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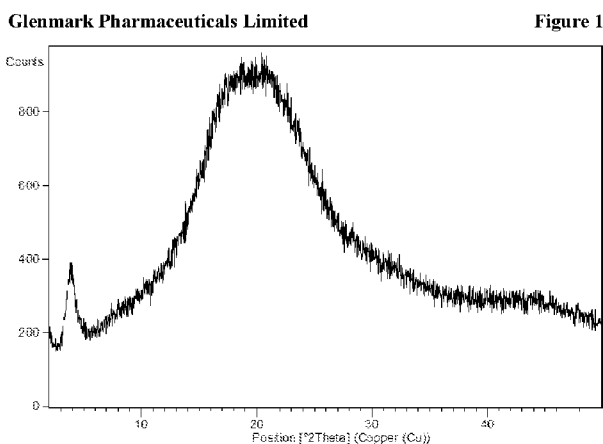
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
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[Continued on next page]

(54) Title: PROCESS FOR PREPARATION OF DAPAGLIFLOZIN



(57) Abstract: The present invention relates to a process for the preparation of amorphous dapagliflozin. The present invention relates to 2,3-butanediol solvate of dapagliflozin and process for its preparation.

- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

PROCESS FOR PREPARATION OF DAPAGLIFLOZIN

PRIORITY

[0001] This application claims the benefit of Indian Provisional Applications 1790/MUM/2015 filed on May 5, 2015 and 201621002175 filed on January 20, 2016, 5 entitled "PROCESS FOR PREPARATION OF DAPAGLIFLOZIN", the contents of which are incorporated herein by reference.

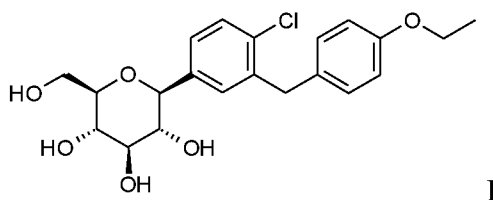
BACKGROUND OF THE INVENTION

Technical Field

[0002] The present invention relates to a process for the preparation of amorphous 10 dapagliflozin. The present invention relates to 2,3-butanediol solvate of dapagliflozin and process for its preparation.

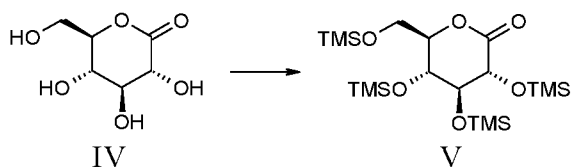
Description of the Related Art

[0003] Dapagliflozin, also known as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, is represented by the structure of formula I.



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[0004] The process for the preparation of dapagliflozin involves the step of silylation of D-glucono-1,5-lactone, a compound of formula IV to give 2,3,4,6-tetra-O-(trimethylsilyl)-D-glucono-1,5-lactone, a compound of formula V.



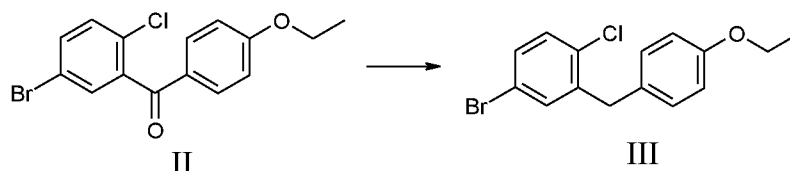
20 [0005] The processes known in the art involve use of trimethylsilyl chloride (TMSCl) for silylation of the compound of formula IV. The present invention provides a process wherein hexamethyldisilazane (HMDS) is used instead of TMSCl for silylation of the compound of formula IV. With use of HMDS, the by-product is ammonia which does not degrade the product. Further, with use of hexamethyldisilazane, the reaction becomes 25 one-pot and the work-up is easier as water is not used during work-up of the reaction.

[0006] The object of the present invention is to provide a process for the preparation of amorphous dapagliflozin with high purity.

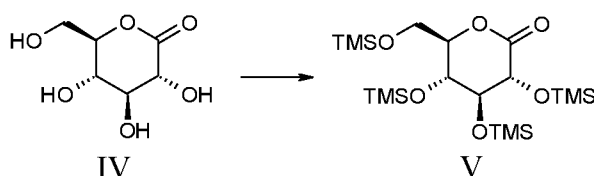
SUMMARY OF THE INVENTION

[0007] The present invention provides a process for the preparation of dapagliflozin in amorphous form, the process comprising:

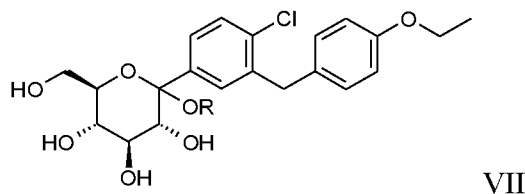
(a) reducing a compound of formula II to a compound of formula III in the presence of a Lewis acid;



(b) silylating a compound of formula IV with hexamethyldisilazane to form a compound of formula V;

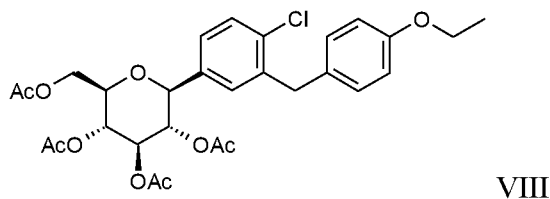


(c) reacting the compound of formula III with the compound of formula V in the presence of a strong base followed by treatment with an acid in the presence of an alcohol to prepare a compound of formula VII, wherein R is an alkyl group selected from C₁₋₅ alkyl;



(d) converting the compound of formula VII to dapagliflozin;

(e) acetylating dapagliflozin to give D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1S)-, a compound of formula VIII;



(f) optionally, purifying the compound of formula VIII with a solvent selected from halogenated hydrocarbons, alcohols, ethers, or mixtures thereof;

(g) hydrolyzing the compound of formula VIII obtained in step (f) to give dapagliflozin;

(h) dissolving dapagliflozin of step (g) in a solvent selected from halogenated hydrocarbons, alcohols, hydrocarbons, or mixtures thereof to form a solution; and

(i) recovering amorphous dapagliflozin from the solution of step (h).

[0008] In another embodiment, the present invention provides a process for the preparation of dapagliflozin in amorphous form, the process comprising:

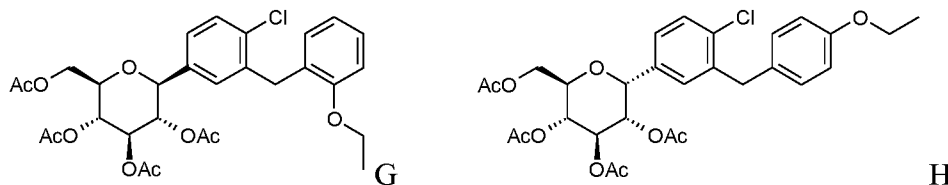
(i) dissolving dapagliflozin in isopropyl alcohol to form a solution;

(ii) optionally, completely evaporating isopropyl alcohol from the solution of step (i) to give a residue;

(iii) adding cyclohexane to the solution of step (i) or the residue of step (ii); and

(iv) isolating amorphous dapagliflozin.

[0009] In another embodiment, the present invention provides a process for the preparation of D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1S)-, a compound of formula VIII, in a purity of $\geq 99.6\%$ and wherein the level of impurity G and impurity H is less than 0.15%,



the process comprising:

(a) treating the compound of formula VIII with an ether solvent to form a reaction mass;

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

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

(d) obtaining the compound of formula VIII from the reaction mass of step (c);

(e) optionally, crystallizing the compound of formula VIII obtained in step (d) with an alcohol solvent; and

(f) isolating the compound of formula VIII with a purity of $\geq 99.6\%$ and wherein the level of impurity G and impurity H is less than 0.15%.

[0010] In another embodiment, the present invention provides a crystalline 2,3-butanediol solvate of dapagliflozin characterized by an X-ray powder diffraction (XRPD) spectrum having peak reflections at about 3.7, 9.6, 14.7, 16.7 and 18.4 ± 0.2 degrees 2 theta.

- 5 [0011] In another embodiment, the present invention provides a process for the preparation of crystalline 2,3-butanediol solvate of dapagliflozin, the process comprising:
- (a) treating dapagliflozin with 2,3-butanediol, optionally in the presence of a solvent, to form a solution;
 - (b) obtaining crystalline 2,3-butanediol solvate of dapagliflozin from the solution of step
 - 10 (a); and
 - (c) isolating the crystalline 2,3-butanediol solvate of dapagliflozin.

[0012] In another embodiment, the present invention provides a process for the preparation of dapagliflozin in amorphous form, the process comprising:

- (a) dissolving 2,3-butanediol solvate of dapagliflozin in a solvent to form a solution; and
- 15 (b) recovering dapagliflozin in amorphous form from the solution of step (a).

[0013] In another embodiment, the present invention provides use of 2,3-butanediol solvate of dapagliflozin in the preparation of amorphous dapagliflozin.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figure 1 is a characteristic XRPD of amorphous dapagliflozin as obtained in

20 example 42.

[0015] Figure 1 is a characteristic XRPD of amorphous dapagliflozin as obtained in example 42.

[0016] Figure 2 is a characteristic XRPD of premix of dapagliflozin and mannitol as obtained in example 11.

25 [0017] Figure 3 is a characteristic XRPD of premix of dapagliflozin and microcrystalline cellulose as obtained in example 12.

[0018] Figure 4 is a characteristic XRPD of crystalline 2,3-butanediol solvate of dapagliflozin as obtained in Example 13.

[0019] Figure 5 is a proton NMR spectrum of crystalline 2,3-butanediol solvate of

30 dapagliflozin as obtained in Example 13.

[0020] Figure 6 is a TGA thermogram of crystalline 2,3-butanediol solvate of dapagliflozin as obtained in Example 13.

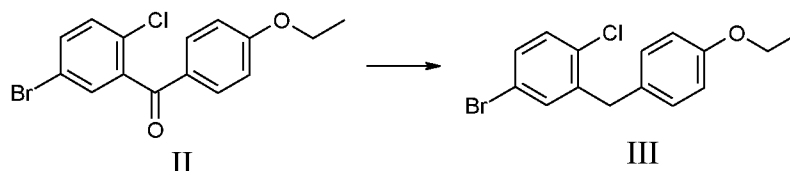
[0021] Figure 7 is an IR spectrum of crystalline 2,3-butanediol solvate of dapagliflozin as obtained in Example 13.

5 [0022] Figure 8 is a characteristic XRPD of dapagliflozin in amorphous form as obtained in Example 35.

