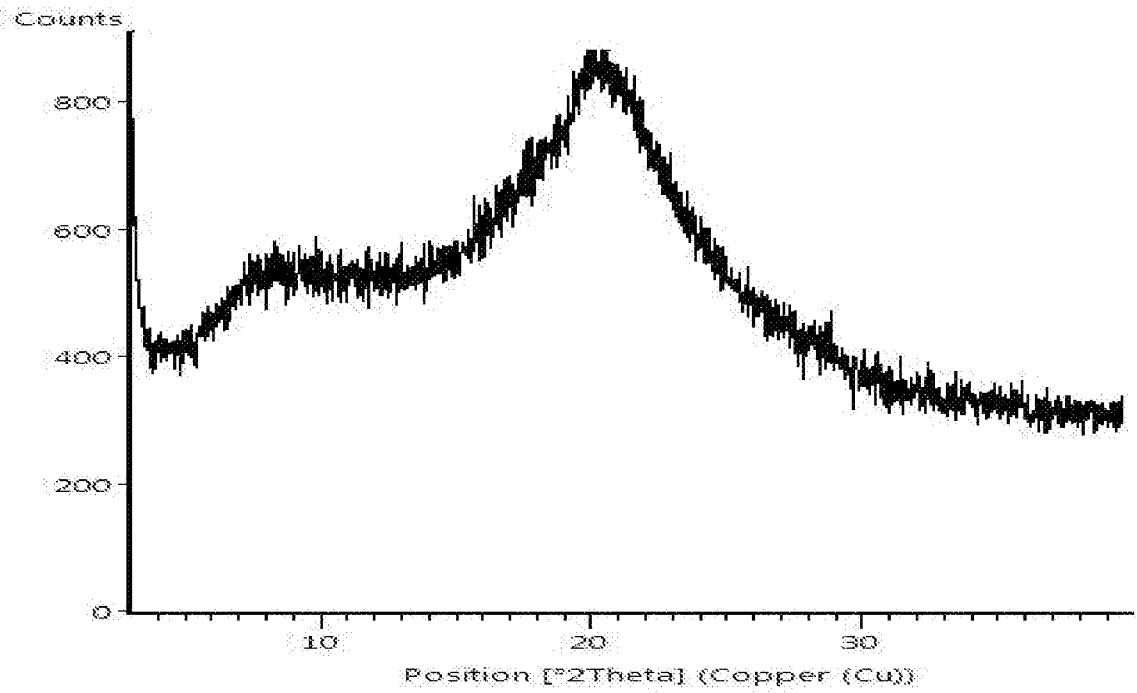


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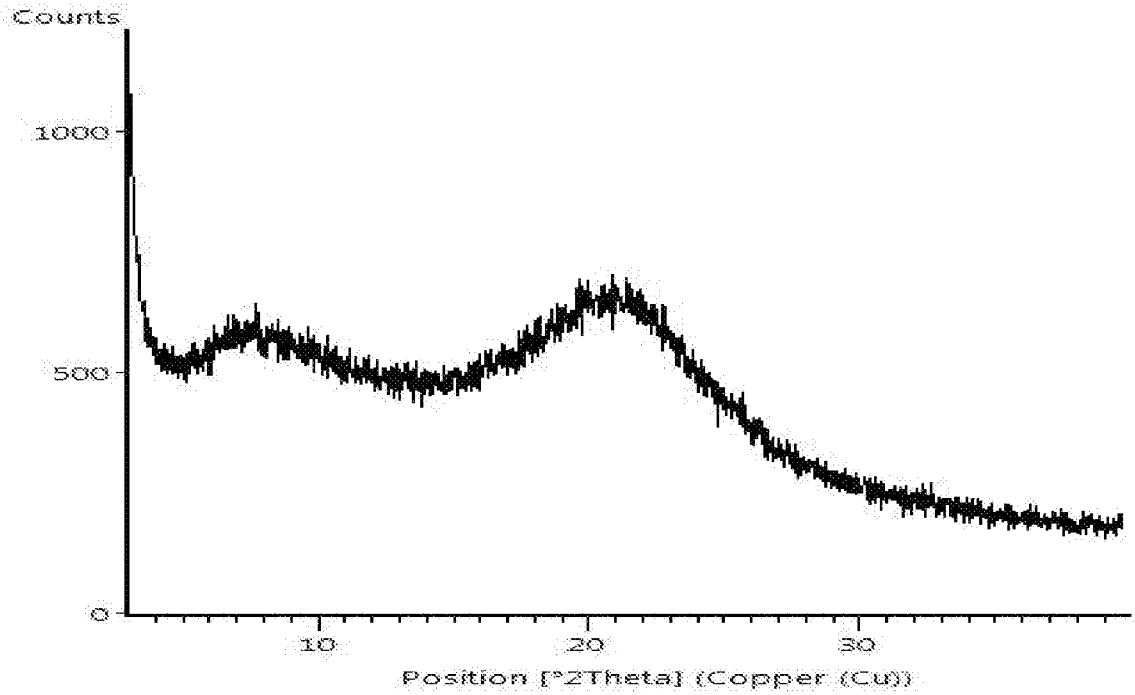


