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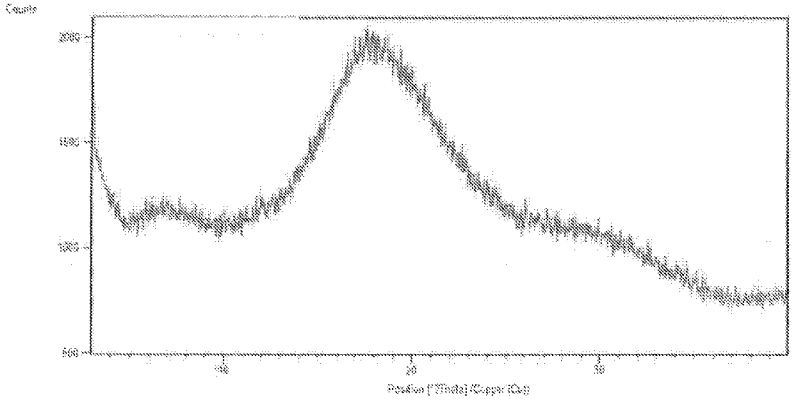

Figure 1

(57) Abstract: Aspects of the present invention relates to an isolated intermediate of Dapagliflozin (Formula III) and its preparation, process for the preparation of Dapagliflozin, process for the preparation of crystalline propane-1,2,3-triol solvate of dapagliflozin, process for the preparation of L-proline complex of Dapagliflozin, solid premix of dapagliflozin with the polymer selected from the group consisting of eudragit, syloid, MCC Avicel PH 102 (1:1) and MCC Avicel PH 102 (1:2).

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ISOLATED INTERMEDIATE OF DAPAGLIFLOZIN, PROCESS FOR THE PREPARATION OF ISOLATED INTERMEDIATE OF DAPAGLIFLOZIN, PROCESS FOR THE PREPARATION OF DAPAGLIFLOZIN

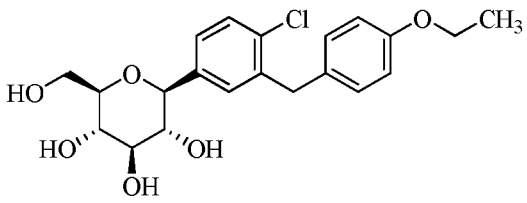
INTRODUCTION

Aspects of the present invention relates to an isolated intermediate of Dapagliflozin (Formula III) and its preparation, process for the preparation of Dapagliflozin, process for the preparation of crystalline propane-1,2,3-triol solvate of dapagliflozin, process for the preparation of L-proline complex of Dapagliflozin, solid premix of dapagliflozin with the polymer selected from the group consisting of eudragit, syloid, MCC Avicel PH 102 (1:1) and MCC Avicel PH 102 (1:2).

Diabetes mellitus is a serious and chronic metabolic disease that is characterized by high blood glucose (hyperglycemia) and affects millions of people world-wide. SGLT2 is a Sodium-dependent GLucose co-Transporter protein which affects the reabsorption of glucose in the kidney. It is estimated that 90% of renal glucose reabsorption is facilitated by SGLT2. Since glucose reabsorption is mediated predominantly by SGLT2 and because high glucose levels have been identified as a cause of disease in diabetes, SGLT2 has become a drug target for type 2 diabetes therapy. Selective inhibition of SGLT2 has the potential to reduce hyperglycemia by inhibiting glucose reabsorption in the kidney with elimination of glucose by excretion in the urine (glucosuria).

Dapagliflozin (trade name: Forxiga) is an active pharmaceutical ingredient (API) and a selective inhibitor of SGLT2 that is being developed for the treatment of type 2 diabetes mellitus.

Dapagliflozin is chemically described as (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol, and is also known as (1S)-1,5-anhydro-1-C-{4-chloro-3-[(4-ethoxyphenyl)methyl] phenyl}-D-glucitol. The structure of dapagliflozin is shown as formula A.



A

U.S. Patent No. 6,515,117 specifically discloses dapagliflozin and its pharmaceutically acceptable salts, a method for treating diabetes and related diseases employing dapagliflozin alone or in combination with another antidiabetic agent or other therapeutic agent.

U.S. Patent No. 6,515,117 discloses process for the preparation of dapagliflozin. As stated at column 5, lines 1-2 of U.S. Patent No. 7,919,598 "The compound of formula A (dapagliflozin) in the form of non-crystalline solid is disclosed in U.S. Patent No. 6,515,117".

Journal of Medicinal Chemistry, 2008, Vol. 51, No. 5 discloses process for the preparation of amorphous dapagliflozin.U.S. Patent No.7,919,598 describes crystalline (S)-propylene glycol solvate hydrate of dapagliflozin and its process.

U.S. Patent application No.2013/0303467A1 describes different crystalline forms of dapagliflozin. International Publication No. WO2013/079501A1 describes crystalline dapagliflozin hydrate and its process. International Publication No. WO2013/064909A2 describes amorphous form of dapagliflozin. International Publication No. WO2015/011113A1 describes Solid premix of Dapagliflozin with polymer is selected from polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), polyacrylic acid (PAA), poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), copovidone, hypromellose acetate succinate (AQOAT), polyacrylates, and mixtures thereof. International Publication No. WO2015/132803A2 describes glycerol solvate of Dapagliflozin.

The occurrences of different solid forms are possible for some compounds. A single compound may exist in different solid forms. Various solid forms of a drug substance can have different chemical and physical properties, including melting point, chemical reactivity, apparent solubility, dissolution rate, optical and mechanical properties, vapor pressure, and density. These properties can have a direct effect on the ability to process and/or manufacture the drug substance and the drug product, as well as on drug product stability, dissolution, and bioavailability. Thus, solid forms can affect the quality, safety, and efficacy of the drug product, regulatory authorities require that efforts shall be made to identify all solid forms, *e.g.*, crystalline, amorphous, solvated, *etc.*, of drug substances.

There still remains an unmet need for solid state forms of dapagliflozin having good physicochemical properties, desirable bioavailability and advantageous pharmaceutical parameters.

Though, there are processes for the preparation of Dapagliflozin available in the literature still there remains a need of process which is environmentally-friendly, cost effective and industrially applicable.

SUMMARY OF THE INVENTION

A first aspect of the present application provides solid premix of dapagliflozin with the polymer selected from the group consisting of eudragit, syloid, MCC Avicel PH 102 (1:1) and MCC Avicel PH 102 (1:2).

A second aspect of the present application provides solid premix of dapagliflozin with eudragit and is characterized by its full X-ray powder diffractogram as substantially shown in FIG. 1

A third aspect of the present application provides a process for the preparation of solid premix of dapagliflozin with eudragit comprising the steps of;

a) providing a solution of dapagliflozin in a solvent;

b) adding eudragit to the solution obtained in step a);

c) optionally filter the reaction mass obtained in step b);

d) isolating the solid premix of dapagliflozin with eudragit.

A fourth aspect of the present application provides solid premix of dapagliflozin with syloid and is characterized by its full X-ray powder diffractogram as substantially shown in FIG. 2

A fifth aspect of the present application provides a process for the preparation of solid premix of dapagliflozin with syloid comprising:

a) mixing the amorphous dapagliflozin with syloid;

b) optionally milling the compound obtained in step a);

c) obtaining solid premix of dapagliflozin with syloid.

A sixth aspect of the present application provides solid premix of dapagliflozin with MCC Avicel PH 102 (1:1) is characterized by its full X-ray powder diffractogram as substantially shown in FIG. 3

A seventh aspect of the present application provides a process for the preparation of solid premix of dapagliflozin with MCC Avicel PH 102 (1:1) comprising:

a) mixing the amorphous dapagliflozin with MCC Avicel PH 102 (1:1);

b) optionally milling the compound obtained in step a);

c) obtaining solid premix of dapagliflozin with MCC Avicel PH 102 (1:1).

An eighth aspect of the present application provides solid premix of dapagliflozin with MCC Avicel PH 102 (1:2) is characterized by its full X-ray powder diffractogram as substantially shown in FIG. 4

A ninth aspect of the present application provides a process for the preparation of solid premix of dapagliflozin with MCC Avicel PH 102 (1:2) comprising:

a) mixing the amorphous dapagliflozin with MCC Avicel PH 102 (1:2);

b) optionally milling the compound obtained in step a);

c) obtaining solid premix of dapagliflozin with MCC Avicel PH 102 (1:1).

A tenth aspect of the present invention also provides pharmaceutical formulations comprising solid premix of dapagliflozin with the polymer selected from the group consisting of eudragit, syloid and MCC Avicel PH 102 together with one or more pharmaceutically acceptable excipients.

A eleventh aspect of the present invention provides a process for the preparation of isolated (2R,3S,4R,5R)-1-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4,5,6-pentahydroxy hexan-1-one (Compound III) comprising condensation of 4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene (Compound I) with (3R,4S,5R,6R)-3,4,5-tris((trimethylsilyl)oxy)-6-(((trimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-one (Compound II).

A twelfth aspect of the present invention provides a process for the preparation of dapagliflozin comprising the use of (2R,3S,4R,5R)-1-(4-chloro-3-(4-ethoxybenzyl) phenyl)-2,3,4,5,6-pentahydroxy hexan-1-one (Compound III), which is produced according to the methods described herein.

A thirteenth aspect of the present application provides a crystalline propane-1,2,3-triol solvate of dapagliflozin.

A fourteenth aspect of the present application provides a process for the preparation of crystalline propane-1,2,3-triol solvate of dapagliflozin, comprising the steps of;

a) providing a solution of dapagliflozin in a solvent;

b) adding propane-1,2,3-triol to the solution obtained in step a);

c) optionally seeding with crystalline propane-1,2,3-triol solvate of dapagliflozin;

d) optionally combining the solution of step b) or c) with suitable anti solvent;

e) optionally adding water to the solution obtained in step b) or c) or d);

f) isolating the crystalline propane-1,2,3-triol solvate of dapagliflozin.

A fifteenth aspect of the present application provides a process for the preparation of crystalline propane-1,2,3-triol solvate of dapagliflozin comprising:

a) mixing the dapagliflozin with Propane-1,2,3-triol;

b) optionally milling the compound obtained in step a);

c) obtaining crystalline propane-1,2,3-triol solvate of dapagliflozin.

A sixteenth aspect of the present application provides a process for the preparation of L-proline complex of dapagliflozin comprising:

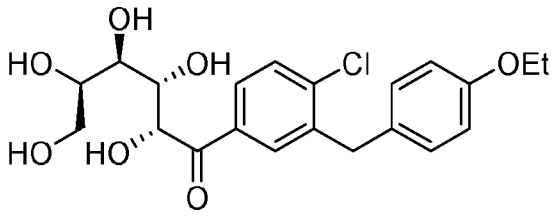
d) preparing a solution of dapagliflozin in a solvent;

e) adding L-proline;

f) isolating the L-proline complex of dapagliflozin.

A seventeenth aspect of the present invention also provides pharmaceutical formulations comprising crystalline propane-1,2,3-triol solvate of dapagliflozin together with one or more pharmaceutically acceptable excipients.

An eighteenth aspect of the present invention provides an isolated compound of formula III



Formula III

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates an X-ray powder diffraction pattern of solid premix of dapagliflozin with eudragit.

Figure 2 illustrates an X-ray powder diffraction pattern of solid premix of dapagliflozin with syloid.

Figure 3 illustrates an X-ray powder diffraction pattern of solid premix of dapagliflozin with MCC Avicel PH 102 (1:1).

Figure 4 illustrates an X-ray powder diffraction pattern of solid premix of dapagliflozin with MCC Avicel PH 102 (1:2).

Figure 5 illustrates an X-ray powder diffraction pattern of crystalline propane-1,2,3-triol solvate of dapagliflozin, obtained according to the procedure of example 6.

Figure 6 illustrates an X-ray powder diffraction pattern of crystalline propane-1,2,3-triol solvate of dapagliflozin, obtained according to the procedure of example 7.

Figure 7 illustrates an X-ray powder diffraction pattern of amorphous dapagliflozin, obtained according to the procedure of example 16.

Figure 8 illustrates an X-ray powder diffraction pattern of crystalline propane-1,2,3-triol solvate of dapagliflozin, obtained according to the procedure of example 18.

DETAILED DESCRIPTION

A first aspect of the present application provides solid premix of dapagliflozin with the polymer selected from the group consisting of eudragit, syloid, MCC Avicel PH 102 (1:1) and MCC Avicel PH 102 (1:2) and process for the preparation thereof.

A second aspect of the present application provides solid premix of dapagliflozin with eudragit is characterized by its full X-ray powder diffractogram as substantially shown in FIG. 1

A third aspect of the present application provides a process for the preparation of solid premix of dapagliflozin with eudragit comprising the steps of;

a) providing a solution of dapagliflozin in a solvent;

b) adding eudragit to the solution obtained in step a);

c) optionally filter the reaction mass obtained in step b);

d) isolating the solid premix of dapagliflozin with eudragit.

Providing a solution of dapagliflozin in step a) includes:

i) direct use of a reaction mixture containing dapagliflozin that is obtained in the course of its synthesis; or

ii) dissolving dapagliflozin in a solvent.

Any physical form of dapagliflozin may be utilized for providing the solution of dapagliflozin in step a). Dapagliflozin that may be used as the input for the process of the present invention may be obtained by the process described in the present application (or) any process including the processes described in the art. For example dapagliflozin may be prepared by the processes described in IN3942/CHE/2010, US6515117B2 or US7375213B2. Suitable solvents that may be used in step a) include, but are not limited to, alcohol solvents, ester solvents;

halogenated hydrocarbon solvents; nitrile solvents; polar aprotic solvents; ketone solvents; ether or mixtures thereof.