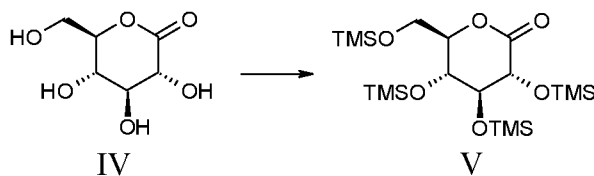
DETAILED DESCRIPTION OF THE INVENTION

[0023] The present invention provides a process for the preparation of dapagliflozin in amorphous form, the process comprising:

10 (a) reducing a compound of formula II to a compound of formula III in the presence of a Lewis acid;

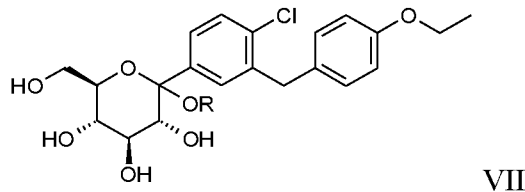


(b) silylating a compound of formula IV with hexamethyldisilazane to form a compound of formula V;

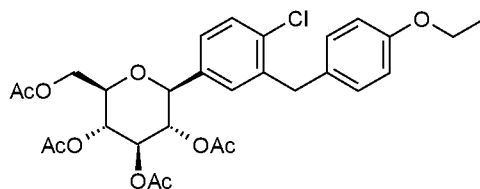


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(c) reacting the compound of formula III with the compound of formula V in the presence of a strong base followed by treatment with an acid in the presence of an alcohol to prepare a compound of formula VII, wherein R is an alkyl group selected from C₁₋₅ alkyl;



20 (d) converting the compound of formula VII to dapagliflozin;
 (e) acetylating dapagliflozin to give D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1S)-, a compound of formula VIII;



(f) optionally, purifying the compound of formula VIII with a solvent selected from halogenated hydrocarbons, alcohols, ethers, or mixtures thereof;

(g) hydrolyzing the compound of formula VIII obtained in step (f) to give dapagliflozin;

5 (h) dissolving dapagliflozin of step (g) in a solvent selected from halogenated hydrocarbons, alcohols, hydrocarbons, or mixtures thereof to form a solution; and

(i) recovering amorphous dapagliflozin from the solution of step (h).

[0024] In the present application, the term “room temperature” means a temperature of about 25°C to about 30°C.

10 [0025] In (a) of the process for the preparation of dapagliflozin in amorphous form, the compound of formula II is reduced to the compound of formula III in the presence of a Lewis acid.

[0026] The Lewis acid may be selected from the group consisting of aluminium chloride, boron trifluoride, titanium tetrachloride and ferric chloride.

15 [0027] The reaction may be performed in the presence of a suitable solvent. The suitable solvent may include a nitrile such as acetonitrile, propionitrile and the like; an ester such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, tert-butyl acetate and the like; a halogenated hydrocarbon such as methylene dichloride, chloroform, ethylene dichloride and the like; an ether such as dimethyl ether, diethyl ether, diisopropyl ether,
20 methyl tert-butyl ether, tetrahydrofuran, dioxane and the like; an aromatic hydrocarbon such as toluene and the like; an aliphatic hydrocarbon such as n-hexane, n-heptane and the like; dimethylformamide; dimethylsulfoxide; dimethylacetamide; N-methylpyrrolidone; water; or mixtures thereof.

[0028] The reduction of the compound of formula II may be performed with a reducing
25 agent, for example triethylsilane.

[0029] In one embodiment, step (a) comprises reducing the compound of formula II with triethylsilane in presence of boron trifluoride in a mixture of methylene dichloride and acetonitrile to give the compound of formula III. After completion of reaction, the

reaction mass is quenched with sodium bicarbonate solution. The layers may be separated and the aqueous layer may then be extracted with a solvent. The solvent used is as discussed supra, preferably an ester solvent like ethyl acetate. The extraction solvent may be removed. The mass obtained may be purified by a hydrocarbon solvent followed by an alcohol solvent. The hydrocarbon solvent may be an aromatic or an aliphatic hydrocarbon solvent as discussed supra, for example toluene and the alcohol solvent may include methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol and the like, for example methanol.

[0030] In (b) of the process for the preparation of dapagliflozin in amorphous form, the compound of formula IV is silylated with hexamethyldisilazane to form the compound of formula V.

[0031] The reaction may be performed in the presence of a suitable solvent. The suitable solvent may include a nitrile such as acetonitrile, propionitrile and the like; an ester such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, tert-butyl acetate and the like; a halogenated hydrocarbon such as methylene dichloride, chloroform, ethylene dichloride and the like; an ether such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane and the like; an aromatic hydrocarbon such as toluene and the like; an aliphatic hydrocarbon such as n-hexane, n-heptane and the like; dimethylformamide; dimethylsulfoxide; dimethylacetamide; N-methylpyrrolidone; water; or mixtures thereof.

[0032] In one embodiment, step (b) may be performed in presence of a suitable catalyst, for example iodine.

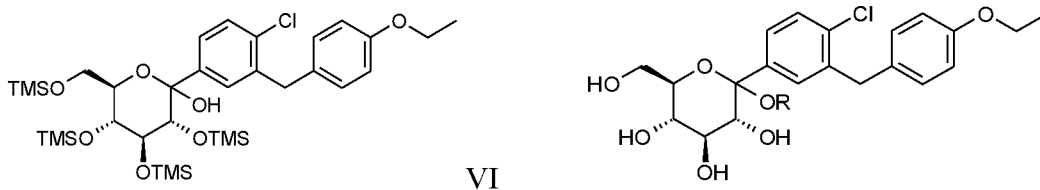
[0033] In one embodiment, step (b) comprises silylating the compound of formula IV with hexamethyldisilazane in presence of methylene dichloride as solvent and iodine as catalyst to form the compound of formula V. After completion of reaction, the reaction mass is filtered through hyflo bed and the filtrate is concentrated to remove the solvent. The compound of formula V is then distilled out under vacuum.

[0034] In (c) of the process for the preparation of dapagliflozin in amorphous form, the compound of formula III is reacted with the compound of formula V in the presence of a strong base.

[0035] The strong base may include an alkyl lithium such as methyl lithium, n-butyl lithium, lithium diisopropylamide and lithium bis(trimethylsilyl)amide.

[0036] The reaction may be performed in the presence of a suitable solvent. The suitable solvent may include a nitrile such as acetonitrile, propionitrile and the like; an ester such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, tert-butyl acetate and the like; a halogenated hydrocarbon such as methylene dichloride, chloroform, ethylene dichloride and the like; an ether such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane and the like; an aromatic hydrocarbon such as toluene and the like; an aliphatic hydrocarbon such as n-hexane, n-heptane and the like; dimethylformamide; dimethylsulfoxide; dimethylacetamide; N-methylpyrrolidone; water; or mixtures thereof.

[0037] In one embodiment, step (c) comprises reacting the compound of formula III with the compound of formula V in the presence of a strong base to obtain a compound of formula VI; and reacting the compound of formula VI with an acid in the presence of an alcohol to prepare the compound of formula VII wherein R is an alkyl group selected from C₁₋₅ alkyl



[0038] In one embodiment, the alcohol may be a C₁₋₅ alcohol. C₁₋₅ alcohol, for example, may include methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol, isobutyl alcohol, n-pentyl alcohol and the like.

[0039] In one embodiment, the acid may be a sulfonic acid which may include methanesulfonic acid, benzenesulfonic acid and the like.

[0040] In one embodiment, the acid used in step (c) is methanesulfonic acid.

[0041] In one embodiment, step (c) comprises reacting the compound of formula III with the compound of formula V in presence of n-butyl lithium in tetrahydrofuran, followed by treatment with methanesulfonic acid in presence of methanol to prepare the compound of formula VII, wherein R is methyl.

[0042] In one embodiment, step (c) comprises reacting the compound of formula III with the compound of formula V in presence of n-butyl lithium in tetrahydrofuran to prepare the compound of formula VI which is further reacted with methane sulfonic acid in presence of methanol to prepare the compound of formula VII, wherein R is methyl.

5 [0043] After treatment with methanesulfonic acid in methanol, the reaction mass may be basified with a base. The base used may be an inorganic base. The inorganic base may include an alkali or an alkaline earth metal hydroxide, an alkali or an alkaline earth metal carbonate and the like, for example sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and the like. The reaction mass may then be extracted
10 with a solvent. The solvent used is as discussed supra, preferably an ester solvent like ethyl acetate. The extraction solvent may be removed. The mass so obtained may be purified using a suitable solvent. The suitable solvent used is as discussed supra. In one embodiment, the solvent used for purification is a mixture of an aromatic and an aliphatic hydrocarbon, preferably a mixture of toluene and cyclohexane.

15 [0044] In one embodiment, the compound of formula V may be isolated before further treatment.

[0045] In one embodiment, the compound of formula VI may be isolated before further treatment.

20 [0046] In one embodiment, the compound of formula VII may be isolated before further treatment.

[0047] In one embodiment, the compound of formula VI may not be isolated.

[0048] In one embodiment, steps (b) and (c) may be performed as one-pot process.

[0049] In (d) of the process for the preparation of dapagliflozin in amorphous form, the compound of formula VII is converted to dapagliflozin.

25 [0050] The reaction may be carried out in the presence of a reducing agent, for example triethylsilane.

[0051] The reaction may be carried out in the presence of a Lewis acid selected from the group consisting of aluminium chloride, boron trifluoride, titanium tetrachloride and ferric chloride.

30 [0052] The reaction may be performed in the presence of a suitable solvent. The suitable solvent may include a nitrile such as acetonitrile, propionitrile and the like; an ester such

as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, tert-butyl acetate and the like; a halogenated hydrocarbon such as methylene dichloride, chloroform, ethylene dichloride and the like; an ether such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane and the like; an aromatic hydrocarbon such as toluene and the like; an aliphatic hydrocarbon such as n-hexane, n-heptane and the like; dimethylformamide; dimethylsulfoxide; dimethylacetamide; *N*-methylpyrrolidone; water; or mixtures thereof.

[0053] In one embodiment, step (d) comprises reducing the compound of formula VII with triethylsilane in presence of boron trifluoride in a mixture of methylene dichloride and acetonitrile to give dapagliflozin. After completion of reaction, the reaction mass is quenched with sodium bicarbonate solution. The layers may be separated and the aqueous layer may then be extracted with a solvent. The solvent used is as discussed supra, preferably an ester solvent like ethyl acetate. The extraction solvent may be removed.

[0054] In (e) of the process for the preparation of dapagliflozin in amorphous form, dapagliflozin is acetylated to give D-glucitol, 1,5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1*S*)-, the compound of formula VIII.

[0055] The acetylating agent includes, but is not limited to acetyl chloride, acetic anhydride.

[0056] The reaction may be carried out in the presence of a suitable base. The suitable base includes, but is not limited to alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide; alkaline earth metal hydroxides; alkali metal carbonates such as sodium carbonate, potassium carbonate, alkaline earth metal carbonates; alkali metal bicarbonates such as sodium bicarbonate; tertiary amines such as triethylamine, *N,N*-diisopropylethylamine; ammonia, pyridine, piperidine, 4-dimethylaminopyridine. Preferably the base selected is *N,N*-diisopropylethylamine, 4-dimethylaminopyridine.

[0057] The reaction may be carried out in the presence of a suitable solvent. The suitable solvent includes, but is not limited to halogenated hydrocarbons such as methylene dichloride, chloroform and the like; ethers such as dimethyl ether, diethyl ether, diisopropyl ether, tert-butyl methyl ether, tetrahydrofuran, dioxane and the like;

hydrocarbons such as toluene, xylene and the like; dimethylsulfoxide; dimethylformamide; dimethylacetamide; *N*-Methyl-2-pyrrolidone; or mixtures thereof. Preferably the solvent selected is methylene dichloride.

5 [0058] In one embodiment, step (e) comprises acetylating dapagliflozin using acetic anhydride and *N,N*-diisopropylethylamine in presence of 4-dimethylaminopyridine in methylene dichloride. After completion of reaction, the reaction mass may be quenched with water. The organic layer may be separated, washed with sodium bicarbonate solution and concentrated.