Figure 27

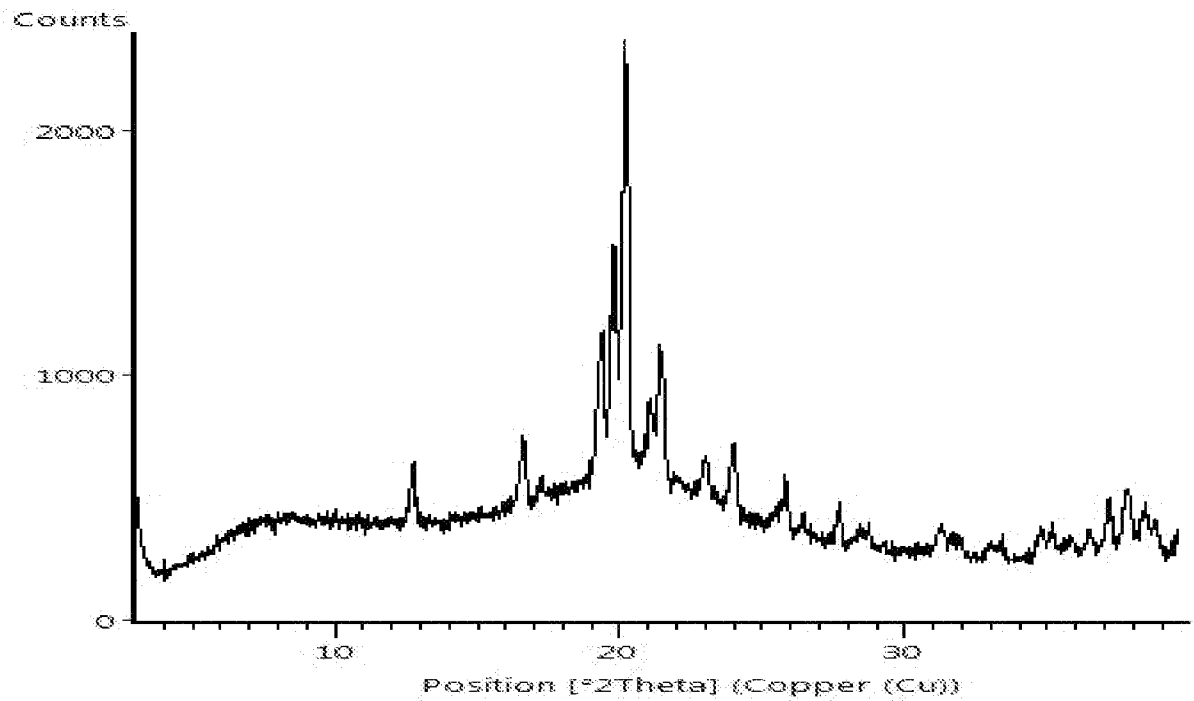


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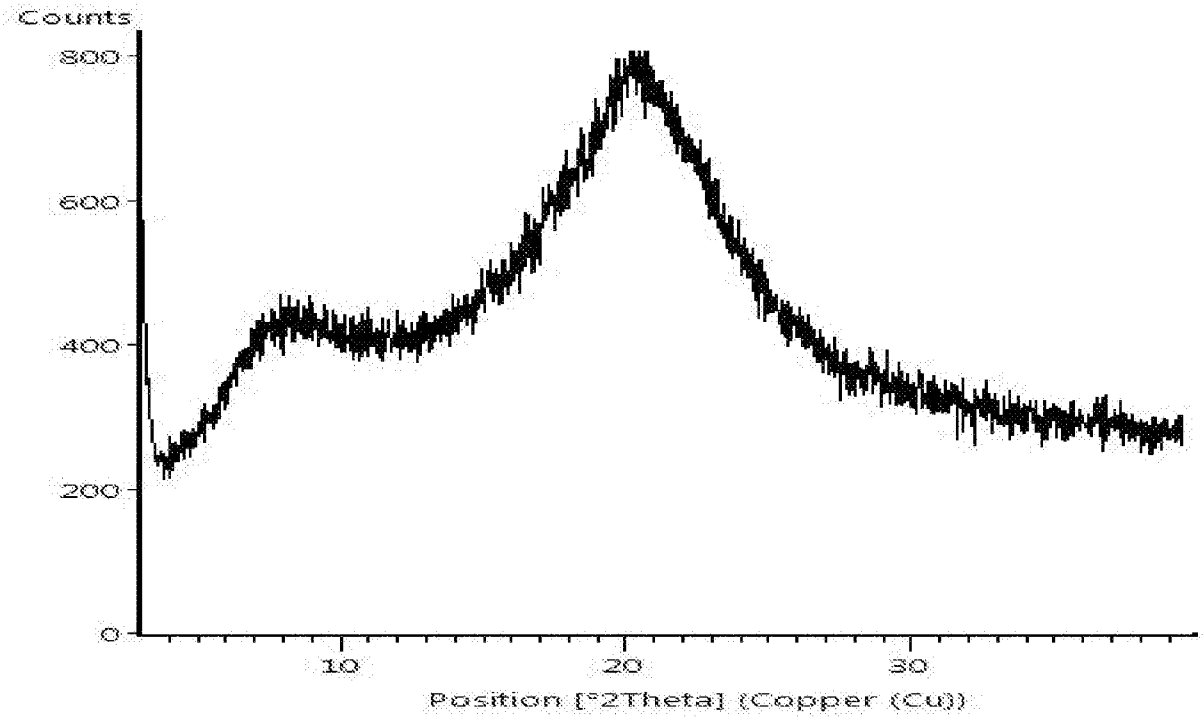