In an embodiments of step b) involves adding eudragit to the solution obtained in step a);

The dissolution temperatures may range from about 10°C to about the reflux temperature of the solvent, depending on the solvent used for dissolution, as long as a clear solution of Dapagliflozin with eudragit is obtained without affecting its quality. The solution may optionally be treated with carbon, flux-calcined diatomaceous earth (Hyflow), or any other suitable material to remove color and/or to clarify the solution.

In an embodiments of step c), optionally involves the solution obtained above may be filtered to remove any insoluble particles. The insoluble particles may be removed suitably by filtration, centrifugation, decantation, or any other suitable techniques. The solution may be filtered by passing through paper, glass fiber, or other membrane material, or a bed of a clarifying agent such as celite or hyflow. 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.

In an embodiments of step d), the isolation of solid premix of dapagliflozin with eudragit may be done using techniques such as removal of the solvent using a rotational distillation device such as a buchi rotavapor, spray drying, thin film drying, freeze drying (lyophilization), Hot-Melt Extrusion (HME) and the like, or any other suitable technique.

The product thus isolated may be optionally further dried to afford solid premix of dapagliflozin with eudragit.

Drying may be suitably 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 50°C, less than about 30°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.

A fourth aspect of the present application provides solid premix of dapagliflozin with syloid is characterized by its full X-ray powder diffractogram as substantially shown in FIG. 2

A fifth aspect of the present application provides a process for the preparation of solid premix of dapagliflozin with syloid comprising:

a) mixing the amorphous dapagliflozin with syloid;

b) optionally milling the compound obtained in step a);

c) obtaining solid premix of dapagliflozin with syloid.

In an embodiment of step a), mixing the amorphous dapagliflozin with syloid using the general procedures known in the art or as the procedure described in this application.

In an embodiment of step b), optionally milling the compound obtained in step a);

Milling methods are well known to a person skilled in the art. Any suitable milling method can be used. Any suitable miller can be used for milling including but not limited to quadro comill, multimill, ball mill, roller mill, hammer mill and jet mill, etc.

In an embodiment of step c), obtained product may be dried to afford solid premix of dapagliflozin with syloid.

A sixth aspect of the present application provides solid premix of dapagliflozin with MCC Avicel PH 102 (1:1) is characterized by its full X-ray powder diffractogram as substantially shown in FIG. 3

A seventh aspect of the present application provides a process for the preparation of solid premix of dapagliflozin with MCC Avicel PH 102 (1:1) comprising:

a) mixing the amorphous dapagliflozin with MCC Avicel PH 102 (1:1);

b) optionally milling the compound obtained in step a);

c) obtaining solid premix of dapagliflozin with MCC Avicel PH 102 (1:1).

In an embodiments of step a), mixing the amorphous dapagliflozin with MCC Avicel PH 102 (1:1) using the general procedures known in the art or as the procedure described in this application.

In an embodiment of step b), optionally milling the compound obtained in step a);

Milling methods are well known to a person skilled in the art. Any suitable milling method can be used. Any suitable miller can be used for milling including but not limited to quadro comill, multimill, ball mills, roller mills hammer mills and jet mills. etc.

In an embodiment of step c), obtained product may be dried to afford solid premix of dapagliflozin with MCC Avicel PH 102 (1:1).

An eighth aspect of the present application provides solid premix of dapagliflozin with MCC Avicel PH 102 (1:2) is characterized by its full X-ray powder diffractogram as substantially shown in FIG. 4

A ninth aspect of the present application provides a process for the preparation of solid premix of dapagliflozin with MCC Avicel PH 102 (1:2) comprising:

a) mixing the amorphous dapagliflozin with MCC Avicel PH 102 (1:2);

b) optionally milling the compound obtained in step a);

c) obtaining solid premix of dapagliflozin with MCC Avicel PH 102 (1:2).

In an embodiment of step a), mixing the amorphous dapagliflozin with MCC Avicel PH 102 (1:2) using the general procedures known in the art or as the procedure described in this application.

In an embodiment of step b), optionally milling the compound obtained in step a);

Milling methods are well known to a person skilled in the art. Any suitable milling method can be used. Any suitable miller can be used for milling including but not limited to quadro comill, multimill, ball mills, roller mills hammer mills and jet mills. etc.

In an embodiment of step c), obtained product may be dried to afford solid premix of dapagliflozin with MCC Avicel PH 102 (1:2).

Solid premix of dapagliflozin with polymer obtained according to certain processes of the present application has a particle size distribution wherein: d(0.5) is less than about 100 μm, or less than about 25 μm, or less than about 10 μm; and d(0.9) is less than about 200 μm, or less than about 50 μm, or less than about 30 μm. Particle size distributions can be determined using any means, including laser light diffraction equipment sold by Malvern Instruments limited, Malvern, Worcestershire, United Kingdom, Coulter counters, microscopic procedures, etc. The term d(x) means that a particular fraction has particles with a maximum size being the value given; 0.5 represents 50% of the particles and 0.9 represents 90% of the particles.

In an aspect, the present application provides the weight ratio of amorphous dapagliflozin and polymer is selected from the group consisting of eudragit, syloid, MCC Avicel PH 102 is in the range of 1:0.1 to 1:10. In an even more preferred embodiment the weight ratio of dapagliflozin and polymer is selected from the group consisting of eudragit, syloid, MCC Avicel PH 102 in the range of 1:0.1 to 1:3.

A tenth aspect of the present application provides pharmaceutical formulations comprising solid premix of dapagliflozin with polymer is selected from the group consisting of eudragit, syloid, MCC Avicel PH 102, together with one or more pharmaceutically acceptable excipients. Solid premix of dapagliflozin with polymer is selected from the group consisting of eudragit, syloid, MCC Avicel PH 102 together with one or more pharmaceutically acceptable excipients of the present application may be formulated as: solid oral dosage forms such as, but not limited to, powders, granules, pellets, tablets, or capsules; liquid oral dosage forms such as, but not limited to, syrups, suspensions, dispersions, or emulsions; or injectable preparations such as, but not limited to, solutions, dispersions, or freeze dried compositions. Formulations may be in the forms of immediate release, delayed release, or modified release. Further, immediate release compositions may be conventional, dispersible, chewable, mouth dissolving, or flash melt preparations, or modified release compositions that may comprise hydrophilic or hydrophobic, or combinations of hydrophilic and hydrophobic, release rate controlling substances to form matrix or reservoir or combination of matrix and reservoir systems. The compositions may be prepared using techniques such as direct mixing, dry granulation, wet granulation, or extrusion and spheronization. Compositions may be presented as uncoated, film coated, sugar coated, powder coated, enteric coated, or modified release coated. Compositions of the present application may further comprise one or more pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients that are useful in the present application include, but are not limited to: diluents such as starches, pregelatinized starches, lactose, powdered celluloses, microcrystalline celluloses, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar, or the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinylpyrrolidones, hydroxypropyl celluloses, hydroxypropyl methyl celluloses, pregelatinized starches, or the like; disintegrants such as starches, sodium starch glycolate, pregelatinized starches, crospovidones, croscarmellose sodium, colloidal silicon dioxide, or the like; lubricants such as stearic acid, magnesium stearate, zinc stearate, or the like; glidants such as colloidal silicon dioxide or the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants; complex forming agents such as various grades of cyclodextrins or resins; release rate controlling agents such as hydroxypropyl celluloses, hydroxymethyl celluloses, hydroxypropyl methylcelluloses, ethylcelluloses, methylcelluloses, various grades of methyl

methacrylates, waxes, or 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, or the like.

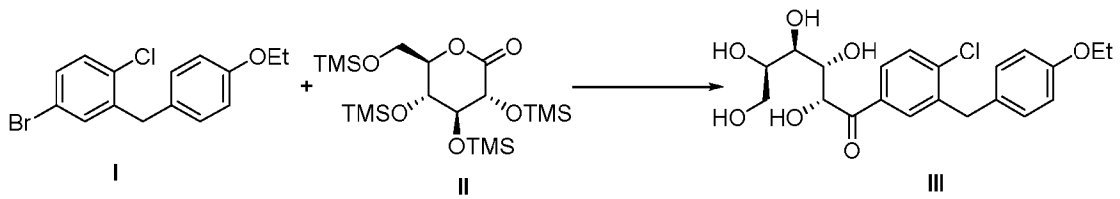
In an aspect of the application, solid premix of dapagliflozin with polymer is selected from the group consisting of eudragit, syloid, MCC Avicel PH 102 prepared according to the processes of the present application can be substantially pure having a chemical purity greater than about 99%, or greater than about 99.5%, or greater than about 99.9%, by weight, as determined using high performance liquid chromatography (HPLC).

Solid premix of dapagliflozin with polymer is selected from the group consisting of eudragit, syloid, MCC Avicel PH 102 produced by the method of present invention can be chemically pure having purity greater than about 99.5% and containing no single impurity in amounts greater than about 0.15%, by HPLC.

Solid premix of dapagliflozin with polymer is selected from the group consisting of eudragit, syloid, MCC Avicel PH 102 can be stable at USP conditions (accelerated, ambient and cooling).

A eleventh aspect of the present invention provides a process for the preparation of isolated (2R,3S,4R,5R)-1-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4,5,6-pentahydroxy hexan-1-one (Compound III) comprising condensation of 4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene (Compound I) with (3R,4S,5R,6R)-3,4,5-tris((trimethylsilyl)oxy)-6-(((trimethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-one (Compound II)

It can be illustrated as given below in Scheme 1.



Scheme 1

In an embodiment, the condensation process can be carried out in a suitable solvent that is not limited to ether solvent; hydrocarbon solvents; alcohol solvents; ester solvents; halogenated hydrocarbon solvents; nitrile solvents; polar aprotic solvents; ketone solvents or mixtures thereof.

In a specific embodiment, the condensation process can be carried out in tetrahydrofuran (THF).

In an embodiment, the condensation process can be carried out in presence of a suitable base. The base can be any organolithium reagent or organic or inorganic base. Bases that are useful in the reaction include, but are not limited to; organolithium reagents such as n-butyllithium, lithium diisopropylamide; inorganic bases such as alkali metal or alkaline earth metal carbonates, hydrogen carbonates, hydroxides, oxides, carboxylates, alkoxides, e.g., potassium carbonate, potassium hydrogen carbonate, potassium hydroxide, potassium acetate, potassium methoxide, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, sodium acetate, sodium methoxide, lithium carbonate, lithium hydrogen carbonate, lithium hydroxide, lithium acetate, lithium methoxide, barium hydroxide, calcium oxide, or the like; organic bases such as, primary, secondary, or tertiary amines, such as ammonia, aqueous ammonia, triethylamine, diisopropylamine, N-methylmorpholine.

In a specific embodiment, the condensation process can be carried out in presence of n-butyllithium.

In specific embodiment, the condensation process can be carried out in presence of trifluoroacetic acid (TFA) and water.

In specific embodiment, the condensation process can be carried out optionally by seeding with (2R,3S,4R,5R)-1-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4,5,6-pentahydroxyhexan-1-one.

In an embodiment, the condensation process can be carried out at a temperature ranging from about -80°C to about 60°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the conditions out lined above, a period of from about 1 hour to about 24 hours or longer.

In an embodiment, after the completion of the condensation reaction optionally water can be added to the reaction mass followed by adjustment of pH to a value from about 7.5 to about 14, by adding a suitable base such as. The bases that are described can be used for this step. The product can be extracted into water immiscible solvents such as ethyl acetate, isopropyl acetate, n-propyl acetate, isobutyl acetate, n-butyl acetate, isobutyl isobutyrate, 2-ethylhexyl acetate, ethylene glycol diacetate, C9 acetate, C10 acetate, methyl ethyl ketone, methyl isobutyl ketone,

methyl isoamyl ketone, methyl n-amyl ketone, diisobutyl ketone, cyclohexanone, isophorone, acetaldehyde, n-butyraldehyde, crotonaldehyde, 2-ethylhexaldehyde, isobutyraldehyde, propionaldehyde, ethyl 3-ethoxypropionate, toluene, xylene, dichloromethane, 1,1,1 trichloroethane, propylene glycol monomethyl ether acetate, ethylene glycol monoethyl ether acetate, ethylene glycol monobutyl ether acetate, diethylene glycol monobutyl ether acetate, dibutyl phthalate, diethyl phthalate, dimethyl phthalate, dioctyl phthalate, dioctyl terephthalate, butyl octyl phthalate, butyl benzyl phthalate, dioctyl adipate, triethylene glycol di-2-ethylhexanoate, trioctyl trimellitate, glyceryl triacetate, glyceryl/tripropionine, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate, decalin, pentane, hexane, heptane, octane, nonane, cyclopentane, cyclohexane, or 1,4-dioxane etc.

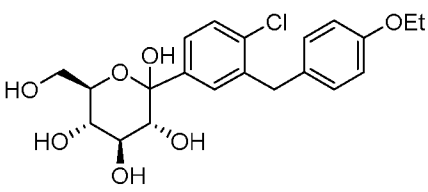
In an embodiment, after the completion of the condensation reaction optionally the reaction mass is purified by washing with sodium chloride solution.

In an embodiment, after the completion of the condensation reaction the product can be optionally isolated from the reaction mass using any suitable techniques known in the art.