10 [0059] In one embodiment, the compound of formula VIII is optionally purified with a solvent selected from halogenated hydrocarbons, alcohols, ethers, or mixtures thereof.

[0060] In (f) of the process for the preparation of dapagliflozin in amorphous form, the compound of formula VIII is purified with a solvent selected from halogenated hydrocarbons, alcohols, ethers, or mixtures thereof.

15 [0061] In one embodiment, halogenated hydrocarbons may include methylene dichloride, chloroform, ethylene dichloride and the like; alcohols may include methanol, ethanol, *n*-propyl alcohol, isopropyl alcohol, *n*-butyl alcohol and the like; and ethers may include dimethyl ether, diethyl ether, diisopropyl ether, methyl *tert*-butyl ether, tetrahydrofuran, dioxane and the like.

[0062] In one embodiment, the alcohol is methanol and the ether is diisopropyl ether.

20 [0063] In one embodiment, the present invention provides a process for the purification of the compound of formula VIII, the process comprising:

- (i) treating the compound of formula VIII with methanol to form a reaction mass;
- (ii) heating the reaction mass of step (i);
- (iii) cooling the reaction mass of step (ii);
- 25 (iv) isolating the compound of formula VIII from the reaction mass of step (iii);
- (v) treating the compound of formula VIII obtained in step (iv) with diisopropyl ether to form a reaction mass;
- (vi) heating the reaction mass of step (v);
- (vii) cooling the reaction mass of step (vi);
- 30 (viii) isolating the compound of formula VIII from the reaction mass of step (vii);

(ix) treating the compound of formula VIII obtained in step (viii) with methanol to form a reaction mass;

(x) heating the reaction mass of step (ix);

(xi) cooling the reaction mass of step (x);

5 (xii) isolating the compound of formula VIII from the reaction mass of step (xi).

[0064] The reaction mass of step (ii) may be optionally treated with charcoal and filtered.

[0065] In (g) of the process for the preparation of dapagliflozin in amorphous form, the compound of formula VIII obtained in step (f) is hydrolyzed to give dapagliflozin.

[0066] The reaction may be carried out in the presence of a suitable base. The suitable
10 base includes, but is not limited to alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide; alkaline earth metal hydroxides; alkali metal carbonates such as sodium carbonate, potassium carbonate, caesium carbonate; alkaline earth metal carbonates; alkali metal bicarbonates such as sodium bicarbonate. Preferably the base selected is sodium hydroxide.

[0067] The reaction may be carried out in the presence of a suitable solvent. The suitable
15 solvent includes, but is not limited to alcohols such as methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol and the like; ethers such as tetrahydrofuran, dioxane and the like; esters such as methyl acetate, ethyl acetate, n-propyl acetate, tert-butyl acetate and the like; halogenated hydrocarbons such as methylene dichloride, chloroform, ethylene dichloride and the like; water or mixtures thereof. Preferably the
20 solvent selected is tetrahydrofuran-methanol-water mixture.

[0068] In one embodiment, step (g) comprises hydrolyzing the compound of formula VIII obtained in step (f) in presence of sodium hydroxide in tetrahydrofuran-methanol-water mixture. After completion of reaction, the reaction mass may be concentrated and
25 treated with aqueous hydrochloric acid. The reaction mass may then be extracted with a solvent. The solvent used is as discussed supra, preferably a halogenated hydrocarbon solvent like methylene dichloride. The extraction solvent may be removed to give dapagliflozin.

[0069] In (h) of the process for the preparation of dapagliflozin in amorphous form,
30 dapagliflozin of step (g) is dissolved in a solvent selected from halogenated hydrocarbons, alcohols, hydrocarbons, or mixtures thereof to form a solution.

[0070] In one embodiment, the halogenated hydrocarbon solvent may include methylene dichloride, chloroform, ethylene dichloride and the like; the alcohol solvent may include methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol and the like; and the hydrocarbon solvent may be an aromatic or an aliphatic hydrocarbon solvent such as
5 toluene, n-hexane, n-heptane, cyclohexane and the like.

[0071] In one embodiment, the alcohol is isopropyl alcohol and the hydrocarbon is cyclohexane.

[0072] Suitable temperature for dissolution of dapagliflozin in the solvent may range from about 25°C to about the reflux temperature of the solvent. Stirring may be continued
10 for any desired time period to achieve a complete dissolution of the compound. The stirring time may range from about 30 minutes to about 1 hour, or longer. The solution may be optionally treated with charcoal and filtered to get a particle-free solution.

[0073] In (i) of the process for the preparation of dapagliflozin in amorphous form, amorphous dapagliflozin is recovered from the solution of step (h).

15 [0074] In one embodiment, dapagliflozin in amorphous form is recovered by removing the solvent from the solution obtained in step (h). Removal of solvent may be accomplished by substantially complete evaporation of the solvent or concentrating the solution, cooling the solution if required and filtering the obtained solid. The solution may also be completely evaporated in, for example, a rotavapor, a vacuum paddle dryer
20 or in a conventional reactor under vacuum above about 720mm Hg, or evaporated by lyophilisation, freeze-drying technique, spray drying, fluid bed drying, flash drying, spin flash drying, thin-film drying.

[0075] In one embodiment, dapagliflozin in amorphous form is recovered by adding an anti-solvent to the solution obtained in step (h) to form a mixture and optionally, cooling
25 and stirring the obtained mixture. The stirring time may range from about 30 minutes to about 10 hours, or longer. The temperature may range from about 0°C to about 30°C.

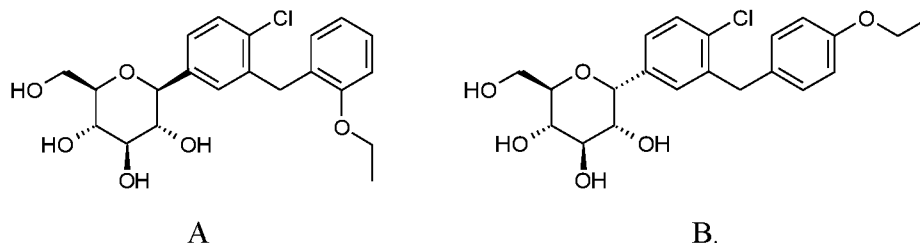
[0076] The anti-solvent is selected such that dapagliflozin in amorphous form is precipitated out from the solution.

[0077] In one embodiment, dapagliflozin is dissolved in isopropyl alcohol to form a
30 solution. Cyclohexane was then added to the solution and the obtained mixture was stirred and filtered to give amorphous dapagliflozin.

[0078] In one embodiment, dapagliflozin is dissolved in isopropyl alcohol to form a solution. The solution was then concentrated by completely evaporating isopropyl alcohol from the solution to obtain a residue. To the residue, cyclohexane was added and the obtained mixture was stirred and filtered to give amorphous dapagliflozin.

5 [0079] In one embodiment, the amorphous dapagliflozin is jet milled.

[0080] In one embodiment, the amorphous dapagliflozin is obtained in a purity of $\geq 99.8\%$ and wherein the level of impurity A and impurity B is less than 0.15%

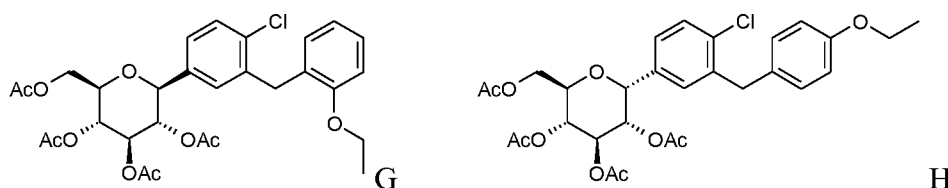


10 [0081] In one embodiment, the present invention provides a process for the preparation of dapagliflozin in amorphous form, the process comprising:

- (i) dissolving dapagliflozin in isopropyl alcohol to form a solution;
- (ii) optionally, completely evaporating isopropyl alcohol from the solution of step (i) to give a residue;
- 15 (iii) adding cyclohexane to the solution of step (i) or the residue of step (ii); and
- (iv) isolating amorphous dapagliflozin.

[0082] The amorphous dapagliflozin is isolated by any method known in the art. The method, may involve any of techniques, known in the art, including filtration by gravity or by suction, centrifugation, and the like.

20 [0083] In one embodiment, the present invention provides a process for the preparation of D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1S)-, a compound of formula VIII, in a purity of $\geq 99.6\%$ and wherein the level of impurity G and impurity H is less than 0.15%,



25 the process comprising:

- (a) treating the compound of formula VIII with an ether solvent to form a reaction mass;

- (b) heating the reaction mass of step (a);
(c) cooling the reaction mass of step (b);
(d) obtaining the compound of formula VIII from the reaction mass of step (c);
(e) optionally, crystallizing the compound of formula VIII obtained in step (d) with an
5 alcohol solvent; and
(f) isolating the compound of formula VIII with a purity of $\geq 99.6\%$ and wherein the level of impurity G and impurity H is less than 0.15%.

[0084] In one embodiment, the ether solvent may include diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane and the like; the alcohol solvent may
10 include methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol and the like.

[0085] In one embodiment, the alcohol is methanol and the ether is diisopropyl ether.

[0086] In one embodiment, the process further comprises converting the compound of formula VIII to amorphous dapagliflozin as discussed supra.

15 [0087] In one embodiment, the present invention provides use of the compound of formula VIII, as obtained by above process, in the preparation of dapagliflozin.

[0088] The present invention provides the compound of formula VIII wherein the level of impurity G and impurity H is less than 0.15% w/w relative to the amount of the compound of formula VIII, obtained by above process, as analyzed by chemical purity
20 using high performance liquid chromatography (HPLC) with the conditions described below:

Reagents and Solvents: Sodium perchlorate monohydrate (AR grade), Perchloric acid 70% (AR grade), Acetonitrile (HPLC grade), Water (Milli Q or equivalent)

Chromatographic Conditions:

25 Apparatus: A High Performance Liquid Chromatograph equipped with quaternary gradient pumps, variable wavelength UV detector attached with data recorder and integrator software.

Column: Inertsil ODS 3V, 250 x 4.6mm, 5 μ ; Column temperature: 25°C

Sample Cooler temperature: 25°C

30 Mobile Phase A: Buffer; Buffer: 0.01M Sodium perchlorate monohydrate in water. Adjust pH 2.5 with diluted Perchloric acid.

Mobile Phase B: Acetonitrile

Time (min.)	% Mobile Phase A	% Mobile Phase B
0.01	70	30
30	60	40
35	50	50
70	15	85
85	15	85
95	70	30

Diluent: Acetonitrile: Water (1: 1, v/v)

Flow Rate: 1.0 mL/min

5 Detection: UV 220nm

Injection Volume: 10 μ L

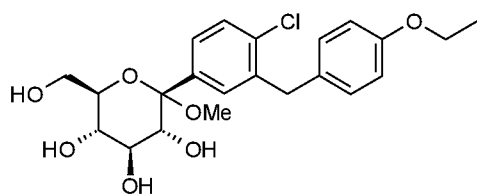
The retention time of the compound of formula VIII is about 61.0 minutes under these conditions.