Figure 29

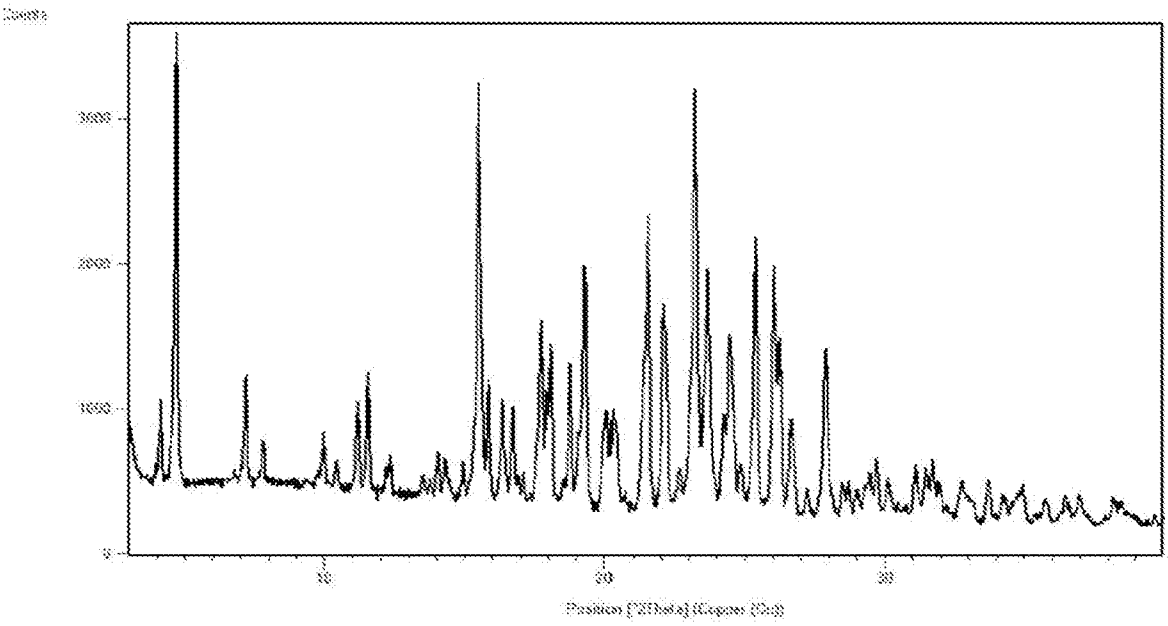


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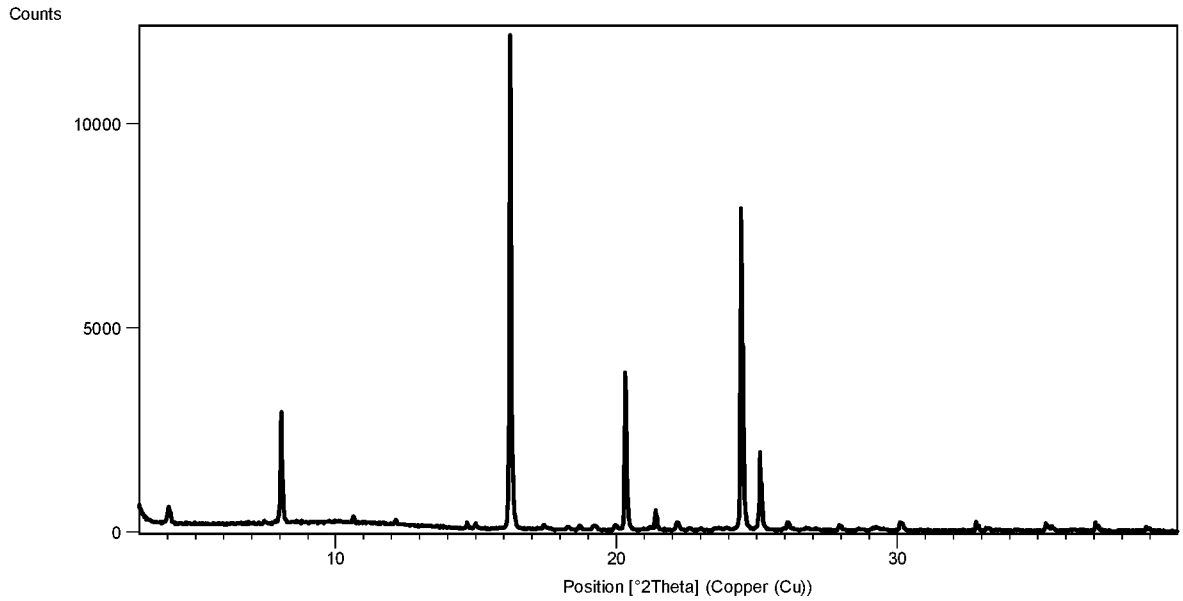