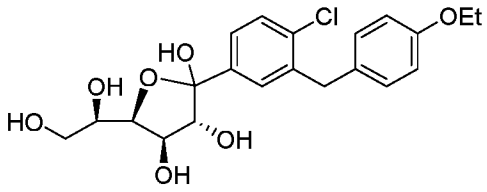
In an embodiment, after the completion of the condensation reaction the organic layer containing Compound III i.e., before or after the purification step as described above can be used in the next stage without isolation i.e. in situ.

The structure of the compound III is confirmed as (2R,3S,4R,5R)-1-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4,5,6-pentahydroxyhexan-1-one based on the solid state 13C NMR and IR, as well as dapagliflozin formation from compound III intermediate. The stereo chemical configurations of compound III is assigned based on the comparison of established stereochemical configuration of dapagliflozin for which compound III is the input starting material. During the conversion of compound III to dapagliflozin, full retention of stereochemical configuration is expected as per the reaction mechanisms as well as the in-situ intermediates formed in the reaction.

The compound III intermediate exists as a mixture of furanose (Compound IIIb), pyranose (Compound IIIa) as well as open structure in the solution state, and slowly will convert to furanose (Compound IIIb) intermediate in DMSO solution on a prolonged maintenance.



IIIa



IIIb

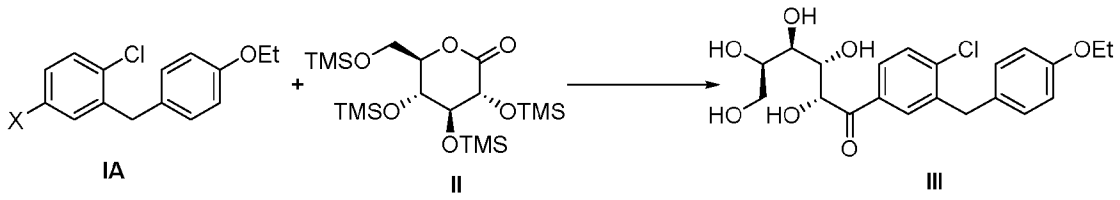
The solution state NMR of compound III clearly confirms the presence of these mixture of compounds in DMSO-D6 when the NMR was recorded in freshly prepared DMSO-D6, however these mixture of compound was then stabilized to furanose (Compound IIIb) structure on prolonged maintenance in NMR solution. When the NMR is recorded in a mixture of DMSO-D6 and D2O only furanose (Compound IIIb) was observed. NMR experiments clearly indicate the existence of dynamic equilibration between the different forms of furanose (Compound IIIb), pyranose (Compound IIIa) as well as open structure of the compound III intermediate in NMR solution. The formation of furanose (Compound IIIb) intermediate in DMSO D6 can be explained by slight acidic nature of DMSO-D6 which favors the 5-exocyclic cyclizations, and further its stabilizations.

Thus our attempts to conclude the structure of compound III intermediate by solution state NMR under any of the plausible NMR experiments were not successful with DMSO-D6. The solubility of compound III in $CDCl_3$ is very minimal. Based on these observations, structural confirmation from solution state NMR is impossible for compound III intermediate.

LCMS analysis compound III is performed then. The LCMS analysis of indicates 449.3 ion peak, which corresponds to M+Na. The LCMS ion peak of 424.3, which corresponds to parent molecular ion peak confirming the molecular weight identical to the structure proposed. IR spectra recorded on KBr pellet indicates the presence of sharp peak at 1682 CM-1 clearly indicates the presence of carbonyl peak in compound III, which proves the presence of open chain structure for compound III. The solid state NMR of compound III is then recorded, and 21 carbon peaks were observed in the 13C, which is in conformity with total number of carbons in compound III. In the solid state 13C NMR of the compound III, a carbon peak was observed at 195.659 δ. This clearly indicates the presence of carbonyl carbon in the compound III, and hence its open chain structure.

Based on the confirmatory observations in the IR as well as 13C NMR in solid state NMR studies, as well as conversion of compound III to Dapagliflozin confirm the open chain structure of compound III.

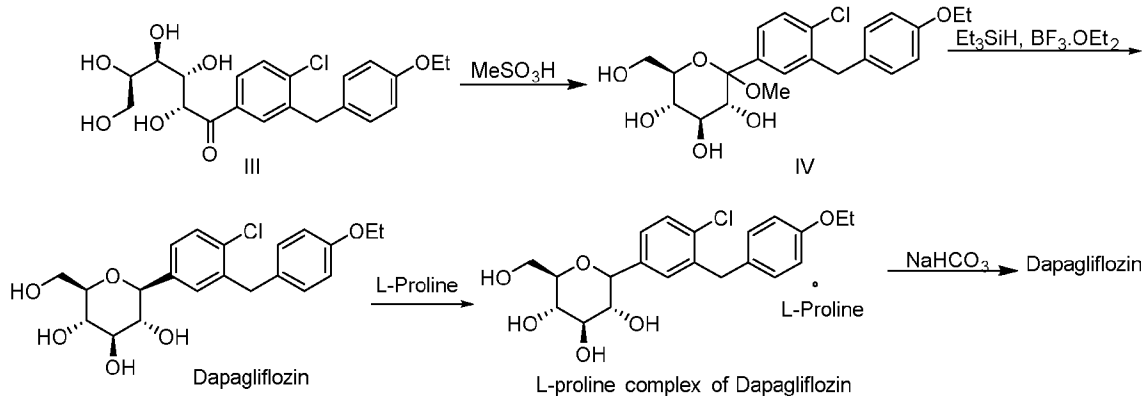
The above conditions may also used to produce the isolated compound of formula III using compound of formula IA and the reaction can be as fallow.



X is Cl or I

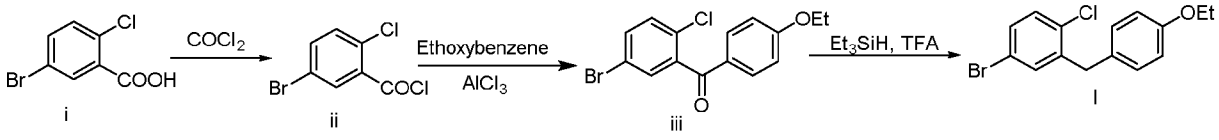
A twelfth aspect of the present invention provides a process for the preparation of dapagliflozin comprising the use of (2R,3S,4R,5R)-1-(4-chloro-3-(4-ethoxybenzyl) phenyl)-2,3,4,5,6-pentahydroxy hexan-1-one, which is produced according to the methods described herein.

A specific process for the preparation of Dapagliflozin by a method of present application can be illustrated as given below in Scheme 2.



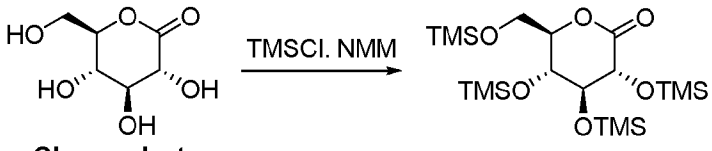
Scheme 2

The starting material (I) of Dapagliflozin can be prepared by any known methods (or) by the process that is illustrated as given below in Scheme 3.



Scheme 3

The starting material (II) of Dapagliflozin can be prepared by any known methods (or) by the process that is illustrated as given below in Scheme 4.



Glucono lactone II

Scheme 4

A thirteenth aspect of the present application provides a crystalline propane-1,2,3-triol solvate of dapagliflozin.

In an aspect, the application provides a crystalline propane-1,2,3-triol solvate of dapagliflozin has an XRPD pattern with characteristic peak at about 21.57, 24.35, 24.69, 25.24, 28.13 and 31.39±0.2°2θ. Crystalline propane-1,2,3-triol solvate of dapagliflozin further characterized by PXRD pattern comprising peaks at about 3.85, 12.35, 15.56, 16.03, 16.60 and 18.60±0.2°2θ.

A fourteenth aspect of the present application provides a process for the preparation of crystalline propane-1,2,3-triol solvate of dapagliflozin, comprising the steps of;

a) providing a solution of dapagliflozin in a solvent;

b) adding propane-1,2,3-triol to the solution obtained in step a);

c) optionally seeding with crystalline propane-1,2,3-triol solvate of dapagliflozin;

d) optionally combining the solution of step b) or c) with suitable anti solvent;

e) optionally adding water to the solution obtained in step b) or c) or d);

f) isolating the crystalline propane-1,2,3-triol solvate of dapagliflozin.

Providing a solution of dapagliflozin in step a) includes:

i) direct use of a reaction mixture containing dapagliflozin that is obtained in the course of its synthesis; or

ii) dissolving dapagliflozin in a solvent.

Any physical form of dapagliflozin may be utilized for providing the solution of dapagliflozin in step a). Dapagliflozin that may be used as the input for the process of the present invention may be obtained by the process described in the present application (or) any process including the processes described in the art. For example dapagliflozin may be prepared by the processes described in IN3942/CHE/2010, US6515117B2 or US7375213B2. Suitable solvents that may be used in step a) include, but are not limited to, ester solvents; alcohol solvents;

halogenated hydrocarbon solvents; nitrile solvents; polar aprotic solvents; ketone solvents; ether or mixtures thereof.

The dissolution temperatures may range from about 10°C to about the reflux temperature of the solvent, depending on the solvent used for dissolution, as long as a clear solution of dapagliflozin is obtained without affecting its quality. The solution may optionally be treated with carbon, flux-calcined diatomaceous earth (Hyflow), or any other suitable material to remove color and/or to clarify the solution.

Optionally, the solution obtained above may be filtered to remove any insoluble particles. The insoluble particles may be removed suitably by filtration, centrifugation, decantation, or any other suitable techniques. The solution may be filtered by passing through paper, glass fiber, or other membrane material, or a bed of a clarifying agent such as celite or hyflow. 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.

In embodiment of step b) involves adding propane-1,2,3-triol to the solution obtained in step a), propane-1,2,3-triol may be added directly to the solution of step a) or it can be combined with any of the solvent described in step a) before the addition.

In embodiment of step b) involves the molar ratio of dapagliflozin and propane-1,2,3-triol is in the range of 1:0.5 to 1:10. In an even more preferred embodiment the molar ratio of dapagliflozin and propane-1,2,3-triol is in the range of 1:1 to 1:3.

In embodiment of step c) involves optionally seeding with crystalline propane-1,2,3-triol solvate of dapagliflozin;

In embodiments of step d), optionally adding suitable anti solvent to the reaction mass of step b) or c), wherein the anti-solvent include, but are not limited to hydrocarbon solvents.

In specific embodiment of step d), suitable antisolvents that may be used include, but are not limited to cyclohexane.

In embodiment of step d), the isolation may be effected by combining the solution of step b) or c) with a suitable anti-solvent. Adding the solution obtained in step b) or c) to the anti-solvent, or adding an anti-solvent to the solution obtained in step b) or c), to effect the crystallization process are both within the scope of the present invention. Optionally, the addition may be carried out after concentrating the solution obtained in step b) or c). After adding anti-solvent, the reaction mass may be maintained from 15 minutes to 10 hours.

In embodiments of step e) involves optionally adding water to the solution obtained in step b) or c) or d);

In embodiments of step f), the compound obtained from step d) may be collected using techniques such as direct filtration or by scraping, or by shaking the container, 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 product thus isolated may be optionally further dried to afford a crystalline propane-1,2,3-triol solvate of dapagliflozin.

Drying may be suitably 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.

The dried product may be optionally milled to get desired particle sizes. Milling or micronization may be performed before drying, or after the completion of drying of the product. Techniques that may be used for particle size reduction include, without limitation, ball, roller and hammer mills, and jet mills. etc., to produce a desired particle size distribution. Dapagliflozin obtained according to certain processes of the present application has a particle size distribution wherein: d(0.5) is less than about 100 µm, or less than about 25 µm, or less than about 10 µm; and d(0.9) is less than about 200 µm, or less than about 50 µm, or less than about 30 µm. Particle size distributions can be determined using any means, including laser light diffraction equipment sold by Malvern Instruments limited, Malvern, Worcestershire, United Kingdom, Coulter counters, microscopic procedures, etc. The term d(x) means that a particular fraction has particles with a maximum size being the value given; 0.5 represents 50% of the particles and 0.9 represents 90% of the particles.

Preferably, in the crystalline propane-1,2,3-triol solvate of dapagliflozin the molar ratio of dapagliflozin and propane-1,2,3-triol is in the range of 1:0.5 to 1:6. In an even more preferred embodiment the molar ratio of dapagliflozin and propane-1,2,3-triol is in the range of 1:1 to 1:3.

In an aspect, the application provides a crystalline propane-1,2,3-triol solvate of dapagliflozin has an XRPD pattern with characteristic peak at about 21.57, 24.35, 24.69, 25.24, 28.13 and 31.39±0.2°2θ. Crystalline propane-1,2,3-triol solvate of dapagliflozin further characterized by PXRD pattern comprising peaks at about 3.85, 12.35, 15.56, 16.03, 16.60 and 18.60±0.2°2θ.

In another embodiment, the crystalline propane-1,2,3-triol solvate of dapagliflozin may contain water and the molar ratio of water may vary between 0.5 moles to 8 moles with respect to 1 mole of dapagliflozin.

In the embodiment, the crystalline propane-1,2,3-triol solvate of dapagliflozin obtained according to the present invention can be used as an intermediate for making any crystalline form of dapagliflozin including solvates, complexes or amorphous form of dapagliflozin or solid dispersion of dapagliflozin along with the other pharmaceutically acceptable excipients.

A fifteenth aspect of the present application provides a process for the preparation of crystalline propane-1,2,3-triol solvate of dapagliflozin comprising:

a) mixing the dapagliflozin with Propane-1,2,3-triol;

b) optionally milling the compound obtained in step a);

c) obtaining crystalline propane-1,2,3-triol solvate of dapagliflozin.