10 Relative retention time for impurity G is about 1.03 and impurity H is about 1.05 with respect to the compound of formula VIII.

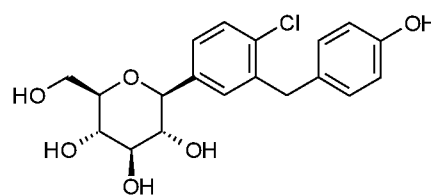
[0089] In one embodiment, the present invention provides a process for the purification of dapagliflozin wherein, the process comprises purification of crude dapagliflozin from a halogenated hydrocarbon. The halogenated hydrocarbon used may include methylene dichloride, chloroform, ethylene dichloride and the like.

15 [0090] In one embodiment, crude dapagliflozin is purified from methylene dichloride.

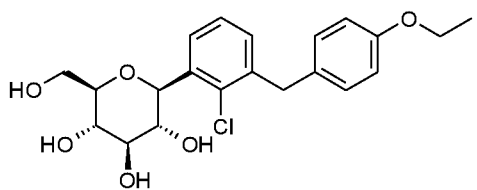
[0091] In one embodiment, the present invention provides dapagliflozin substantially free of the following compounds:



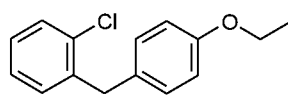
VII (R=Me)



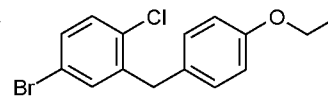
C



D

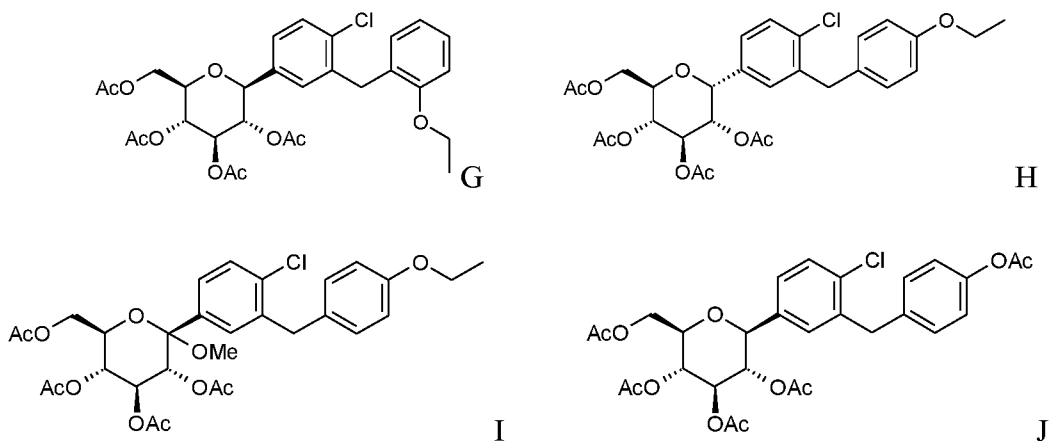


E



F

20



[0092] “Substantially free”, as used herein implies that the compounds VII and C - J are each present to an extent of less than 0.5% relative to the amount of dapagliflozin, preferably less than 0.15%, more preferably absent.

[0093] The process for the preparation of the compound of formula III leads to the formation of a side-product namely, 5-bromo-2-chloro-2'-ethoxydiphenylmethane, which leads to the formation of impurity A and impurity G in the subsequent steps of preparing dapagliflozin. The impurity A and impurity G are isolated by preparative HPLC.

[0094] Impurity B may be prepared by reacting the compound of formula VII with a reducing agent in the presence of a Lewis acid at room temperature. The impurity B is purified by preparative HPLC. Impurity H may be formed by acetylation of impurity B.

[0095] Impurity C may be prepared by treating dapagliflozin with Lewis acid such as boron tribromide and the like.

[0096] Impurity D may be prepared by starting from 3-bromo-2-chlorobenzoic acid instead of 5-bromo-2-chlorobenzoic acid and by following similar steps as for preparation of dapagliflozin.

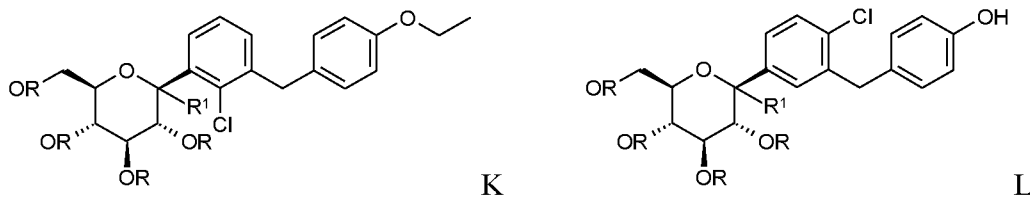
[0097] Impurity E may be prepared by reacting 2-chlorobenzoic acid with thionyl chloride to give 2-chlorobenzoyl chloride which on reaction with ethoxybenzene in presence of aluminium chloride gives impurity E.

[0098] Impurity I may be prepared by acetylation of the compound of the formula VII.

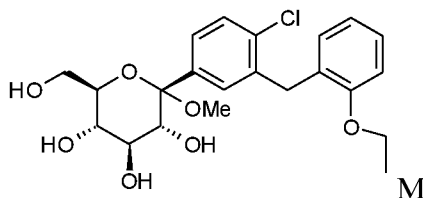
[0099] Impurity J may be prepared by treatment of the compound of formula VIII with Lewis acid such as boron tribromide, followed by acetylation step to give impurity J.

[0100] In one embodiment, the present invention provides the compound of formula VIII substantially free of compounds E, F, G, H, I and J.

[0101] In one embodiment, the present invention provides dapagliflozin free of any of the below listed impurities K – M.



wherein in K and L, R = H, Ac; R¹ = H, -OCH₃; and when R = H then R¹ = -OCH₃



5

[0102] In one embodiment, the present invention provides a premix comprising dapagliflozin and a pharmaceutically acceptable carrier.

[0103] The pharmaceutically acceptable carrier may be selected from the group consisting of a cellulose derivative such as croscarmellose sodium, microcrystalline cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), hydroxymethylethylcellulose (HEMC), ethylcellulose (EC), methylcellulose (MC), cellulose esters, cellulose glycolate, hydroxypropyl methyl cellulose phthalate, polymethylacrylate (HPMCP), hypromellose; vinylpyrrolidone polymer such as polyvinylpyrrolidone and polyols such as mannitol, sorbitol and the like; sugars such as lactose.

15

[0104] In one embodiment, the present invention provides a process for the preparation of a premix comprising dapagliflozin and a pharmaceutically acceptable carrier selected from the group consisting of mannitol, microcrystalline cellulose, or mixtures thereof, the process comprising:

20

- (a) dissolving dapagliflozin in a solvent;
- (b) adding a pharmaceutically acceptable carrier to the solution prepared in step (a); and
- (c) removing the solvent from the mixture obtained in step (b).

[0105] In one embodiment, the removal of solvent in step (c) may be performed by techniques known in the art. The techniques used may include vacuum evaporation, fluid bed drying, spray drying, freeze drying, vacuum drying, tray drying and the like.

25

[0106] In one embodiment, dissolution of dapagliflozin in the solvent may be carried out at a temperature of about 20°C to about 30°C. If required, the dissolution may be performed under heating. The pharmaceutically acceptable carrier may then be added at a temperature of about 20°C to about 30°C and the reaction mixture may optionally be heated. The solvent may then be removed and optionally the residue may be degassed to obtain the premix.

[0107] In one embodiment, the present invention provides a premix of dapagliflozin and mannitol.

[0108] In one embodiment, the present invention provides a premix of dapagliflozin and microcrystalline cellulose.

[0109] In one embodiment, the present invention provides a premix of dapagliflozin and mannitol characterized by X-ray powder diffraction pattern which is substantially in accordance with Figure 2.

[0110] In one embodiment, the present invention provides a premix of dapagliflozin and microcrystalline cellulose characterized by X-ray powder diffraction pattern which is substantially in accordance with Figure 3.

[0111] In one embodiment, the present invention provides a premix of dapagliflozin with mannitol wherein, the premix contains substantially amorphous dapagliflozin.

[0112] In one embodiment, the present invention provides a premix of dapagliflozin with mannitol wherein, the premix contains substantially amorphous dapagliflozin in stable form.

[0113] In one embodiment, the present invention provides a premix of dapagliflozin with microcrystalline cellulose wherein, the premix contains substantially amorphous dapagliflozin.

[0114] In one embodiment, the present invention provides a premix of dapagliflozin with microcrystalline cellulose wherein, the premix contains substantially amorphous dapagliflozin in stable form.

[0115] As used herein, “substantially amorphous dapagliflozin” has less than about 50% crystalline dapagliflozin. In one embodiment, substantially amorphous dapagliflozin has less than about 30% crystalline dapagliflozin. In one embodiment, substantially amorphous dapagliflozin has less than about 20% crystalline dapagliflozin. Preferably,

the substantially amorphous dapagliflozin has less than about 15% crystalline dapagliflozin.

[0116] As used herein, “substantially amorphous dapagliflozin in stable form” implies substantially amorphous dapagliflozin which is stable for a period of 6 months when kept
5 under conditions of temperature of about 2°C to about 8°C and ambient temperature (about 20°C to about 30°C).

[0117] The present invention provides a crystalline 2,3-butanediol solvate of dapagliflozin characterized by an X-ray powder diffraction (XRPD) spectrum having peak reflections at about 3.7, 9.6, 14.7, 16.7 and 18.4 ± 0.2 degrees 2 theta.

10 [0118] The present invention provides a crystalline 2,3-butanediol solvate of dapagliflozin characterized by an X-ray powder diffraction (XRPD) pattern as depicted in Figure 1, a TGA thermogram as depicted in Figure 3, an IR spectrum as depicted in Figure 4.

[0119] In one embodiment, the present invention provides a crystalline 2,3-butanediol
15 solvate of dapagliflozin characterized by TGA thermogram, showing a weight loss of about 18 weight% to 26 weight% up to 250°C determined over the temperature range of 0°C to 350°C and heating rate 10°C/min.

[0120] In one embodiment, the present invention provides a crystalline 2,3-butanediol
20 solvate of dapagliflozin characterized by TGA thermogram, showing a weight loss of about 18 weight% to 26 weight% up to 250°C determined over the temperature range of 0°C to 350°C and heating rate 10°C/min which is in accordance with Figure 3.

[0121] In one embodiment, the present invention provides a crystalline 2,3-butanediol
25 monohydrate of dapagliflozin characterized by TGA thermogram, showing a weight loss of about 24.3 weight% up to 250°C determined over the temperature range of 0°C to 350°C and heating rate 10°C/min which corresponds to one mole of water and one mole of butanediol per mole of structure analyzed.

[0122] In one embodiment, the crystalline 2,3-butanediol solvate of dapagliflozin is a mono-butanediol solvate of dapagliflozin (1:1 solvate).

[0123] In one embodiment, the crystalline 2,3-butanediol solvate of dapagliflozin is in
30 the form of a hydrate.

[0124] In one embodiment, the crystalline 2,3-butanediol solvate of dapagliflozin is in the form of a monohydrate.

[0125] In one embodiment, the crystalline 2,3-butanediol solvate of dapagliflozin is in the form of a dihydrate.