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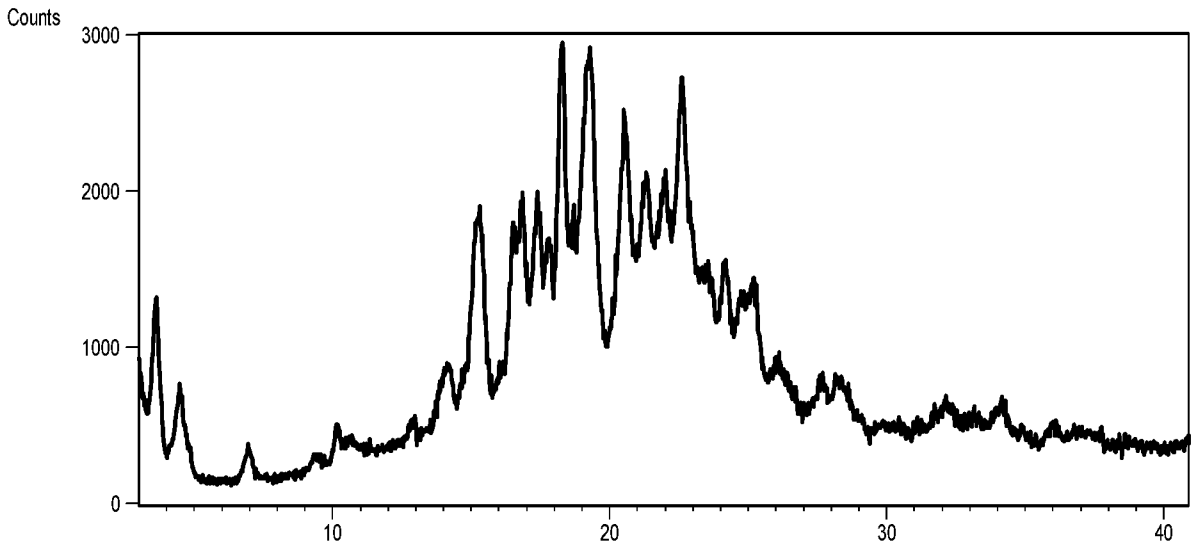