In an embodiment of step a), mixing the dapagliflozin with Propane-1,2,3-triol using the general procedures known in the art or as the procedure described in this application.

In an embodiment of step b), optionally milling the compound obtained in step a);
Milling methods are well known to a person skilled in the art. Any suitable milling method can be used. Any suitable miller can be used for milling including but not limited to quadro comill, multi mill, ball mill, roller mill, hammer mill and jet mill, etc.

In an embodiments of step c), the obtained product may be dried to afford crystalline propane-1,2,3-triol solvate of dapagliflozin.

In an aspect, the present application provides crystalline propane-1,2,3-triol solvate of dapagliflozin is characterized by its full X-ray powder diffractogram as substantially shown in FIG. 6

A sixteenth aspect of the present application provides a process for the preparation of L-proline complex of dapagliflozin comprising:

a) preparing a solution of dapagliflozin in a solvent;

b) adding L-proline;

c) isolating the L-proline complex of dapagliflozin.

In embodiments of step a), suitable solvents that may be used include, but are not limited to, ester solvents, halogenated hydrocarbon solvents, ether solvent; nitrile solvents; alcohol solvents; polar aprotic solvents; ketone solvents; or mixtures thereof.

In specific embodiments suitable solvents that may be used in step a) is selected from ethyl acetate, dichloromethane or mixtures thereof.

In embodiments of step a), preparing a solution of dapagliflozin includes:

i) direct use of a reaction mixture containing dapagliflozin that is obtained in the course of its synthesis; or

ii) dissolving dapagliflozin in a solvent.

The dissolution temperatures may range from about 20°C to about the reflux temperature of the solvent, depending on the solvent used for dissolution, as long as a clear solution of dapagliflozin is obtained without affecting its quality.

In embodiments of step b), the L-proline used as solid or making the solution using solvents which are mentioned under step a. In embodiments of step b), the L-proline or L-proline solution may be added to the dapagliflozin solution obtained in step a) or vice-versa.

In embodiments of step b), the reaction mass is maintained at the temperature 10°C to about 70°C for about 15 minutes to about 10 hours, or longer.

In embodiments of step c), the isolation may be done using techniques such as direct filtration or by scraping, or by shaking the container, removal of the solvent include 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 product thus isolated may be optionally further dried to afford L-proline complex of dapagliflozin.

Drying may be suitably 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 an aspect, the present application provides a purifying the L-proline complex of dapagliflozin can be done by any of the procedures known in the art which include but not limited to recrystallization, slurry washing, purification through column chromatography etc. The solvents that can be used for the purification of L-proline complex of dapagliflozin may be selected from alcohol solvents; ether solvent; nitrile solvents; halogenated hydrocarbon solvents; ester solvents; polar aprotic solvents; ketone solvents; or mixtures thereof.

In specific embodiments suitable solvents that may be used for the purification of L-proline complex of dapagliflozin is selected from methanol, ethyl acetate or mixtures thereof.

In the embodiment, the L-proline complex of dapagliflozin obtained according to the present invention can be used as an intermediate for making any crystalline solvate form of Dapagliflozin including solvates, complexes or amorphous form of dapagliflozin or solid dispersion of dapagliflozin along with the other pharmaceutically acceptable excipients.

A seventeenth aspect of the present application provides pharmaceutical formulations comprising crystalline propane-1,2,3-triol solvate of dapagliflozin, together with one or more pharmaceutically acceptable excipients. crystalline propane-1,2,3-triol solvate of dapagliflozin together with one or more pharmaceutically acceptable excipients of the present application may be formulated as: solid oral dosage forms such as, but not limited to, powders, granules, pellets, tablets, or capsules; liquid oral dosage forms such as, but not limited to, syrups, suspensions, dispersions, or emulsions; or injectable preparations such as, but not limited to, solutions, dispersions, or freeze dried compositions. Formulations may be in the forms of immediate release, delayed release, or modified release. Further, immediate release compositions may be conventional, dispersible, chewable, mouth dissolving, or flash melt preparations, or modified release compositions that may comprise hydrophilic or hydrophobic, or combinations of hydrophilic and hydrophobic, release rate controlling substances to form matrix or reservoir or combination of matrix and reservoir systems. The compositions may be prepared using techniques such as direct blending, dry granulation, wet granulation, or extrusion and spheronization. Compositions may be presented as uncoated, film coated, sugar coated, powder

coated, enteric coated, or modified release coated. Compositions of the present application may further comprise one or more pharmaceutically acceptable excipients.

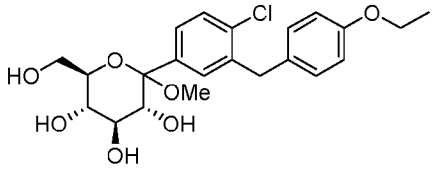
Pharmaceutically acceptable excipients that are useful in the present application include, but are not limited to: diluents such as starches, pregelatinized starches, lactose, powdered celluloses, microcrystalline celluloses, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar, or the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinylpyrrolidones, hydroxypropyl celluloses, hydroxypropyl methyl celluloses, pregelatinized starches, or the like; disintegrants such as starches, sodium starch glycolate, pregelatinized starches, crospovidones, croscarmellose sodium, colloidal silicon dioxide, or the like; lubricants such as stearic acid, magnesium stearate, zinc stearate, or the like; glidants such as colloidal silicon dioxide or the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants; complex forming agents such as various grades of cyclodextrins or resins; release rate controlling agents such as hydroxypropyl celluloses, hydroxymethyl celluloses, hydroxypropyl methylcelluloses, ethylcelluloses, methylcelluloses, various grades of methyl methacrylates, waxes, or 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, or the like.

Different solid forms are characterized by scattering techniques, *e.g.*, x-ray powder diffraction pattern, by spectroscopic methods, *e.g.*, infra-red, ^{13}C nuclear magnetic resonance spectroscopy, and by thermal techniques, *e.g.*, differential scanning calorimetry or differential thermal analysis. The compound of this application is best characterized by the X-ray powder diffraction pattern determined in accordance with procedures that are known in the art. For a discussion of these techniques see J. Haleblian, J. Pharm. Sci. 1975 64:1269-1288, and J. Haleblian and W. McCrone, J. Pharm. Sci. 1969 58:911-929. Crystalline propane-1,2,3-triol solvate of dapagliflozin can be further processed to modulate particle size. For example, crystalline propane-1,2,3-triol solvate of dapagliflozin can be milled to reduce average crystal size and/or to prepare a sample suitable for manipulation or formulation.

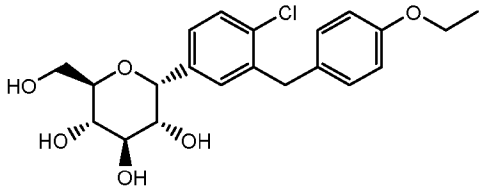
In an aspect of the application, dapagliflozin prepared according to the process of the present application can be substantially pure having a chemical purity greater than about 99%, or greater than about 99.5%, or greater than about 99.9%, by weight, as determined using high performance liquid chromatography (HPLC).

Dapagliflozin produced by the method of present invention can be chemically pure having purity greater than about 99.5% and containing no single impurity in amounts greater than about 0.15%, by HPLC.

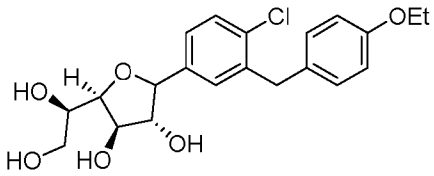
Potential Impurities possible in dapagliflozin, described in the present application, can have structures as illustrated below.



(3R,4S,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl) phenyl)- 6-(hydroxy methyl)-2-methoxytetrahydro-2H-pyran-3,4,5-triol



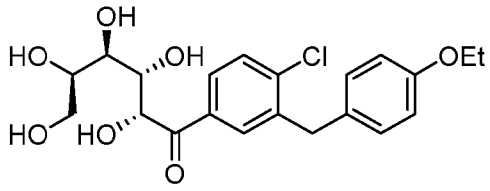
(2R,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol



(3R,4R,5R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-5-((R)-1,2-dihydroxyethyl) tetrahydro furan-3,4-diol

The possible impurities mentioned above are found to be less than 0.15% in the dapagliflozin produced according to the processes of the present application.

An eighteenth aspect of the present invention provides an isolated compound of formula III



Formula III

The isolated compound of formula III is at least 50%, preferably at least 90%, even more preferably at least5 95%, and most preferably at least 99% pure, as judged by GC or HPLC.

DEFINITIONS

The following definitions are used in connection with the present application unless the context indicates otherwise. In general, the number of carbon atoms present in a given group or compound is designated "C_x-C_y", where x and y are the lower and upper limits, respectively. For example, a group designated as "C_1-C_6" contains from 1 to 6 carbon atoms. The carbon number as used in the definitions herein refers to carbon backbone and carbon branching, but does not include carbon atoms of the substituents, such as alkoxy substitutions and the like.

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, isopropyl acetate, n-propyl acetate, n-butyl acetate, isobutyl acetate, t-butyl acetate, ethyl formate, methyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, C_{3-6} esters, or the like.

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, C_{1-6} alcohols, 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 "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, C_{2-6}nitriles, 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), N-methylpyrrolidone (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).

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 isobutyl ketone, C_{3-6}ketones, 4-methyl-pentane-2-one or the like.

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, 2-methyltetrahydrofuran, 1,4-dioxane, dibutyl ether, dimethylfuran, 2-methoxyethanol, 2-ethoxyethanol, anisole, C_{2-6} ethers, or the like.

A “hydrocarbon solvent” refers to aliphatic hydrocarbon solvent.

An “aliphatic or alicyclic 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 solvents include, but are not limited to, cyclohexane, 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, methylcyclohexane, cycloheptane, C_5-C_8 aliphatic hydrocarbons, petroleum ethers, or mixtures thereof.

The term "about" when used in the present invention preceding a number and referring to it, is meant to designate any value which lies within the range of ±10%, preferably within a range of ±5%, more preferably within a range of ±2%, still more preferably within a range of ±1 % of its value. For example "about 10" should be construed as meaning within the range of 9 to 11 , preferably within the range of 9.5 to 10.5, more preferably within the range of 9.8 to 10.2, and still more preferably within the range of 9.9 to 10.1 .

The term “solvate” as used herein designates a crystalline molecular compound in which molecules of the solvent(s) other than water are incorporated into the crystal lattice.

Hence, the term "crystalline propane-1,2,3-triol solvate of dapagliflozin" as used herein means a crystalline form of dapagliflozin containing propane-1,2,3-triol molecules combined in a definite ratio as an integral part of the crystal.

The term "anti-solvent" refers to a liquid that, when combined with a solution of dapagliflozin, reduces solubility of the dapagliflozin in the solution, causing crystallization or precipitation in some instances spontaneously.

As used herein, the term "isolated" refers to a compound that is at least 50%, preferably at least 90%, even more preferably at least5 95%, and most preferably at least 99% pure, as judged by GC or HPLC.

Certain specific aspects and embodiments 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 solid premix of dapagliflozin with eudragit

Dapagliflozin (5 g), eudragit (5 g) and methanol (60 mL) were charged into a round bottom flask at 26°C. The reaction mass was stirred to dissolve dapagliflozin completely. The reaction mass was filtered and washed with methanol (10 mL). The solvent was removed from the reaction mass under vacuum at 50°C. The solid premix of dapagliflozin with eudragit was obtained.

EXAMPLE 2: Preparation of solid premix of dapagliflozin with syloid

Amorphous form of Dapagliflozin (5 g) and syloid (5 g) were charged into a round bottom flask at 28°C. The reaction mass was stirred for 1 hour at 28°C. The solid premix of dapagliflozin with syloid was obtained.

EXAMPLE 3: Preparation of solid premix of dapagliflozin with MCC Avicel PH 102 (1:1)

Amorphous form of Dapagliflozin (2 g) and MCC Avicel PH 102 (2 g) were charged into a motor stator at 25°C. The reaction mass was mixed for 10 minutes at 25°C. The solid premix of dapagliflozin with MCC Avicel PH 102 (1:1) was obtained.

EXAMPLE 4: Preparation of solid premix of dapagliflozin with MCC Avicel PH 102 (1:2)

Amorphous form of Dapagliflozin (2 g) and MCC Avicel PH 102 (4 g) were charged into a motor stator at 25°C. The reaction mass was mixed for 10 minutes at 25°C. The solid premix of dapagliflozin with MCC Avicel PH 102 (1:2) was obtained.

EXAMPLE 5: Preparation of solid premix of dapagliflozin with syloid (3:1)

Amorphous form of Dapagliflozin (6.56 g) and syloid 244FPNF (2 g) were charged into a round bottom flask at 30°C. The reaction mass was stirred for 1 hour at 38°C. The solid premix of dapagliflozin with syloid was obtained.

EXAMPLE 6: Preparation of **c**rystalline propane-1,2,3-triol solvate of Dapagliflozin

Dapagliflozin (10 g) and isopropyl acetate (50 mL) were charged into a round bottom flask at 30°C. The reaction mass was stirred to dissolve dapagliflozin completely. Propane-1,2,3-triol (2.478 g) was charged into a flask at 30°C. The reaction mass was stirred for 10 minutes at 30°C. Cyclohexane (100 mL) was added to the reaction mass under stirring at 30°C. The reaction mass was stirred for 1 hour at 30°C. The reaction mass was cooled to 12°C and stirred for 1 hour. Water (0.440 g) was added to the flask containing the gummy mass and stirred for 1 hour at 12°C. The reaction mass was stirred for 1 hour at 28°C. The gummy solid taken into petry dish and dried under vacuum for 11 hours at 30°C. The gummy solid was dried under vacuum for 16 hours at 60°C. The gummy solid was kept at 27°C for 15 days and the resulting solid product was obtained as **c**rystalline propane-1,2,3-triol solvate of Dapagliflozin. Purity by HPLC: 99.97%.