5 [0126] In one embodiment, the present invention provides a crystalline 2,3-butanediol solvate of dapagliflozin characterized by a proton NMR spectrum having peak positions at 7.40-7.25 (m,2H), 7.25-7.18 (d,1H), 7.12-7.00 (d,2H), 6.81-6.75 (d,2H), 4.97 (brs,2H), 4.84 (brs,1H), 4.46 (brs,1H), 4.32 (brs,2H), 4.10-3.90 (m,4H), 3.80-3.60 (m,1H), 3.55-3.05 (m,8H), 1.29 (t,3H), 1.05-0.85 (m,6H) ppm.

10 [0127] In one embodiment, the present invention provides a crystalline 2,3-butanediol solvate of dapagliflozin characterized by DSC thermogram having an endothermic peak at about $61 \pm 2^\circ\text{C}$.

[0128] In another embodiment, the present invention provides a process for the preparation of crystalline 2,3-butanediol solvate of dapagliflozin, the process comprising:

- 15 (a) treating dapagliflozin with 2,3-butanediol, optionally in the presence of a solvent, to form a solution;
- (b) obtaining crystalline 2,3-butanediol solvate of dapagliflozin from the solution of step (a); and
- (c) isolating the crystalline 2,3-butanediol solvate of dapagliflozin.

20 [0129] In (a) of the process for the preparation of crystalline 2,3-butanediol solvate of dapagliflozin, dapagliflozin is treated with 2,3-butanediol, optionally in the presence of a solvent, to form a solution.

[0130] The 2,3-butanediol used may be the (2*R*,3*R*)-enantiomer, or the (2*S*,3*S*)-enantiomer, or the meso compound (2*R*,3*S*) (or equivalently (2*S*,3*R*)), or the racemic
25 compound. Preferably, racemic 2,3-butanediol is used.

[0131] The solvent includes but is not limited to haloalkanes such as dichloromethane, chloroform, ethylene dichloride, and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; alcohols such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 1-octanol and the like; ethers
30 such as diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane and the like; esters such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl

acetate, butyl acetate, tert-butyl acetate and the like; hydrocarbons such as toluene, xylene, chlorobenzene, heptane, hexane, cyclohexane and the like; dimethyl sulfoxide; dimethyl formamide; dimethyl acetamide; water; or mixtures thereof.

5 [0132] The reaction may be carried out at a temperature in the range from about 20°C to about 120°C. Preferably, the reaction is carried out at about 25°C to about 80°C. The stirring time may range from about 30 minutes to about 10 hours, or longer. The solution may be optionally treated with charcoal and filtered to get a particle-free solution.

10 [0133] In (b) of the process for the preparation of crystalline 2,3-butanediol solvate of dapagliflozin, crystalline 2,3-butanediol solvate of dapagliflozin is obtained from the solution of step (a).

[0134] In one embodiment, the step (b) of obtaining crystalline 2,3-butanediol solvate of dapagliflozin comprises:

- (i) optionally cooling and stirring the solution obtained in (a); or
- (ii) removing the solvent from the solution obtained in (a); or
- 15 (iii) treating the solution of step (a) with an anti-solvent to form a mixture and optionally, cooling and stirring the obtained mixture.

20 [0135] In (i) of the above process, crystalline 2,3-butanediol solvate of dapagliflozin is obtained by optionally cooling and stirring the solution obtained in step (a). The stirring time may range from about 30 minutes to about 10 hours, or longer. The temperature may range from about 0°C to about 90°C.

25 [0136] In (ii) of the above process, crystalline 2,3-butanediol solvate of dapagliflozin is obtained by removing the solvent from the solution obtained in step (a). Removal of solvent may be accomplished by substantially complete evaporation of the solvent or concentrating the solution, cooling the solution if required and filtering the obtained solid. The solution may be completely evaporated in, for example, a rotavapor, a vacuum paddle dryer or in a conventional reactor under vacuum above about 720mm Hg, or evaporated by lyophilisation, freeze-drying technique, spray drying, fluid bed drying, flash drying, spin flash drying, thin-film drying. The solution may also be completely evaporated as discussed supra, adding a second solvent, optionally cooling and stirring

30 the obtained mixture and filtering the obtained solid.

[0137] The second solvent includes but is not limited to haloalkanes such as dichloromethane, chloroform, ethylene dichloride, and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; alcohols such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 1-octanol and the like; ethers such as diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane and the like; esters such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, butyl acetate, tert-butyl acetate and the like; hydrocarbons such as toluene, xylene, chlorobenzene, heptane, hexane, cyclohexane and the like; dimethyl sulfoxide; dimethyl formamide; dimethyl acetamide; water; or mixtures thereof.

[0138] In (iii) of the above process, crystalline 2,3-butanediol solvate of dapagliflozin is obtained by adding an anti-solvent to the solution obtained in step (a) to form a mixture and optionally, cooling and stirring the obtained mixture. The stirring time may range from about 30 minutes to about 10 hours, or longer. The temperature may range from about 0°C to about 90°C.

[0139] The anti-solvent is selected such that crystalline 2,3-butanediol solvate dapagliflozin is precipitated out from the solution.

[0140] The anti-solvent includes but is not limited to haloalkanes such as dichloromethane, chloroform, ethylene dichloride, and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; alcohols such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 1-octanol and the like; ethers such as diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane and the like; esters such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, butyl acetate, tert-butyl acetate and the like; hydrocarbons such as toluene, xylene, chlorobenzene, heptane, hexane, cyclohexane and the like; dimethyl sulfoxide; dimethyl formamide; dimethyl acetamide; water; or mixtures thereof.

[0141] In (c) of the process for the preparation of crystalline 2,3-butanediol solvate of dapagliflozin, the crystalline 2,3-butanediol solvate of dapagliflozin is isolated by any method known in the art. The method, may involve any of techniques, known in the art, including filtration by gravity or by suction, centrifugation, and the like.

[0142] In one embodiment, the crystalline 2,3-butanediol solvate of dapagliflozin obtained by the above process is a mono-butanediol solvate of dapagliflozin (1:1 solvate).

[0143] In one embodiment, the crystalline 2,3-butanediol solvate of dapagliflozin obtained by the above process is in the form of a hydrate.

[0144] In one embodiment, the crystalline 2,3-butanediol solvate of dapagliflozin obtained by the above process is in the form of a monohydrate.

5 [0145] In one embodiment, the crystalline 2,3-butanediol solvate of dapagliflozin obtained by the above process is in the form of a dihydrate.

[0146] In one embodiment, the present invention provides a process for the preparation of crystalline 2,3-butanediol solvate of dapagliflozin, the process comprising:

- (a) reacting D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl] phenyl]-, 2,3,4,6-tetraacetate, (1*S*)- with a base in the presence of a solvent to give dapagliflozin;
- 10 (b) treating dapagliflozin with 2,3-butanediol, optionally in the presence of a solvent, to form a solution;
- (c) obtaining crystalline 2,3-butanediol solvate of dapagliflozin from the solution of step (b); and
- 15 (d) isolating the crystalline 2,3-butanediol solvate of dapagliflozin.

[0147] In (a) of the process for the preparation of crystalline 2,3-butanediol solvate of dapagliflozin, D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl] phenyl]-, 2,3,4,6-tetraacetate, (1*S*)- is reacted with a base in the presence of a solvent to give dapagliflozin.

20 [0148] The suitable base includes, but is not limited to alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide; alkaline earth metal hydroxides; alkali metal hydrides such as sodium hydride, potassium hydride; alkali metal alcoholates such as lithium methoxide, sodium methoxide, potassium methoxide, sodium ethoxide, potassium ethoxide, potassium tert-butoxide; alkaline earth metal alcoholates such as calcium ethoxide, magnesium iso-propoxide. Preferably the base

25 selected is sodium hydroxide.

[0149] In (b) of the process for the preparation of crystalline 2,3-butanediol solvate of dapagliflozin, dapagliflozin is treated with 2,3-butanediol, optionally in the presence of a solvent, to form a solution.

30 [0150] The process steps (b), (c) and (d) are as discussed supra.

[0151] In one embodiment, the dapagliflozin obtained in step (a) is isolated and then treated with 2,3-butanediol.

[0152] In one embodiment, the dapagliflozin obtained in step (a) is in-situ treated with 2,3-butanediol.

5 [0153] The present invention provides a process for the preparation of dapagliflozin in amorphous form, the process comprising:

(a) dissolving 2,3-butanediol solvate of dapagliflozin in a solvent to form a solution; and

(b) recovering dapagliflozin in amorphous form from the solution of step (a).

10 [0154] In (a) of the process for the preparation of dapagliflozin in amorphous form, 2,3-butanediol solvate of dapagliflozin is dissolved in a solvent to form a solution.

[0155] The solvent used for dissolution of 2,3-butanediol solvate of dapagliflozin includes but is not limited to haloalkanes such as dichloromethane, chloroform, ethylene dichloride, and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; alcohols such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 1-octanol and the like; ethers such as diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane and the like; esters such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, tert-butyl acetate and the like; hydrocarbons such as toluene, xylene, chlorobenzene, heptane, hexane and the like; dimethyl sulfoxide; dimethyl formamide; dimethyl acetamide; water; or mixtures thereof.

20 [0156] Suitable temperature for dissolution of 2,3-butanediol solvate of dapagliflozin in a solvent may range from about 0°C to about the reflux temperature of the solvent. Stirring may be continued for any desired time period to achieve a complete dissolution of the compound. The stirring time may range from about 30 minutes to about 1 hour, or longer.

25 The solution may be optionally treated with charcoal and filtered to get a particle-free solution.

[0157] In (b) of the process for the preparation of dapagliflozin in amorphous form, dapagliflozin in amorphous form is recovered from the solution of step (a).

30 [0158] In one embodiment, dapagliflozin in amorphous form is recovered by removing the solvent from the solution obtained in step (a). Removal of solvent may be accomplished by substantially complete evaporation of the solvent or concentrating the

solution, cooling the solution if required and filtering the obtained solid. The solution may also be completely evaporated in, for example, a rotavapor, a vacuum paddle dryer or in a conventional reactor under vacuum above about 720mm Hg, or evaporated by lyophilisation, freeze-drying technique, spray drying, fluid bed drying, flash drying, spin
5 flash drying, thin-film drying, agitated nutsche filter dryer.

[0159] In one embodiment, dapagliflozin in amorphous form is recovered by adding an anti-solvent to the solution obtained in step (a) to form a mixture and optionally, cooling and stirring the obtained mixture. The stirring time may range from about 30 minutes to about 10 hours, or longer. The temperature may range from about 0°C to about 30°C.

10 [0160] The anti-solvent is selected such that dapagliflozin in amorphous form is precipitated out from the solution.

[0161] The anti-solvent includes but is not limited to esters such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, tert-butyl acetate and the like; hydrocarbons such as toluene, xylene, chlorobenzene, heptane, hexane and the like; ethers such as
15 diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; alcohols such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 1-octanol and the like; haloalkanes such as dichloromethane, chloroform, ethylene dichloride, and the like; dimethyl formamide; dimethyl sulfoxide; dimethyl
20 acetamide; water; or mixtures thereof.

[0162] The present invention provides use of 2,3-butanediol solvate of dapagliflozin in the preparation of amorphous dapagliflozin.