Figure 32

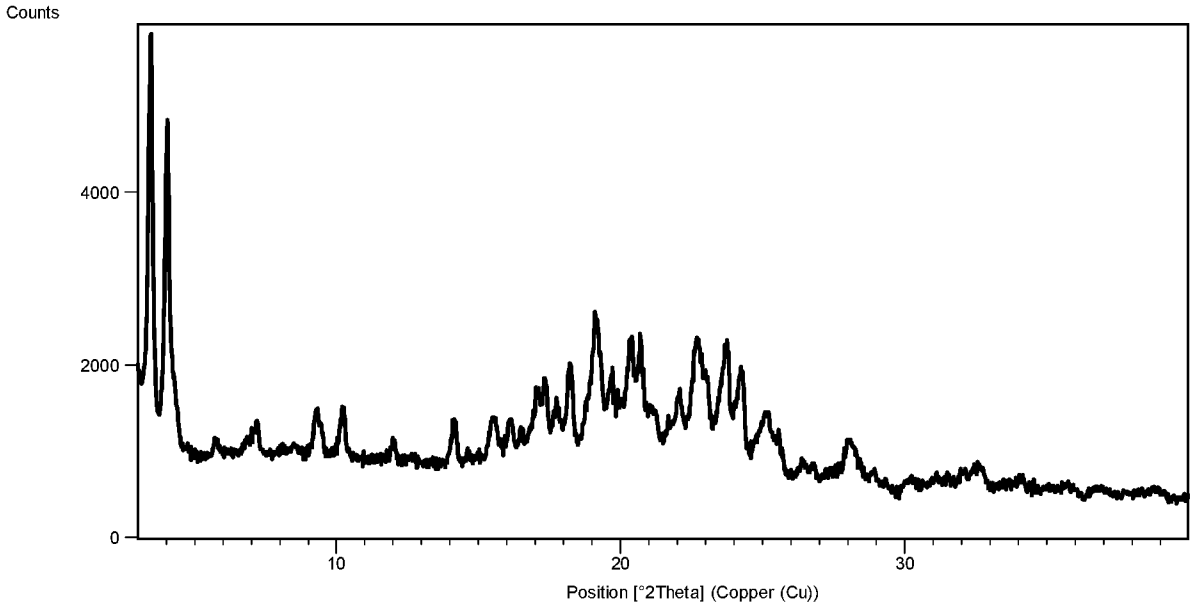


Figure 33

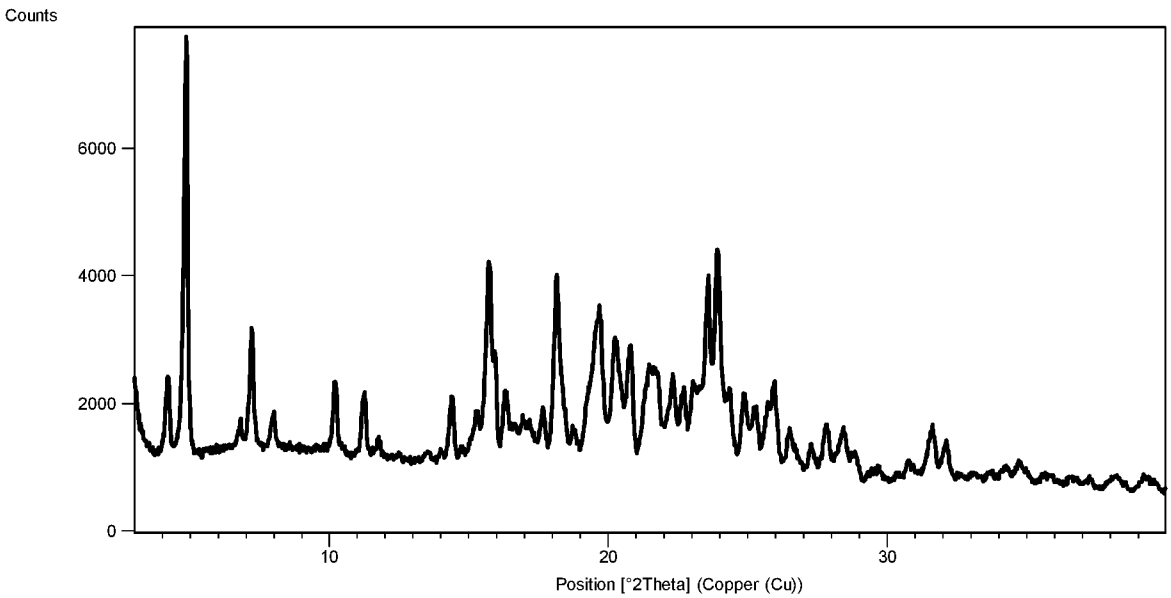


Figure 34

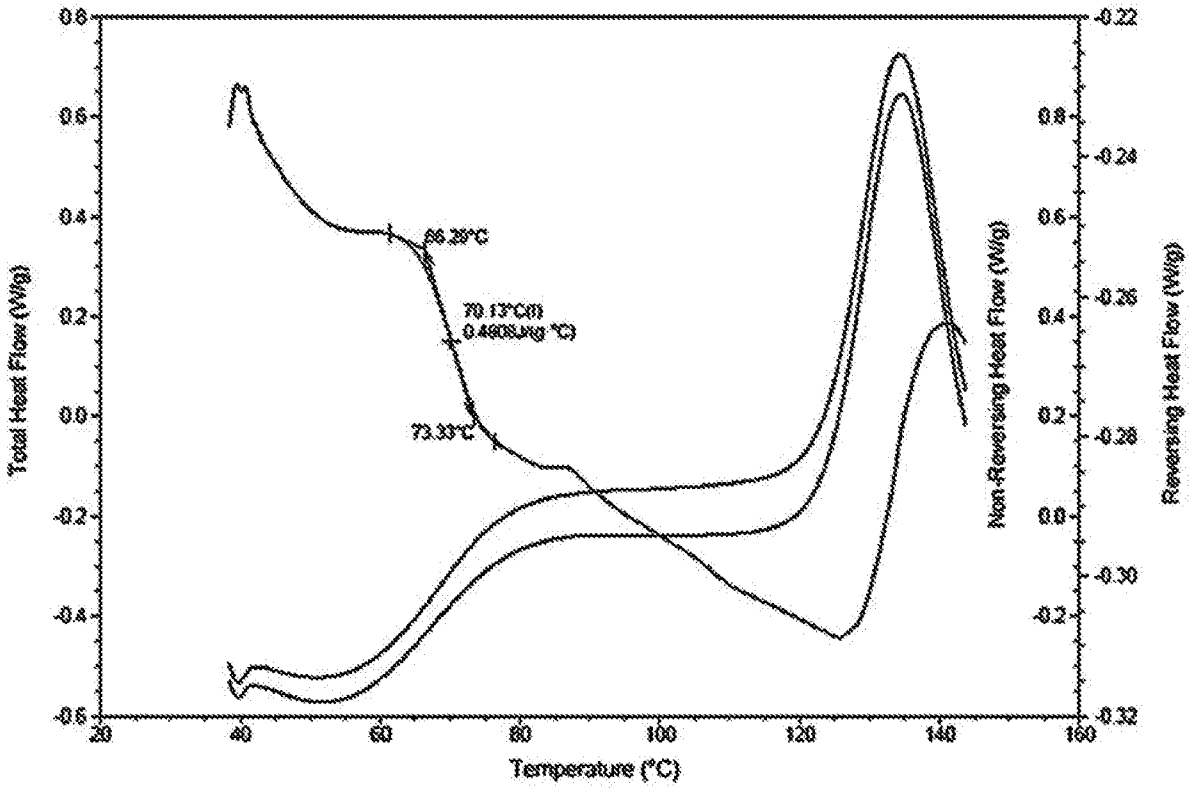

Total Heat Flow (W/g)
Non-Reversing Heat Flow (W/g)
Reversing Heat Flow (W/g)
Temperature (°C)
66.28°C
73.33°C

Figure 35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2017/053079

A. CLASSIFICATION OF SUBJECT MATTER
C07D407/12 Version=2017.01

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)

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)

Patseer, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US7713938 B2; Frank ET AL; 11-05-2010 (11 May 2010). Claim 7	1-4
Y	WO2014101865 A1; Zusheng ET AL; 03-07-2014 (03 July 2014). The whole document	5-7
Y	WO2008002824 A1; Gougoutas ET AL; 03-01-2008 (03 January 2008). The whole document	5-7