EXAMPLE 7: Preparation of **c**rystalline propane-1,2,3-triol solvate of Dapagliflozin

Dapagliflozin (2 g) and Propane-1,2,3-triol (0.496 g) were charged into a mortar pestle. The reaction mass was grind for 10 minutes at 30°C. The gummy solid was dried under vacuum for 17 hours at 60°C. The gummy solid was further dried for 24 hours at 30°C. The gummy solid was kept at 27°C for 15 days and the resulting solid product was obtained as **c**rystalline propane-1,2,3-triol solvate of Dapagliflozin. Purity by HPLC: 99.91%.

EXAMPLE 8: Preparation of **c**rystalline propane-1,2,3-triol solvate of Dapagliflozin

Dapagliflozin (2 g) and Propane-1,2,3-triol (0.496 g) were charged into a mortar pestle. The reaction mass was grind for 10 minutes at 30°C. The gummy solid was dried under vacuum for 17 hours at 60°C. The gummy solid was further dried for 24 hours at 30°C. The gummy solid was kept at 27°C for 15 days and the resulting solid product was obtained as **c**rystalline propane-1,2,3-triol solvate of Dapagliflozin. Purity by HPLC: 99.91%.

EXAMPLE 9: Preparation of **c**rystalline propane-1,2,3-triol solvate of Dapagliflozin

Dapagliflozin (10 g) and Propane-1,2,3-triol (2.478 g) were charged into a mortar pestle. The reaction mass was grind for 90 minutes at 27°C. The gummy solid was kept at 27°C for 2 days and the resulting solid product was obtained as crystalline propane-1,2,3-triol solvate of Dapagliflozin. Purity by HPLC: 99.96%.

EXAMPLE 10: Preparation of amorphous form of dapagliflozin.

Dapagliflozin (10 g) and methanol (50 mL) were charged into a round bottom flask at 30°C. The reaction mass was stirred to dissolve dapagliflozin completely. The obtained solution was filtered and washed with methanol (10 mL). The resulting clear solution was subjected to spray drying in a Spray Dryer at the inlet temperature of 80°C with purging of nitrogen gas. The solid product was obtained as amorphous dapagliflozin. Yield: 3.6g.

EXAMPLE 11: Preparation of amorphous form of dapagliflozin.

Dapagliflozin (10 g) and ethyl acetate (50 mL) were charged into a round bottom flask at 30°C. The reaction mass was stirred to dissolve dapagliflozin completely. The obtained solution was filtered and washed with ethyl acetate (10 mL). The resulting clear solution was subjected to spray drying in a Spray Dryer at the inlet temperature of 65°C with purging of nitrogen gas. The solid product was obtained as amorphous dapagliflozin. Yield: 3.6g.

EXAMPLE 12: Preparation of amorphous form of dapagliflozin.

Dapagliflozin (25 g) and methanol (125 mL) were charged into a round bottom flask at 30°C. The reaction mass was stirred to dissolve dapagliflozin completely. The resulting clear solution was subjected to ATFD at jacket temperature of 60°C with purging of nitrogen gas. The solid product was obtained as amorphous dapagliflozin.

EXAMPLE 13: Preparation of (2R,3S,4R,5R)-1-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4,5,6-pentahydroxyhexan-1-one.

4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene (20 g), tetrahydrofuran (240 mL), (3R,4S,5R,6R)-3,4,5-tris((trimethylsilyl)oxy)-6-(((trimethylsilyl)oxy)methyl) tetrahydro-2H-pyran-2-one (57.3 g) were charged into a round bottom flask at 26°C. The reaction mass was stirred under nitrogen atmosphere for 15 minutes. The reaction mass was cooled to -74°C. n-butyl lithium (10.23 g) was added drop wise to the reaction mass at -74°C. The reaction mass was stirred for 1 hour at -75°C. The above obtained reaction mass was added to trifluoroacetic acid solution (42 g in 40 mL of water). The reaction mass was stirred for 1 hour at 1°C. The reaction mass was adjusted to pH 7.5 with 25% sodium carbonate solution (70 mL) at 2°C. The temperature of the reaction

mass was raised to 30°C. The organic and aqueous layers were separated. The aqueous layer was washed with ethyl acetate (300 mL). The combined organic layer was washed with 10% sodium chloride solution (100 mL). The reaction mass was evaporated under vacuum at 55°C. Ethyl acetate (100 mL) was added to the above obtained crude. The temperature of the reaction mass was raised to 45°C. The reaction mass was seeded with (2R,3S,4R,5R)-1-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4,5,6-pentahydroxyhexan-1-one (0.5g) at 45°C. Toluene (200 mL) was added to the reaction mass at 45°C. The reaction mass was stirred for 4 hours at 42°C. The reaction mass was cooled to 30°C and stirred for 3 hours. The precipitated solid was filtered off and washed with toluene (50 mL). The solid was dried under vacuum at 55°C for 6 hours. Product weight: 23 g; purity by HPLC: 99.69%.

Example 14: Preparation of L-proline complex of dapagliflozin.

2R,3S,4R,5R)-1-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4,5,6-pentahydroxy hexan-1-one (50 g) and methanol (500 mL) were charged into a round bottom flask at 26°C. The reaction mass was stirred for 30 minutes at 26°C. The reaction mass was cooled to 2°C. Methanesulfonic acid (11.31g) was added to the reaction mass at 2°C. The reaction mass temperature raised to 17°C. The reaction mass was stirred for 9 hours at 17°C. Dichloromethane (350 mL) was added to the reaction mass at 22°C. 5% $NaHCO_3$ solution (500 mL) was added to the reaction mass at 22°C. The reaction mass was stirred for 15 minutes at 25°C. The organic and aqueous layers were separated. The aqueous layer was washed with dichloromethane (350 mL). The combined organic layer was washed with 10% sodium chloride solution (250 mL). The organic extract was evaporated under vacuum at 45°C. Dichloromethane (500 mL) was added to the above obtained residue and evaporated under vacuum at 45°C. The residue product was obtained as (3R,4S,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)-2-methoxytetrahydro-2H-pyran-3,4,5-triol.

(2S,3R,4S,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxy methyl)-2-methoxytetrahydro-2H-pyran-3,4,5-triol solution (51.5 g in 50 mL of dichloromethane) was charged into a round bottom flask. The solution was cooled to -35°C. Triethylsilane (34.1 g) was added to the reaction mass at -35°C. Boron trifluoride etherate (37.5 g) was added to the reaction mass at -40°C. The reaction mass was stirred for 2 hours at -38°C. The reaction mass temperature raised to -5°C. The reaction mass was stirred for 4 hours at -5°C. Water (500 mL) was slowly added to the reaction mass. The reaction mass temperature raised to 28°C. The organic and

aqueous layers were separated. The organic layer was washed with water (500 mL). 5% $NaHCO_3$ solution (250 mL) was added to the reaction mass. The reaction mass was stirred for 20 minutes at 28°C. Methanol (500 mL) and 20% NaCl solution (250 mL) were added to the reaction mass at 28°C. The organic and aqueous layers were separated. The organic layer was washed with 10% NaCl solution (250 mL). The reaction mass was evaporated under vacuum at 45°C. The residue product was obtained as dapagliflozin. Ethyl acetate (150 mL) was added to the reaction mass. The reaction mass was evaporated under vacuum at 55°C.

Dapagliflozin residue (48.11 g in 50 mL of ethyl acetate) and ethyl acetate (350 mL) were charged into a round bottom flask at 28°C. The reaction mass temperature raised to 55°C. L-proline (20.25 g) was added to the reaction mass at 55°C. L-proline (6.75 g) was added to the reaction mass at 55°C. Flushed the funnel with ethyl acetate (25 mL). The reaction mass was stirred for 2 hours at 55°C. L-proline (6.75 g) was added to the reaction mass at 55°C. Flushed the funnel with ethyl acetate (25 mL).). The reaction mass was stirred for 2 hours at 55°C. The reaction mass temperature cooled to 28°C. The reaction mass was stirred for 5 hours at 28°C. The resulting slurry was filtered and washed with ethyl acetate (150 mL). The solid was dried with suction at 28°C. Product weight: 75 g; purity by HPLC: 99.2%.

Example 15: Purification of L-proline complex of Dapagliflozin.

L-proline complex of Dapagliflozin (20 g) and methanol (60 mL) were charged into a round bottom flask at 28°C. The reaction mass was stirred for 20 minutes at 28°C. The reaction mass temperature raised to 52°C. Ethyl acetate (400 mL) was added to the reaction mass at 52°C. The reaction mass was stirred for 4 hours at 52°C. The resulting slurry was filtered and washed with ethyl acetate (60 mL). The solid was dried with suction at 28°C. The solid was further dried for 5 hours at 55°C. Product weight: 17.35 g; purity by HPLC: 99.97%.

Example 16: Preparation of amorphous Dapagliflozin.

L-proline complex of Dapagliflozin (200 g) and ethyl acetate (2000 mL) were charged into a round bottom flask at 27°C. The reaction mass was stirred for 10 minutes at 27°C. 5% sodium bicarbonate solution (1000 mL) was added to the reaction mass at 27°C. The reaction mass was stirred for 10 minutes at 27°C. The organic and aqueous layers were separated. The organic layer charged into a round bottom flask at 27°C. 5% sodium bicarbonate solution (1000 mL) was added to the reaction mass at 27°C. The reaction mass was stirred for 10 minutes at 27°C. The organic and aqueous layers were separated. The organic layer charged into a round bottom flask

at 27°C. Water (1000 mL) was added to the reaction mass at 27°C. The reaction mass was stirred for 10 minutes at 27°C. The organic and aqueous layers were separated. The reaction mass was evaporated at 52°C. Methanol (600 mL) was added to the reaction mass at 30°C. The reaction mass was evaporated at 55°C. Methanol (600 mL) was added to the reaction mass at 27°C. The reaction mass was evaporated at 55°C. Methanol (600 mL) was added to the reaction mass. The solution was filtered to remove any insoluble particles. The clear solution was subjected to spray drying in a Spray Dryer at the inlet temperature of 90°C and nitrogen pressure 5kg. The resulting solid was dried for 6 hours at 55°C. The solid product was obtained as amorphous dapagliflozin. Yield: 11.1 g.

Example 17: Purification of L-proline complex of Dapagliflozin.

L-proline complex of Dapagliflozin (1.3 KG) and methanol (2250 mL) were charged into a round bottom flask at 28°C. The reaction mass was stirred for 20 minutes at 28°C. The reaction mass temperature raised to 59°C. Ethyl acetate (18 L) was charged into another round bottom flask and heated to 59°C. The above obtained reaction mass was added to ethyl acetate at 62°C. The reaction mass was stirred for 60 minutes at 60°C. The reaction mass was cooled to 35°C and maintained for 4 hours. The resulting slurry was filtered and washed with ethyl acetate (2.7 L). The solid was dried with suction at 28°C. The solid was further dried for 5 hours at 55°C. Product weight: 945 g.

EXAMPLE 18: Preparation of **c**rystalline propane-1,2,3-triol solvate of Dapagliflozin

Dapagliflozin (1 g) and isopropyl acetate (10 mL) were charged into a round bottom flask under nitrogen atmosphere at 28°C. The reaction mass was stirred to dissolve dapagliflozin completely. Propane-1,2,3-triol (0.2 mL) was charged into a flask under stirring at 28°C. The reaction mass was cooled to 10°C. Cyclohexane (30 mL) was added to the above obtained clear solution under stirring at 12°C. Water (0.044ml) was added to the flask containing the gummy mass and stirred for 50 minutes at 15°C. The resulting slurry was filtered under nitrogen atmosphere. The solid product was obtained as **c**rystalline propane-1,2,3-triol solvate of dapagliflozin. Yield: 16.4%; Purity by HPLC: 99.57%.

EXAMPLE 19: Preparation of L-proline cocrystals of Dapagliflozin.

Dapagliflozin (63 g) and ethyl acetate (825 mL) were charged into a round bottom flask at 28°C. The reaction mass was heated to 44°C to produce a clear solution. L-proline (37.3 g) was added to the reaction mass at 44°C. The reaction mass was stirred for 2 hour at 44°C. The reaction mass

cooled to 28°C and stirred for 5 hours. The resulting slurry was filtered and washed with ethyl acetate (125 mL). The solid was dried with suction at 28°C. The obtained solid (120 g) and methanol (63 mL) were charged into a round bottom flask at 28°C. The reaction mass was heated to 63°C to produce a clear solution. Ethyl acetate (630 mL) was added to the reaction mass at 63°C for 5 minutes. The reaction mass was stirred for 1 hour at 60°C. The reaction mass cooled to 28°C and stirred for 4 hours. The resulting slurry was filtered and washed with ethyl acetate (125 mL). The solid was dried with suction at 28°C. The solid was dried under vacuum at 53°C for 5 hours. The solid was dried at 53°C for 16 hours. Product weight: 81.0 g; Purity: 99.8% by HPLC.

EXAMPLE 20: Preparation of L-proline cocrystals of Dapagliflozin.