[0163] In one embodiment, the present invention provides a process for the preparation of amorphous dapagliflozin, the process comprising:

- 25 (a) dissolving dapagliflozin, or solvate thereof, in a suitable solvent to form a solution;
(b) obtaining amorphous dapagliflozin from the solution of step (a); and
(c) isolating the amorphous dapagliflozin.

[0164] In (a) of the process for the preparation of amorphous dapagliflozin, dapagliflozin or solvate thereof, is dissolved in a suitable solvent to form a solution.

30 [0165] The solvate of dapagliflozin includes solvate with water, methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, tert-butanol, ethylene glycol, butanediol,

ethyl acetate, n-butyl acetate, isobutyl acetate, acetonitrile, acetone, butanone, methyl isobutyl ketone, tetrahydrofuran, 2-methyl tetrahydrofuran, dioxane, chloroform, dichloromethane, hexane, n-heptane, toluene, N-methyl pyrrolidone, dimethyl formamide or dimethyl sulfoxide.

5 [0166] The solvent used for dissolution of solvate of dapagliflozin is as discussed supra for dissolution of 2,3-butanediol solvate of dapagliflozin.

[0167] In (b) of the process for the preparation of amorphous dapagliflozin, amorphous dapagliflozin is obtained from the solution of step (a).

10 [0168] In one embodiment, the amorphous dapagliflozin is obtained by removing the solvent from the solution obtained in (a). Removal of solvent may be accomplished as discussed supra.

[0169] In one embodiment, the amorphous dapagliflozin is obtained by adding an anti-solvent to the solution obtained in (a) to form a mixture and optionally, cooling and stirring the obtained mixture. The anti-solvent is selected such that amorphous
15 dapagliflozin is precipitated out from the solution. The anti-solvent is as discussed supra.

[0170] In (c) of the process for the preparation of amorphous dapagliflozin, the amorphous dapagliflozin is isolated by any method known in the art. The method, may involve any of techniques, known in the art, including filtration by gravity or by suction, centrifugation, and the like.

20 [0171] The present invention provides dapagliflozin in substantially amorphous form.

[0172] In one embodiment, the present invention provides amorphous dapagliflozin in a purity of about 99.9% w/w, as determined by HPLC.

[0173] The present invention provides amorphous dapagliflozin in stable form.

25 [0174] In one embodiment, the present invention provides pure amorphous dapagliflozin in stable form.

[0175] In one preferred embodiment, the present invention provides pure amorphous dapagliflozin in stable form with a purity of about 99.9% w/w, as determined by HPLC.

[0176] In one embodiment, the present invention provides a process for the preparation of solvates of dapagliflozin, the process comprising:

30 (a) dissolving dapagliflozin in a suitable solvent, optionally in presence of additional solvent, to form a solution;

(b) obtaining solvate of dapagliflozin from the solution of step (a); and

(c) isolating the solvate of dapagliflozin.

[0177] The solvate of dapagliflozin includes solvate with water, methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, tert-butanol, ethylene glycol, butanediol, 5 ethyl acetate, n-butyl acetate, isobutyl acetate, acetonitrile, acetone, butanone, methyl isobutyl ketone, tetrahydrofuran, 2-methyl tetrahydrofuran, dioxane, chloroform, dichloromethane, hexane, n-heptane, toluene, N-methyl pyrrolidone, dimethyl formamide or dimethyl sulfoxide.

[0178] The solvent used for dissolution of dapagliflozin is as discussed supra.

10 [0179] The additional solvent includes but is not limited to esters such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, tert-butyl acetate and the like; hydrocarbons such as toluene, xylene, chlorobenzene, heptane, hexane and the like; ethers such as diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl 15 ketone and the like; alcohols such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 1-octanol and the like; haloalkanes such as dichloromethane, chloroform, ethylene dichloride, and the like; dimethyl formamide; dimethyl sulfoxide; dimethyl acetamide; water; or mixtures thereof.

[0180] In (b) of the process for the preparation of solvate of dapagliflozin, the solvate of 20 dapagliflozin is obtained from the solution of step (a), the process comprising:

(i) optionally cooling and stirring the solution obtained in (a); or

(ii) removing the solvent from the solution obtained in (a); or

(iii) treating the solution of step (a) with an anti-solvent to form a mixture and optionally, cooling and stirring the obtained mixture.

25 [0181] The anti-solvent is selected such that the solvate of dapagliflozin is precipitated out from the solution. The anti-solvent is as discussed supra for 2,3-butanediol solvate dapagliflozin.

[0182] In one embodiment, the present invention provides pharmaceutical compositions comprising dapagliflozin or solvate thereof obtained by the processes herein described, 30 having a D_{50} and D_{90} particle size of less than about 150 microns, preferably less than about 100 microns, more preferably less than about 50 microns, still more preferably less

than about 20 microns, still more preferably less than about 15 microns and most preferably less than about 10 microns. The particle size disclosed here can be obtained by, for example, any milling, grinding, micronizing or other particle size reduction method known in the art to bring the solid state dapagliflozin or solvate thereof into any
5 of the foregoing desired particle size range.

[0183] In one embodiment, the present invention provides pharmaceutical composition/formulation comprising crystalline 2,3-butanediol solvate of dapagliflozin and at least one pharmaceutically acceptable carrier.

[0184] The pharmaceutically acceptable carrier may comprise bulking agents such as
10 microcrystalline cellulose, lactose, or the like; binders such as pregelatinized starch, or the like; disintegrants such as sodium starch glycolate, crospovidone, croscarmellose sodium, or the like; glidants such as silicon dioxide, talc, or the like; lubricants such as magnesium stearate, or the like; as well as others known in the art.

[0185] In one embodiment, the crystalline 2,3-butanediol solvate of dapagliflozin
15 formulation is in a form selected from the group consisting of a tablet, a stock granulation, and a capsule.

[0186] In one embodiment, the present invention provides a method for treating or
20 delaying the progression or onset of Type I and Type II diabetes, impaired glucose tolerance, insulin resistance, nephropathy, retinopathy, neuropathy, cataracts, hyperglycemia, hyperinsulinemia, hypercholesterolemia, dyslipidemia, elevated blood levels of free fatty acids or glycerol, hyperlipidemia, hypertriglyceridemia, obesity, wound healing, tissue ischemia, atherosclerosis, hypertension, or Syndrome X (Metabolic Syndrome) comprising administering to a mammalian subject or patient in need of such
25 treatment a therapeutically effective amount of an immediate release pharmaceutical formulation comprising crystalline 2,3-butanediol solvate of dapagliflozin and a pharmaceutically acceptable carrier.

[0187] The examples that follow are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the features and advantages.

EXAMPLES**[0188] EXAMPLE 1: Preparation of 5-bromo-2-chlorobenzoyl chloride**

To a suspension of 5-bromo-2-chlorobenzoic acid (10g) in methylene dichloride (40mL), dimethylformamide (0.2g) and thionyl chloride were added and the reaction mixture was
5 refluxed for about 2h. After completion of reaction, the solvent was distilled out. The mass obtained was degassed under vacuum followed by stripping with cyclohexane to give crude 5-bromo-2-chlorobenzoyl chloride (10.8g).

[0189] EXAMPLE 2: Preparation of 5-bromo-2-chloro-4'-ethoxybenzophenone (compound of Formula II)

10 5-bromo-2-chlorobenzoyl chloride (10.7g) was dissolved in methylene dichloride (40mL) and the reaction mixture was cooled to about -8°C to about -12°C under inert atmosphere. Aluminum chloride (5.65g) was added to the reaction mixture followed by addition of a solution of ethoxybenzene in methylene dichloride. The reaction mixture was stirred for about 1h at about -8°C to -12°C and then quenched in dilute hydrochloric acid followed
15 by extraction with methylene dichloride. The organic layer was washed with sodium bicarbonate solution and concentrated. The residue obtained was crystallized from methanol to give 5-bromo-2-chloro-4'-ethoxybenzophenone (8.5g). HPLC purity: 99.34%

[0190] EXAMPLE 3: Preparation of 5-bromo-2-chloro-4'-ethoxydiphenylmethane (compound of formula III)

20 To a mixture of 5-bromo-2-chloro-4'-ethoxybenzophenone (10g) and methylene dichloride (50mL), cooled to about 0°C to about 5°C, triethylsilane (11.98g) and titanium chloride (22.3g) were added. The reaction mixture was stirred for about 3h at about 10°C to about 15°C. The reaction mixture was quenched into chilled water. The organic layer was separated, washed with water and sodium bicarbonate solution and concentrated
25 under vacuum followed by stripping with toluene. The residue obtained was stirred with methanol, filtered and dried to give 5-bromo-2-chloro-4'-ethoxydiphenylmethane (9g). HPLC purity: 99.4%

[0191] EXAMPLE 4: Preparation of 2,3,4,6-tetra-O-(trimethylsilyl)-D-glucono-1,5-lactone (compound of Formula V)

30 To a mixture of D-glucono-1,5-lactone (10g) and iodine (0.28g) in methylene dichloride (80mL), hexamethyldisilazane (36.1g) was added and the reaction mixture was refluxed.

After completion of reaction, the reaction mixture was concentrated and degassed to give 2,3,4,6-tetra-*O*-(trimethylsilyl)-D-glucono-1,5-lactone as liquid (25g). HPLC purity: 95%

[0192] EXAMPLE 5: Preparation of D-glucopyranoside, methyl 1-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl] (compound of Formula VII wherein R is methyl)

- 5 To a mixture of 2,3,4,6-tetra-*O*-(trimethylsilyl)-D-glucono-1,5-lactone (25g) and 5-bromo-2-chloro-4'-ethoxydiphenylmethane (8.7g) in tetrahydrofuran (174mL), cooled to about -75°C to about -88 °C under nitrogen atmosphere, *n*-butyl lithium in hexane (50mL) was slowly added. The reaction mixture was stirred at about the same temperature and then mixture of methanol and methanesulphonic acid was added to it.
- 10 The reaction mixture was quenched into sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was separated, washed with saturated sodium chloride solution and concentrated under vacuum to obtain a residue. The residue was purified with a mixture of toluene and cyclohexane. Yield: 11g as thick mass with 80-85% HPLC purity.

15 [0193] EXAMPLE 6: Preparation of D-glucitol, 1,5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl) methyl]phenyl]

- To a mixture of D-glucopyranoside, methyl 1-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl] in methylene dichloride (40mL) and acetonitrile (40mL), cooled to about -40°C to about -45°C, triethylsilane (8.74g) was added followed by
- 20 addition of boron trifluoride etherate (10.67g) maintaining the temperature at about -40°C to about -45°C. The reaction mixture was quenched in sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was separated, concentrated and degassed under vacuum to give title compound (11g) as thick residue with 80-85% HPLC purity.