Y	US2014031540 A1; Eckhardt ET AL; 30-01-2014 (30 January 2014). The whole document	5-7
X,Y	IN1985MUM2013 A; CADILA HEALTHCARE LTD; 29-05-2015 (29 May 2015). Claims 1-17	8-10, 11-15
Y	Vasconcelos ET AL, "Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs", DRUG DISCOVERY TODAY, 31-12-2007 (30 December 2007), Volume 12, Issue 23-24, Pages 1068-1075. The whole document	11-15
Y	Leuner ET AL, "Improving drug solubility for oral	

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"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)
"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
20-09-2017	20-09-2017
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer A. Reddy Telephone No. +91-1125300200

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	delivery using solid dispersions", European Journal of Pharmaceutics and Biopharmaceutics, 03-07-2000 (03 July 2000), Volume 50, Issue 1, Pages 47-60. The whole document	11-15
X	WO 2015101916 A1; Kaushik ET AL; 09-07-2015 (09 Jul 2015). Scheme B	16-17

International application No.
PCT/IB2017/053079

Citation	Pub.Date	Family	Pub.Date
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		DE 602006011310 D1	04-02-2010
		EP 2166007 A1	24-03-2010
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		EP 2940026 A1	04-11-2015
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		CN 101479287 A	08-07-2009
		EP 2069374 A1	17-06-2009
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		CN 104470908 A	25-03-2015
		EP 2877460 A1	03-01-2015
		US 9145434 B2	29-09-2015
WO 2015101916 A1	09-07-2015	US 20160318965 A1	03-11-2016