Dapagliflozin (10 g), dichloromethane (220 mL) and L-proline (5.91 g) were charged into a round bottom flask at 28°C. The reaction mass was stirred for 5 hours at 28°C. The resulting slurry was filtered and washed with dichloromethane (20 mL). The solid was dried with suction at 28°C. The obtained solid (15.5 g) and methanol (15 mL) were charged into a round bottom flask at 28°C. The reaction mass was heated to 60°C to produce a clear solution. Ethyl acetate (100 mL) was added to the reaction mass at 60°C. The reaction mass cooled to 30°C and stirred for 2 hours. The resulting slurry was filtered and washed with ethyl acetate (20 mL). The solid was dried with suction at 28°C. The solid was dried under vacuum at 55°C for 6 hours.

Example 21: Preparation of 4-bromo-1-chloro-2-(4-ethoxybenzyl) benzene.

5-Bromo-2-chlorobenzoic acid (15 g, 63.7 mmol) and chlorobenzene (150 mL) were charged into a clean RB flask at 25 °C under nitrogen atmosphere. To this dimethyl formamide (0.75 mL) was added and the reaction mass cooled to 10 °C under Nitrogen atmosphere. To this, oxalyl chloride (10.5 g, 83 mmol, 1.3 eq.) was added drop wise in 30 min. The reaction mixture was warmed to 25 °C and stirred at this temperature for 1-2 hours. The RM was distilled under vacuum at 55 °C till 7-8 volumes remained in the reactor. The reaction mixture was then cooled 30 °C and chlorobenzene (60mL) was charged into the reactor under nitrogen atmosphere. The reaction mass was then cooled to 10 °C and aluminum chloride (9.34 g, 70.1 mmol, 1.1 eq.) was charged into the reaction mass followed by slow addition of ethoxy benzene (8.17 g, 66.9 mmol, 1.05 eq.) over a period of 60-90. The reaction mass was stirred at this temperature for 3-4 h. After the completion of the reaction (monitored by TLC), the reaction was quenched by adding the reaction mass into ice cold water (150 mL) The reaction mass was then warmed to 25 °C and

the layers were separated. Aqueous layer was extracted with Chlorobenzene (30 mL). The combined organic layers were washed with aqueous saturated sodium bicarbonate (500 mL) and water (150 mL). Organic layer was distilled under vacuum at 65 °C and the crude chased with methanol (2 x 70 mL) in order to remove traces of chlorobenzene. To the crude, methanol (75 mL) was added and the mixture stirred at 45 °C for 15-30 min to get a clear solution. The reaction mass was stirred at 30 °C for 1 h and then at -5 °C for 2-3 h. The solid obtained was filtered, washed with chilled methanol (30 mL) and then dried under vacuum at 45-50 °C.

The dry solid was taken in a clean reactor and Trifluoroacetic acid (89 g, 781 mmol, 12.2 eq.) was charged into the reactor at 30 °C. To this, triethylsilane (15.41 g, 133 mmol, 2.08 eq.) was added slowly over a period of 45-60 min at 30 °C. The reaction mass was heated to 70-75 °C and stirred for 3-4 h. After the completion of the reaction (monitored by TLC), TFA was distilled off under vacuum at 65 °C. The crude was chased twice with Toluene (30 mL) at 65 °C to remove any traces of TFA. The crude was cooled to 30 °C and toluene (150 mL) was charged into the reaction mass. The reaction mixture was washed with saturated aqueous sodium carbonate (150 mL). The aqueous layer was extracted with toluene (45 mL) and the organic layers combined. The combined organic layers were washed with water (150 mL). The organic layer was distilled under vacuum at 50 °C and chased twice with methanol (30 mL). Fresh methanol (60 mL) was added to the crude and stirred for 1 h at 42 °C followed by stirring at -5 °C for 2-3 h. The solid was filtered, washed with chilled methanol (15 mL) and dried at 30 °C under vacuum. 12 g white solid was obtained with 58% isolated yield.

EXAMPLE 22: Preparation of (2R,3S,4R,5R)-1-(4-chloro-3-(4-Ethoxybenzyl)phenyl)-2,3,4,5,6-pentahydroxyhexan-1-one.

4-bromo-1-chloro-2-(4-ethoxybenzyl) benzene (30.0 kg), tetrahydrofuran (360 Lt), (3R,4S,5R,6R)-3,4,5-tris((trimethylsilyl)oxy)-6-(((trimethylsilyl)oxy)methyl) tetrahydro-2H-pyran-2-one (90.86 kg) were charged into a reactor at 28°C. The reaction mass was stirred under nitrogen atmosphere for 15 minutes. n-butyl lithium (150 Lt) was added drop wise to the reaction mass at -78°C. The reaction mass was stirred for 1 hour at -77°C. The above reaction mass was added to trifluoroacetic acid solution (63.5 kg in 60 Lt of water) at 3°C. The reaction mass was stirred for 3 hours at 4°C. The reaction mass was adjusted to pH 7.5 with saturated sodium bicarbonate solution (51.0 kg in 600 Lt of water) at 3°C. The temperature of the reaction mass was raised to 27°C. The organic and aqueous layers were separated. The aqueous layer was washed with ethyl acetate (300 Lt) and again aqueous layer was washed with ethylacetate (150 Lt). The combined organic layer was washed with 10%

sodium chloride solution (9.0 kg in 90Lt of water).The reaction mass was evaporated under vacuum below 45°C until 1-2 volumes remain in the reactor. Charged toluene (60 Lt) into the reactor and distill under vaccum below 45°C until 1-2 volumes remain in the reactor. Ethyl acetate (150 Lt)was added to the above obtained crude. The temperature of the reaction mass was raised to 42°C. The reaction mass was seeded with (2R,3S,4R,5R)-1-(4-chloro-3-(4- -ethoxybenzyl)phenyl)-2,3,4,5,6-pentahydroxyhexan-1-one (0.15 kg) at 42°C. Toluene (300 Lt) was added to the reaction mass at 42°C. The reaction mass was stirred for 3 hours at 42°C. The reaction mass was cooled to 32°C and stirred for 3 hours. The precipitated solid was filtered off and washed with toluene (60 Lt). The solid was dried under vacuum at 46°C for 6 hours. Product weight: 29.3kg; purity by HPLC: 99.69%.

EXAMPLE 23: Preparation of L-proline complex of dapagliflozin.

2R,3S,4R,5R)-1-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3,4,5,6-pentahydroxy hexan-1-one (50 g) and methanol (500 mL) were charged into a round bottom flask at 28°C. The reaction mass was stirred for 30 minutes at 28°C. The reaction mass was cooled to 5°C. Methanesulfonic acid (11.31g) was added to the reaction mass at 2°C . The reaction mass temperature raised to 17°C. The reaction mass was stirred for 9 hours at 17°C. Dichloromethane (350 mL) was added to the reaction mass at 22°C. 5% $NaHCO_3$ solution (500 mL) was added to the reaction mass at 22°C. The reaction mass was stirred for 15 minutes at 25°C. The organic and aqueous layers were separated. Extracted the the product from aqueous layer with dichloromethane (2X200 mL). The combined organic layer was washed with 10% sodium chloride solution (2X250 mL). The organic layer was evaporated under vacuum at 45°C. Dichloromethane (2X200 mL) was added to the above obtained residue and evaporated under vacuum at 45°C. The residue product was obtained as (3R,4S,5S,6R)-2-(4-chloro-3-(4- ethoxybenzyl)phenyl)-6-(hydroxymethyl)-2-methoxytetrahydro-2H-pyran-3,4,5-triol.

(2S,3R,4S,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxy methyl)-2-methoxytetrahydro-2H-pyran-3,4,5-triol solution (51.5 g in 50 mL of dichloromethane) was charged into a round bottom flask. Charged dichloromethane(750mL) to the residue.The solution was cooled to -35°C. Triethylsilane (34.1 g) was added to the reaction mass at -35°C. Boron trifluoride etherate (88.3 g ; 48%) was added to the reaction mass at -35°C. The reaction mass was stirred for 3 hours at -35°C. The reaction mass temperature raised to -5°C. The reaction mass was stirred for 4 hours at -5°C. Add slowly water (500 mL) to the reaction mass. The reaction mass temperature raised to 28°C. The organic and aqueous layers were separated. The organic layer was washed with water (500 mL). 2% $NaHCO_3$ solution (250 mL), methanol (100 mL) and 20% NaCl solution (250mL) were added to the reaction mass. The reaction mass was stirred for 20 minutes. The organic and aqueous layers were

separated. Methanol (100 mL) and 2% NaCl solution (250mL) were added to the reaction mass. The reaction mass was stirred for 20 minutes. The organic and aqueous layers were separated. The reaction mass was evaporated under vacuum at 45 °C. The residue product was obtained as crude dapagliflozin. Ethyl acetate (250 mL) was added to the reaction mass. The reaction mass was evaporated under vacuum at 55°C. Dapagliflozin residue (48.11 g in 50 mL of ethyl acetate) and ethyl acetate (350 mL) were charged into a round bottom flask. The reaction mass temperature raised to 57 °C. L-proline (13.5 g) was added to the reaction mass at 57°C, Flushed the funnel with ethyl acetate (25 mL) and stir the reaction mass for 2 hours at 57°C. L-proline (6.75 g) was added to the reaction mass at 57°C, Flushed the funnel with ethyl acetate (25 mL). The reaction mass was stirred for 1 hour at 57°C. L-proline (6.75 g) was added to the reaction mass at 57°C, Flushed the funnel with ethyl acetate (25 mL). The reaction mass was stirred for 1 hour at 55 °C. The reaction mass temperature cooled to 28°C. The reaction mass was stirred for 5 hours at 28°C. The resulting slurry was filtered and washed with ethyl acetate (150 mL). The solid was suck dried with suction at 28°C. Compound was dried under vaccume at 55°C for 4 hours to get LOD below 10 %.

Example 24: Purification of L-proline complex of Dapagliflozin.

Methanol (40 mL) was charged into a round bottom flask at 28°C. The reaction mass temperature was raised to 52 °C. L-proline complex of Dapagliflozin (20 g) was added to the reaction mass at 52°C. Flushed the funnel with methanol (10 mL). The reaction mass temperature was raised to 63°C.The reaction mass was stirred for 15 minutes at 63°C. Ethyl acetate (400 mL) was charged into separate round bottom flask at 28°C. Ethyl acetate temperature was raised to 60 °C. The reaction mass was slowly added to ethyl acetate at 60°C. Flushed the round bottom flask funnel with methanol (10 mL) and charged into reaction mass at 60°C. Stirred the reaction mass for 1 hour at 60°C. The reaction mass temperature cooled to 30°C. Stirred the reaction mass for 4 hours at 30°C. The resulting slurry was filtered and washed with ethyl acetate (60 mL). The solid was dried with suction at 28°C. The solid was further dried for 6 hours at 55°C. Product weight: 17.35 g; purity by HPLC: 99.97%.

Example 25: Purification of L-proline complex of Dapagliflozin.

Methanol (1.25 liters) was charged into a round bottom flask at 28°C. The reaction mass temperature was raised to 52 °C. L-proline complex of Dapagliflozin (1.0 Kg) was added to the reaction mass at 52°C. The reaction mass temperature was raised to 63°C.The reaction mass was stirred for 15 minutes at 63°C. Ethyl acetate (10 liters) was charged into separate round bottom flask at 28°C. Ethyl acetate temperature was raised to 60 °C. The reaction mass was slowly added to ethyl acetate at 60°C. Flushed the round bottom flask funnel with methanol (250 mL) and charged into reaction mass

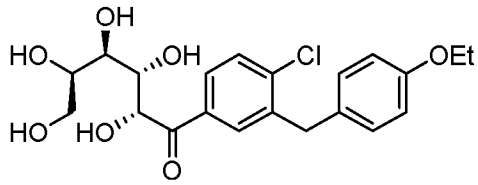
at 60°C. Stirred the reaction mass for 1 hour 20 minutes at 60°C. The reaction mass temperature cooled to 30°C. Stirred the reaction mass for 5 hours at 30°C. The resulting slurry was filtered and washed with ethyl acetate (500 mL). The solid was dried with suction at 28°C. The solid was further dried for 9 hours at 55°C. Product weight: 542 g; purity by HPLC: 99.86%.

Example 26: Preparation of amorphous Dapagliflozin.

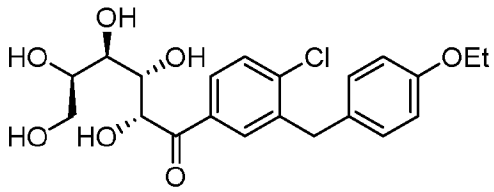
L-proline complex of Dapagliflozin (18kg) and ethyl acetate (180 Lt) were charged into the reactor at 30±5°C. 5% sodium bicarbonate solution (90 Lt) was added to the reaction mass at 30±5°C. The reaction mass was stirred for 20-30 minutes at 30±5°C. The aqueous layer was separated. Water (90 Lt) was added to the reaction mass at 30±5°C. The reaction mass was stirred for 15-30 minutes at 30±5°C. The aqueous layer was separated. Water (90 Lt) was added to the reaction mass at 30±5°C. The reaction mass was stirred for 15-30 minutes at 30±5°C. The aqueous layer was separated. The reaction mass was evaporated at 45°C. Methanol (45 Lt) was added to the reaction mass and the reaction mass was evaporated till 0.5-1.0 volume at 45°C. Methanol (45Lt) was added to the reaction mass and the reaction mass was evaporated till 0.5- 1.0 at 45°C. Methanol (36 Lt) was added to the reaction mass. The solution was filtered to remove any insoluble particles. The clear solution was subjected to spray drying in a Spray Dryer at the inlet temperature of 70±5°C and nitrogen pressure 4±1 Kg/cm2. The resulting solid was dried for 6 hours at 46±4°C. The solid product was obtained as amorphous dapagliflozin. Yield: 6.7kg.