25 [0194] EXAMPLE 7: Preparation of D-Glucitol, 1,5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1*S*)-

- To a cooled solution of D-glucitol, 1,5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl) methyl]phenyl]- (11g) in methylene dichloride (55mL) at about 0°C to about 5°C, diisopropylethylamine, dimethylaminopyridine and acetic anhydride were added and the reaction mixture was stirred. After completion of reaction, the reaction mixture was
- 30 quenched by adding water. The aqueous layer was separated and extracted with methylene dichloride. The organic layer was separated, washed with sodium bicarbonate

solution and concentrated under vacuum to obtain residue which was stripped out with methanol. The residue was purified with methanol and charcoal, followed by diisopropyl ether and methanol crystallization. Yield: 10g; HPLC purity: 99.6%

[0195] EXAMPLE 8: Preparation of D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl] (Dapagliflozin)

To a stirred solution of D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1S)-, (10g) in THF:methanol:water mixture (50mL:50mL:30mL), sodium hydroxide was added and the reaction mixture was stirred. After completion of reaction, the solvents were distilled out under vacuum and the residue obtained was dissolved in methylene dichloride and washed with water and brine and dried over sodium sulfate. The reaction mixture was concentrated and degassed to give off-white to white solids of D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]- (dapagliflozin) Yield: 7g (XRD matches with amorphous form) HPLC purity: 99.8%

[0196] EXAMPLE 9: Preparation of D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S), compounded with (2S)-propane-1,2-diol (1:1) monohydrate

To D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]- (7g) in isopropyl acetate cooled to about 0°C to about 5°C, was added (S)-1,2-propanediol and water and the reaction mixture was stirred. The solid obtained was filtered and dried to give title compound (6.3g) with 99.7% HPLC purity.

[0197] EXAMPLE 10: Preparation of D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1S)- from D-glucono-1,5-lactone (One-pot Synthesis)

To a mixture of D-glucono-1,5-lactone (10g) in methylene dichloride (80mL), hexamethyldisilazane (36.1g) was added and the reaction mixture was refluxed. After completion of reaction, the reaction mixture was concentrated and degassed. The residue obtained was dissolved in tetrahydrofuran. 5-Bromo-2-chloro-4'-ethoxydiphenylmethane (8.7g) was added to the reaction mixture which was cooled to about -75°C to about -85°C under nitrogen atmosphere. n-Butyl lithium in hexane (50mL) was slowly added to the reaction mixture maintaining the temperature between -75°C to about -85°C. The

reaction mixture was stirred at about the same temperature and then mixture of methanol and methanesulphonic acid was added to it. The reaction mixture was quenched into sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was separated, washed with saturated sodium chloride solution and concentrated under vacuum to obtain a residue. This residue was purified by a mixture of toluene and cyclohexane. To the product obtained, methylene dichloride and acetonitrile were added and the reaction mixture was cooled to about -40°C to about -45°C. Triethylsilane (8.74g) was added to the reaction mixture followed by addition of boron trifluoride etherate (10.67g) maintaining temperature at about -40°C to about -45°C. The reaction mixture was quenched in sodium bicarbonate solution. The aqueous layer was separated and extracted with ethyl acetate. The organic layer was separated, concentrated and degassed under vacuum. The thick residue obtained was dissolved in methylene dichloride and cooled to about 0°C to about 5°C. Diisopropylethylamine, dimethylaminopyridine and acetic anhydride were added to the reaction mixture which was stirred. After completion of reaction, the reaction mixture was quenched by adding water. The aqueous layer was separated and extracted with methylene dichloride. The organic layer was separated, washed with sodium bicarbonate solution and concentrated under vacuum to obtain residue which was stripped out with methanol. The residue obtained was recrystallized with methanol and charcoal to give title compound (10g) with 99.7% HPLC purity.

[0198] EXAMPLE 11: Preparation of dapagliflozin-mannitol premix

To a stirred mixture of dapagliflozin amorphous form (5g) and methylene dichloride (25mL), mannitol (5g) was added and the reaction mixture was stirred. The reaction mixture was concentrated under reduced pressure and degassed. To the obtained residue, cyclohexane was added and the reaction mixture was stirred. The solid obtained was filtered, washed with cyclohexane and dried under vacuum to give title compound (9.8g) with 99.74% HPLC purity. (XRD as per figure 2)

[0199] EXAMPLE 12: Preparation of dapagliflozin-microcrystalline cellulose premix

To a stirred mixture of dapagliflozin amorphous form (5g) and methylene dichloride (25mL), microcrystalline cellulose (5g) was added and the reaction mixture was stirred. The reaction mass was concentrated under reduced pressure and degassed. To the obtained residue, cyclohexane was added and the reaction mixture was stirred. The solid

obtained was filtered, washed with cyclohexane and dried under vacuum to give title compound (9.4g) with 99.57% HPLC purity. (XRD as per figure 3)

[0200] EXAMPLE 13: Preparation of 2,3-butanediol solvate of dapagliflozin

Dapagliflozin (2g) was dissolved in ethyl acetate (10mL) and 2,3-butanediol (0.463g) and water (0.13g) were added to it. The reaction mixture was concentrated and cyclohexane (30mL) was added to it. The reaction mixture was stirred overnight. The solid obtained was filtered and dried. Yield: 1.8g

¹H NMR (300 MHz in DMSO-d₆): δ 7.40-7.25 (m,2H), 7.25-7.18 (d,1H), 7.12-7.00 (d,2H), 6.81-6.75 (d,2H), 4.97 (brs,2H), 4.84 (brs,1H), 4.46 (brs,1H), 4.32 (brs,2H), 4.10-3.90 (m,4H), 3.80-3.60 (m,1H), 3.55-3.05 (m,8H), 1.29 (t,3H), 1.05-0.85 (m,6H)

¹H NMR (300 MHz in DMSO-d₆+D₂O): 7.40-7.25 (m,2H), 7.25-7.18 (d,1H), 7.12-7.00 (d,2H), 6.81-6.75 (d,2H), 4.10-3.90 (m,4H), 3.80-3.60 (m,1H), 3.55-3.05 (m,8H), 1.29 (t,3H), 1.05-0.85 (m,6H)

TGA analysis of 2,3-butanediol solvate of dapagliflozin: 24.3% weight loss up to 250°C corresponds to one mole of water and one mole of butanediol per mole of structure analyzed.

Water content: 2.92%

XRPD peaks of 2,3-butanediol solvate of dapagliflozin:

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]	Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]	Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
2.11	41.77	0.45	20.64	4.30	6.23	29.54	3.02	5.60
3.69	23.91	100.00	21.34	4.16	16.12	30.02	2.97	3.80
8.65	10.21	6.13	22.04	4.03	2.66	30.49	2.93	2.53
9.56	9.24	7.14	22.79	3.90	2.90	31.99	2.79	4.12
10.72	8.24	6.31	23.47	3.78	6.38	32.46	2.75	5.45
14.60	6.03	50.84	24.20	3.67	4.77	33.30	2.68	0.91
15.78	5.61	8.65	24.73	3.59	5.27	34.21	2.62	3.29
16.10	5.50	2.09	25.22	3.53	3.13	37.22	2.41	3.63
16.63	5.33	77.16	25.81	3.45	3.75	38.43	2.34	1.45
18.34	4.83	19.62	26.96	3.30	5.04	39.81	2.26	2.13
18.62	4.76	6.49	27.39	3.25	3.74	40.97	2.20	3.65
19.97	4.44	16.57	28.44	3.13	1.13	42.49	2.12	0.92
20.20	4.39	5.96	28.92	3.08	1.09	43.23	2.09	0.49

[0201] The following examples follow similar process as described in EXAMPLE 13 for preparation of 2,3-butanediol solvate of dapagliflozin wherein ethyl acetate (first solvent) and cyclohexane (second solvent) are replaced by below combinations.

EXAMPLE No.	First Solvent	Second Solvent
EXAMPLE 14	isopropyl acetate	cyclohexane
EXAMPLE 15	methyl acetate	cyclohexane
EXAMPLE 16	methylene chloride	cyclohexane
EXAMPLE 17	ethylene dichloride	cyclohexane
EXAMPLE 18	butyl acetate	cyclohexane
EXAMPLE 19	isopropyl acetate	hexane
EXAMPLE 20	ethyl acetate	hexane
EXAMPLE 21	methyl acetate	hexane
EXAMPLE 22	butyl acetate	hexane

5 [0202] **EXAMPLE 23: Preparation of 2,3-butanediol solvate of dapagliflozin**

Dapagliflozin (2g) was dissolved in ethyl acetate (10mL) and 2,3-butanediol (0.463g) and water (0.13g) were added to it. The reaction mixture was stirred for about 30min. Cyclohexane was added to the reaction mixture which was stirred overnight. The solid obtained was filtered and dried.

10 [0203] The following examples follow similar process as described in EXAMPLE 23 for preparation of 2,3-butanediol solvate of dapagliflozin wherein ethyl acetate (first solvent) and cyclohexane (second solvent) are replaced by below combinations.

EXAMPLE No.	First Solvent	Second Solvent
EXAMPLE 24	methyl acetate	cyclohexane
EXAMPLE 25	isopropyl acetate	cyclohexane
EXAMPLE 26	butyl acetate	cyclohexane
EXAMPLE 27	methylene chloride	cyclohexane
EXAMPLE 28	ethylene dichloride	cyclohexane
EXAMPLE 29	ethyl acetate	hexane
EXAMPLE 30	methyl acetate	hexane
EXAMPLE 31	isopropyl acetate	hexane

EXAMPLE 32	butyl acetate	hexane
EXAMPLE 33	methylene chloride	hexane
EXAMPLE 34	ethylene dichloride	hexane

[0204] EXAMPLE 35: Preparation of amorphous dapagliflozin

To a stirred solution of 2,3-butanediol solvate of dapagliflozin (2g) in ethyl acetate, water was added and stirred for about 30min. The two layers were separated and the organic layer was concentrated under reduced pressure. Isopropyl alcohol was added to the obtained residue and the reaction mixture was concentrated under reduced pressure and degassed for about 4h to give amorphous dapagliflozin.

[0205] EXAMPLE 36: Preparation of amorphous dapagliflozin

To a stirred solution of 2,3-butanediol solvate of dapagliflozin (2g) in methylene dichloride, water was added and the reaction mixture was stirred for about 30min. The two layers were separated and the organic layer was concentrated under reduced pressure. Isopropyl alcohol was added to the obtained residue and the reaction mixture was concentrated under reduced pressure and degassed for about 4h to give amorphous dapagliflozin.

[0206] EXAMPLE 37: Preparation of amorphous dapagliflozin

To a stirred solution of D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1*S*)-, in tetrahydrofuran: methanol: water mixture, was added sodium hydroxide and the reaction mixture was stirred for about 6h. The reaction mixture was concentrated to give a residue and ethyl acetate and water were added it. The two layers were separated and the organic layer was concentrated and degassed to give amorphous dapagliflozin.

[0207] EXAMPLE 38: Preparation of dapagliflozin

To a stirred solution of D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1*S*)-, (10g) in tetrahydrofuran: methanol: water mixture, was added sodium hydroxide and the reaction mixture was stirred. The reaction mixture was concentrated to give a residue and methylene dichloride and water were added it. The two layers were separated and the organic layer was

concentrated and isopropyl alcohol was added to it. The reaction mixture was concentrated and degassed to give dapagliflozin. Yield: 7g

Isopropyl alcohol content: 3.5%

HPLC purity: 99.8%

5 **[0208] EXAMPLE 39: Preparation of 5-bromo-2-chloro-4'-ethoxydiphenylmethane**

To a stirred mixture of 5-bromo-2-chloro-4'-ethoxybenzophenone (10g), methylene dichloride (40mL), acetonitrile (40mL) and triethylsilane (13.69g) was added boron trifluoride (14.6g) at about 20°C to about 50°C. The reaction mixture was stirred for about 1h at about 40°C to about 50°C and then sodium bicarbonate solution was added to
10 it. The two layers were separated and the organic layer was washed with water and sodium chloride solution. The organic layer was concentrated under vacuum followed by stripping with toluene. The residue obtained was stirred with methanol, filtered and dried. Yield: 7g; HPLC purity: 99.4%

15 **[0209] EXAMPLE 40: Preparation of D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S), compounded with (2S)-propane-1,2-diol (1:1) monohydrate**

To D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]- (7g) in ethyl acetate was added (*S*)-1,2-propanediol and water and the reaction mixture was stirred. Cyclohexane was added to the reaction mixture. The solid obtained was filtered
20 and dried to give title compound (6.3g). HPLC purity: 99.7%.