CLAIMS:

1. An isolated compound of formula III

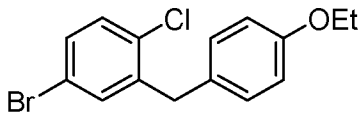


2. A process for the a process for the preparation of an isolated compound of formula III



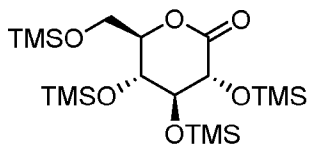
Formula III

comprising reacting the compound of formula I



Formula I

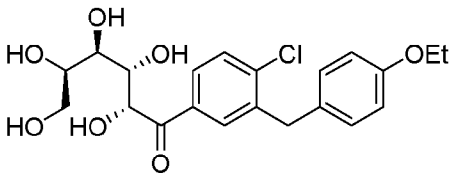
with compound of formula II.



Formula II

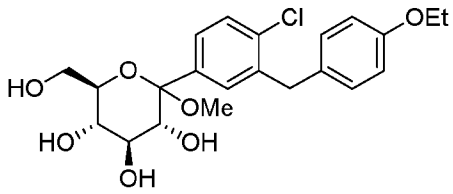
3. A process for the preparation of dapagliflozin comprises the steps of:

a) reacting an isolated compound of formula III



Formula III

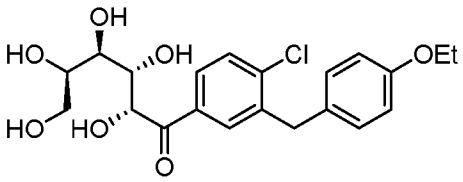
with methanesulfonic acid to obtained compound of formula IV;



Formula IV

b) converting the compound of formula IV into dapagliflozin;

4. A process for the preparation of dapagliflozin comprising the use of an isolated compound of formula III



Formula III

5. A solid premix of dapagliflozin with the polymer selected from the group consisting of eudragit, syloid, MCC Avicel PH 102 (1:1) and MCC Avicel PH 102 (1:2).
6. A process for the preparation of crystalline propane-1,2,3-triol solvate of dapagliflozin comprising the steps of;
   a) providing a solution of dapagliflozin in a solvent;
   b) adding propane-1,2,3-triol to the solution obtained in step a);
   c) optionally seeding with crystalline propane-1,2,3-triol solvate of dapagliflozin;
   d) optionally combining the solution of step b) or c) with suitable anti solvent;
   e) optionally adding water to the solution obtained in step b) or c) or d);
   f) isolating the crystalline propane-1,2,3-triol solvate of dapagliflozin.
7. A process for the preparation of crystalline propane-1,2,3-triol solvate of dapagliflozin comprising:

a) mixing the dapagliflozin with propane-1,2,3-triol;
b) optionally milling the compound obtained in step a);
c) obtaining crystalline propane-1,2,3-triol solvate of dapagliflozin.

8. A process for the preparation of L-proline complex of dapagliflozin comprising:

a) preparing a solution of dapagliflozin in a solvent selected from ester solvents, halogenated hydrocarbon solvents; nitrile solvents, polar aprotic solvents, ketone solvents, ether or mixtures thereof.

b) adding L-proline to the above obtained dapagliflozin solution;

c) isolating the L-proline complex of dapagliflozin;

d) optionally purifying the above obtained L-proline complex of dapagliflozin.

9. The process according to claim 8, wherein the ester solvent is selected from ethyl acetate, isopropyl acetate, n-propyl acetate, n-butyl acetate, isobutyl acetate, t-butyl acetate, ethyl formate, methyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate.

10. The process according to claim 8, wherein the ester solvent is ethyl acetate.

Drawings

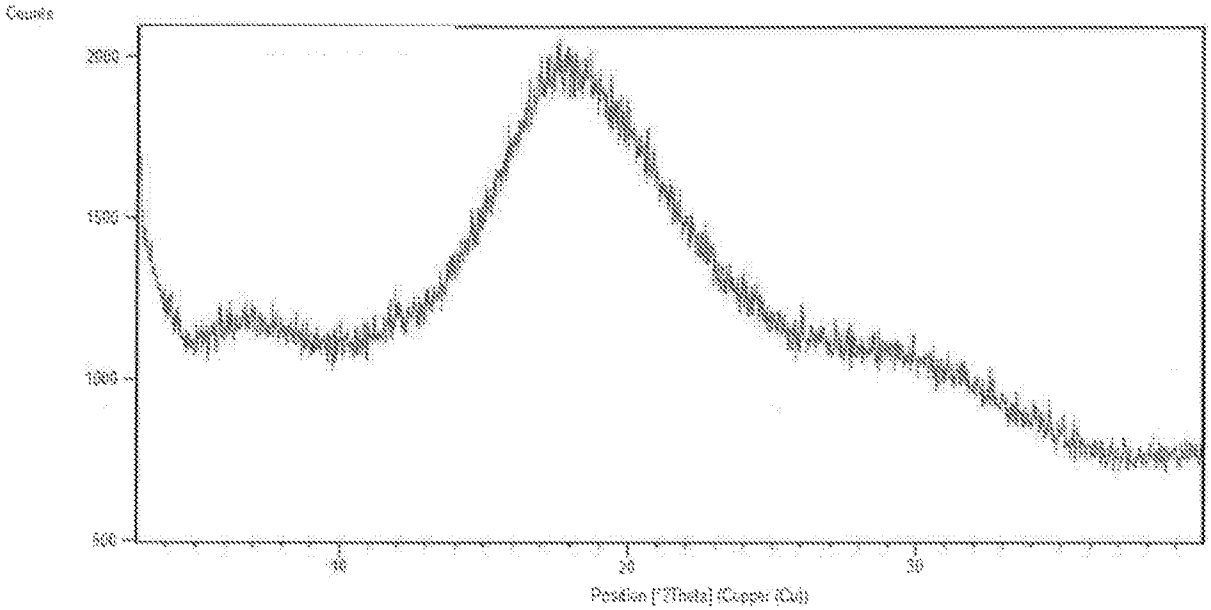


Figure 1

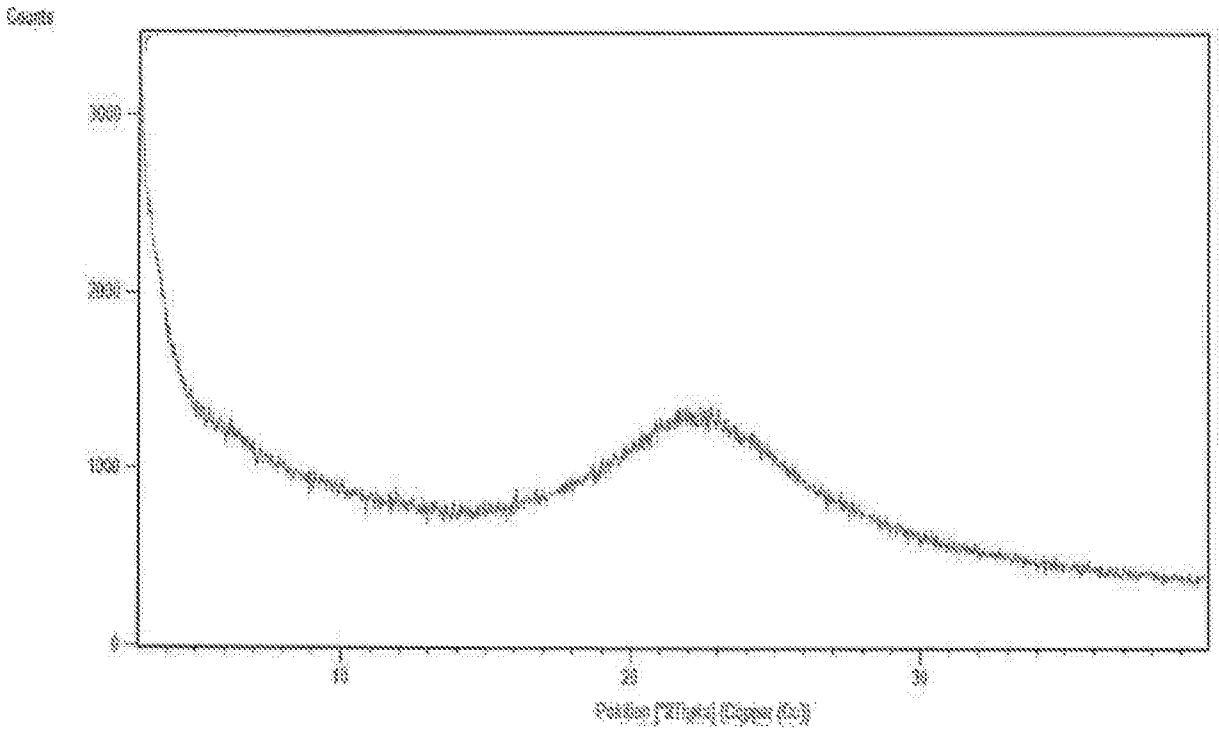


Figure 2

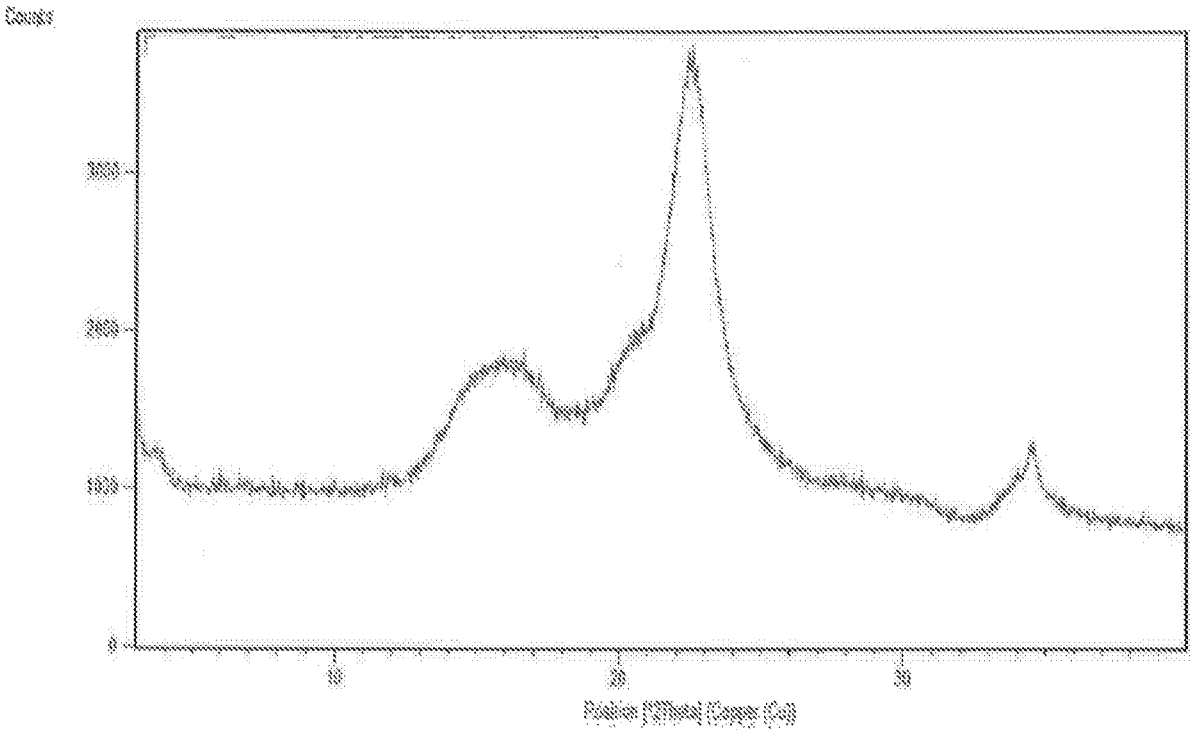


Figure 3

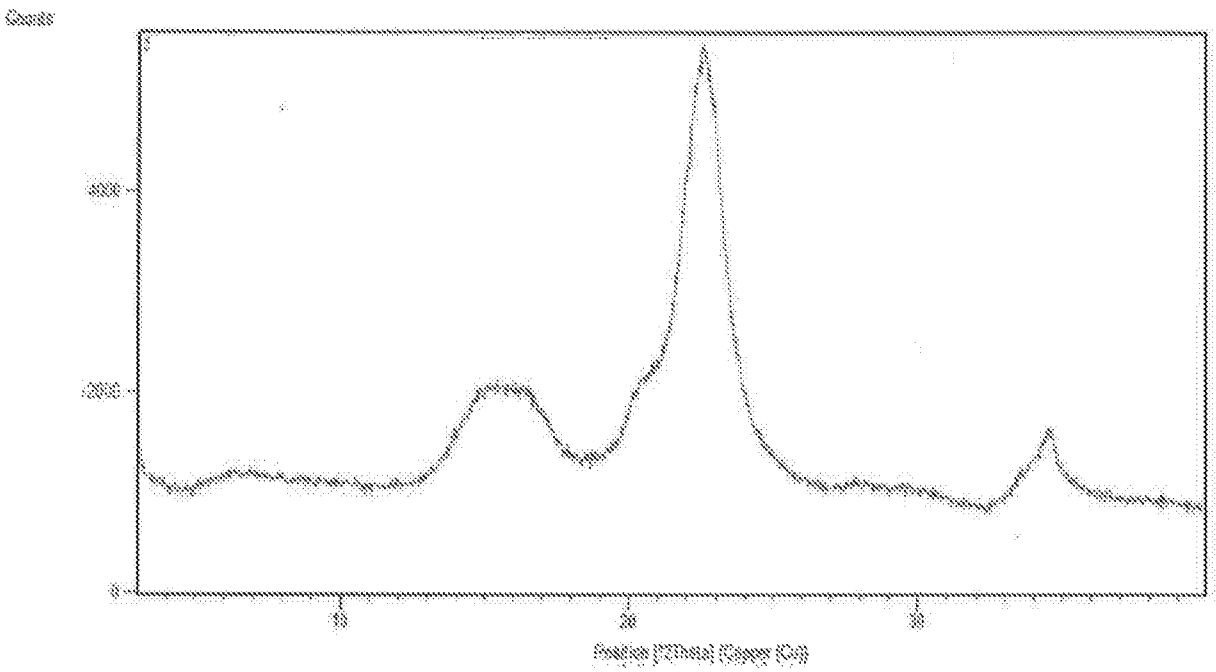


Figure 4

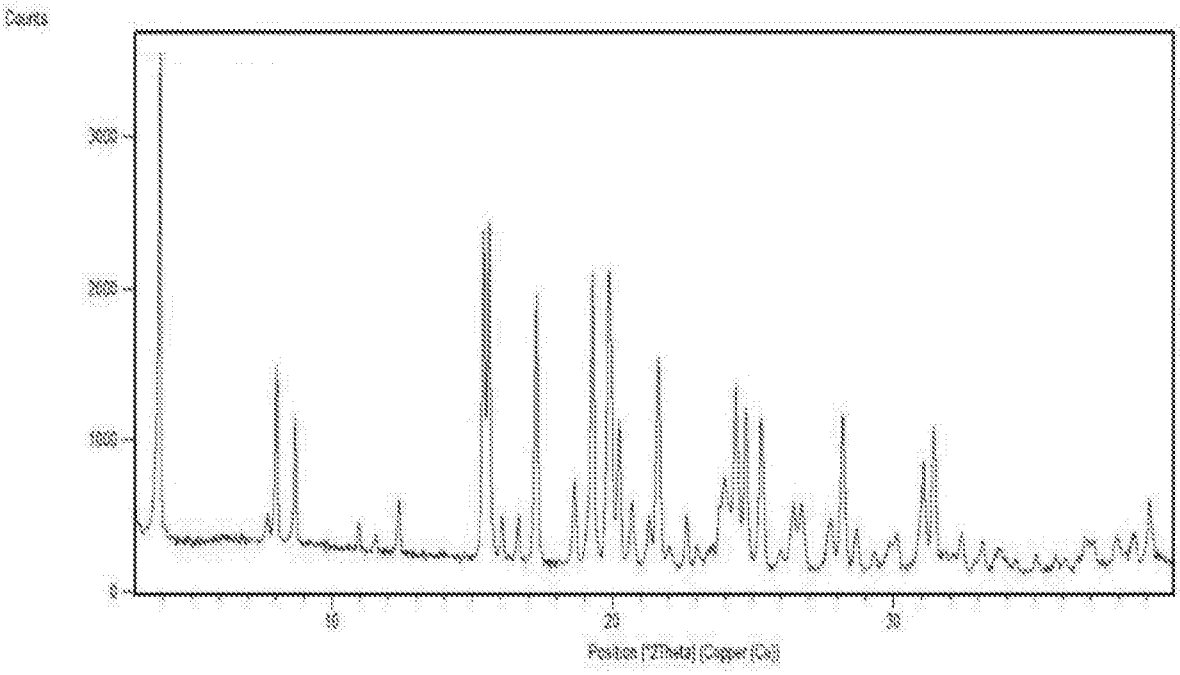


Figure 5

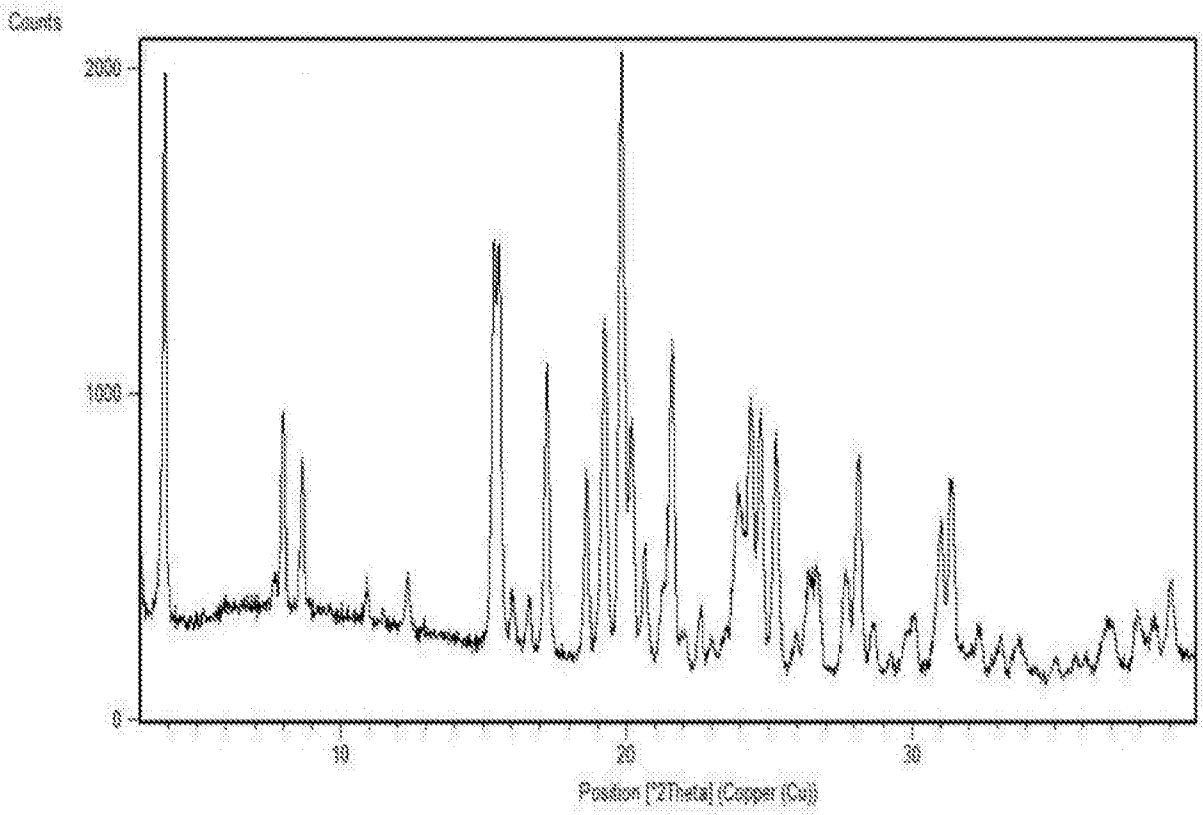


Figure 6

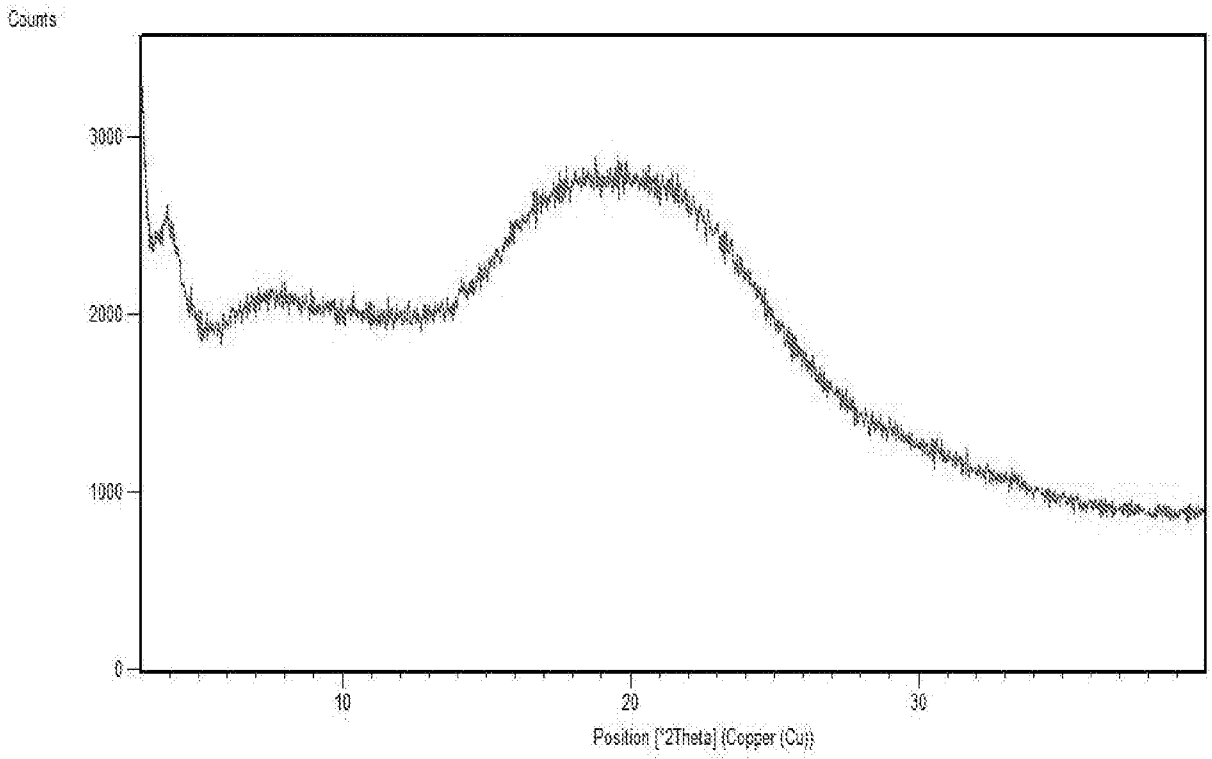


Figure 7

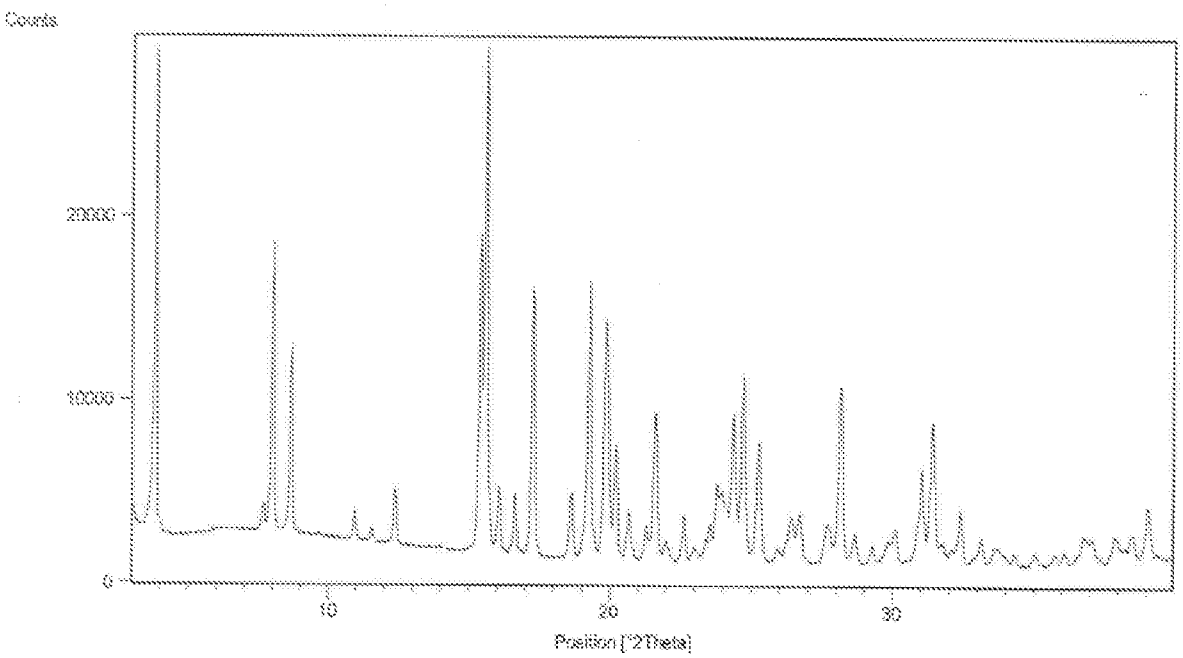


Figure 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/055309

A. CLASSIFICATION OF SUBJECT MATTER
C07C43/225,C07C41/18,C07C49/84 Version=2016.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C

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

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

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D1: WO2015011113 A1, 29 Jan 2015, SANDOZ AG Abstract and page 19-21	5
X	D2: WO 2015128853 A1, 03 Sep 2015, SUN PHARMACEUTICAL INDUSTRIES LIMITED abstract and claims	5
X	D3: WO2008002824, 03 Jan 2008, BRISTOL-MYERS SQUIBB COMPANY Claims 48-50, example 13-14	8-10
A	D4: CN104478839 A, 1 Apr 2015, SUZHOU JONATHAN NEW MATERIALS TECHNOLOGY CO LTD paragraph [0004] and abstract	1-4, 6-7
A	D5: US 2004/0138439 A1, 15 Jul 2004, BRISTOL-MYERS SQUIBB COMPANY paragraph [0010] and example 17	1-4, 6-7

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"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

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Date of the actual completion of the international search	Date of mailing of the international search report
25-11-2016	25-11-2016

Name and mailing address of the ISA/	Authorized officer
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Facsimile No.	Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2016/055309

Citation	Pub.Date	Family	Pub.Date
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