[0210] EXAMPLE 41: Preparation of amorphous dapagliflozin

To a stirred solution of 2,3-butanediol solvate of dapagliflozin (2g) in ethyl acetate, water was added and stirred for 30min. The two layers were separated and the organic layer was concentrated under reduced pressure. Isopropyl alcohol was added to the obtained
25 residue and the reaction mixture was concentrated under reduced pressure and degassed for 12h. Cyclohexane was added to the obtained residue and stirred. The solid obtained was filtered to give amorphous dapagliflozin.

[0211] EXAMPLE 42: Preparation of amorphous dapagliflozin

To a stirred solution of D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1*S*)-, (10g) in tetrahydrofuran:
30 methanol: water mixture, was added sodium hydroxide and the reaction mixture was

stirred. The solvents were distilled out under vacuum and the residue obtained was treated with methylene dichloride, water and neutralized by using dilute hydrochloric acid. The two layers were separated and the organic layer washed with brine solution. The organic layer was concentrated and isopropyl alcohol was added to it. The organic layer was concentrated and degassed. The solid obtained was stirred with cyclohexane, filtered and dried to give amorphous dapagliflozin (7g).

After jet-milling:

D ₁₀	D ₅₀	D ₉₀
2.608μm	15.013μm	64.645μm

[0212] EXAMPLE 43: Preparation of amorphous dapagliflozin

To a stirred solution of D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1S)-, (10g) in tetrahydrofuran:methanol: water mixture, was added sodium hydroxide and the reaction mixture was stirred for 24h . The solvents were distilled out under vacuum and the residue obtained was treated with methylene dichloride, water and neutralized by using dilute hydrochloric acid. The two layers were separated and the organic layer washed with brine solution. The organic layer was concentrated and isopropyl alcohol was added to it. Polyethylene glycol (PEG) was added to the reaction mixture which was stirred for about 3h. The reaction mixture was concentrated, degassed. The solid obtained stirred with cyclohexane, filtered and dried to give amorphous dapagliflozin containing less than 1% of PEG (7.5g).

[0213] EXAMPLE 44: Preparation of D-Glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1S)- from D-glucono-1,5-lactone

To a mixture of D-glucono-1,5-lactone (10g) in methylene dichloride (80mL), hexamethyldisilazane (36.1g) was added and the reaction mixture was refluxed. After completion of reaction, the reaction mixture was concentrated and degassed. The residue obtained was dissolved in tetrahydrofuran. 5-Bromo-2-chloro-4'-ethoxydiphenylmethane (8.7g) was added to the reaction mixture which was cooled to about -75°C to about -85°C under nitrogen atmosphere. n-Butyl lithium in hexane (50mL) was slowly added to the reaction mixture maintaining the temperature between -75°C to about -85°C. The

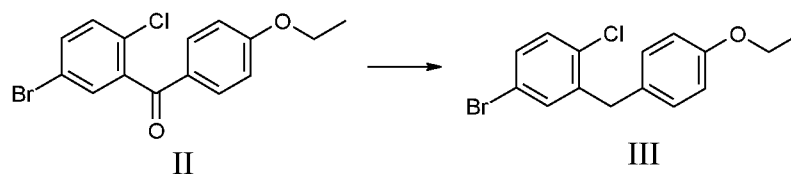
reaction mixture was stirred at about the same temperature and then mixture of methanol and methanesulphonic acid was added to it. The reaction mixture was quenched into sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was separated, washed with saturated sodium chloride solution and concentrated under vacuum to obtain a residue. This residue was purified by a mixture of toluene and cyclohexane. To the product obtained, methylene dichloride and acetonitrile were added and the reaction mixture was cooled to about -20°C to about -30°C. Triethylsilane (8.74g) was added to the reaction mixture followed by addition of boron trifluoride etherate (10.67g) maintaining temperature at about -20°C to about -30°C. The reaction mixture was quenched in sodium bicarbonate solution. The aqueous layer was separated and extracted with ethyl acetate. The organic layer was separated, concentrated and degassed under vacuum. The thick residue obtained was dissolved in methylene dichloride and cooled to about 0°C to about 5°C. Diisopropylethylamine, dimethylaminopyridine and acetic anhydride were added to the reaction mixture which was stirred. After completion of reaction, the reaction mixture was quenched by adding water. The aqueous layer was separated and extracted with methylene dichloride. The organic layer was separated, washed with sodium bicarbonate solution and concentrated under vacuum to obtain residue which was stripped out with methanol. The residue obtained was recrystallized with methanol and charcoal. The residue obtained was recrystallized with diisopropyl ether and then with methanol to give title compound (10g). HPLC purity: $\geq 99.8\%$

	Compound VIII	Impurity G	Impurity H
Before purification	86.97%	4.21	1.82
1 st methanol purification	98.76	0.05	0.08
Diisopropyl ether purification	99.08	Not detected	0.02
2 nd methanol purification	99.85	Not detected	0.01

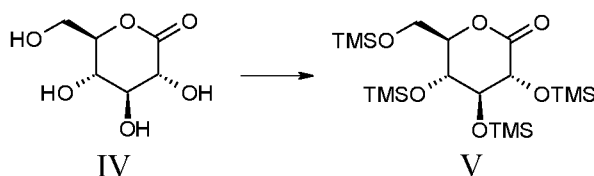
CLAIMS:

1. A process for the preparation of dapagliflozin in amorphous form, the process comprising:

- 5 (a) reducing a compound of formula II to a compound of formula III in the presence of a Lewis acid;

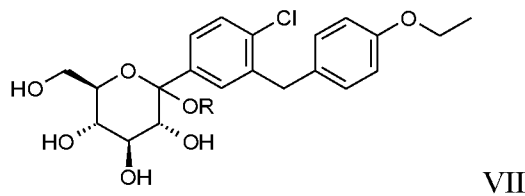


- (b) silylating a compound of formula IV with hexamethyldisilazane to form a compound of formula V;

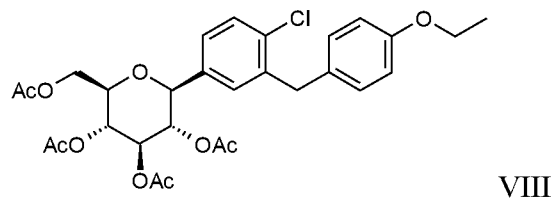


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- (c) reacting the compound of formula III with the compound of formula V in the presence of a strong base followed by treatment with an acid in the presence of an alcohol to prepare a compound of formula VII, wherein R is an alkyl group selected from C₁₋₅ alkyl;



- 15 (d) converting the compound of formula VII to dapagliflozin;
 (e) acetylating dapagliflozin to give D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1S)-, a compound of formula VIII;

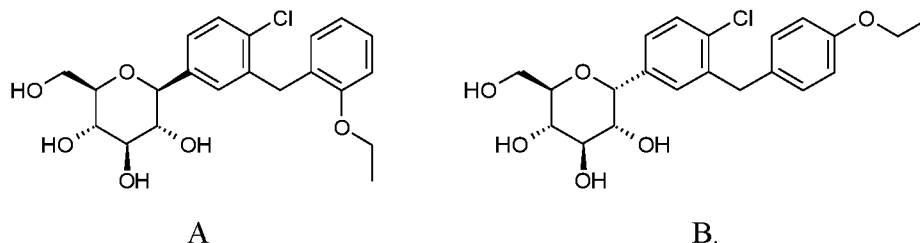


- (f) optionally, purifying the compound of formula VIII with a solvent selected from
 20 halogenated hydrocarbons, alcohols, ethers, or mixtures thereof;

- (g) hydrolyzing the compound of formula VIII obtained in step (f) to give dapagliflozin;
 (h) dissolving dapagliflozin of step (g) in a solvent selected from halogenated hydrocarbons, alcohols, hydrocarbons, or mixtures thereof to form a solution; and
 (i) recovering amorphous dapagliflozin from the solution of step (h).

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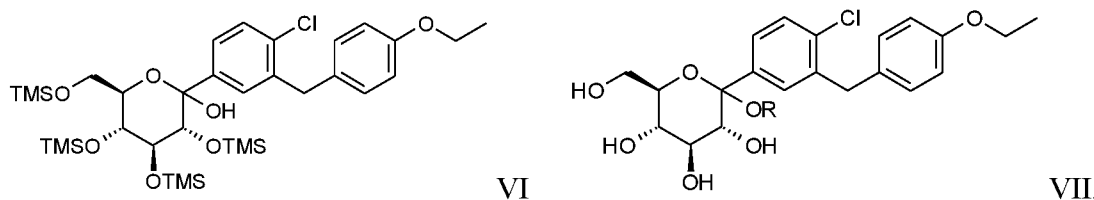
2. The process of claim 1, wherein the amorphous dapagliflozin is obtained in a purity of $\geq 99.8\%$ and wherein the level of impurity A and impurity B is less than 0.15%



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3. The process of claim 1, wherein step (c) comprises reacting the compound of formula III with the compound of formula V in the presence of a strong base to obtain a compound of formula VI; and reacting the compound of formula VI with an acid in the presence of an alcohol to prepare the compound of formula VII wherein R is an alkyl group selected from C₁₋₅ alkyl

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4. The process of claim 1, wherein in step (f), the alcohol is methanol and the ether is diisopropyl ether.

20

5. The process of claim 1, wherein in step (h), the alcohol is isopropyl alcohol and the hydrocarbon is cyclohexane.

25

6. The process of claim 1, wherein the step (i) of recovering dapagliflozin in amorphous form comprises:

- (i) removing the solvent from the solution obtained in step (h); or
 (ii) treating the solution of step (h) with an anti-solvent.

7. The process of claim 6, wherein the solvent is removed from the solution by concentrating the solution, or completely evaporating the solvent, or removing the solvent by lyophilisation, freeze-drying, spray drying, fluid bed drying, flash drying, spin
5 flash drying, thin-film drying.

8. A process for the preparation of dapagliflozin in amorphous form, the process comprising:

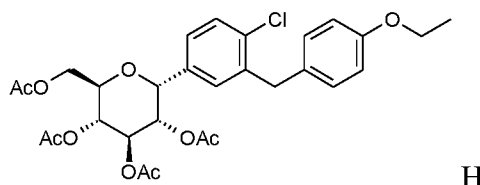
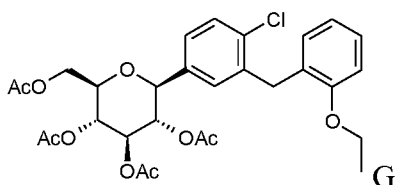
(i) dissolving dapagliflozin in isopropyl alcohol to form a solution;

10 (ii) optionally, completely evaporating isopropyl alcohol from the solution of step (i) to give a residue;

(iii) adding cyclohexane to the solution of step (i) or the residue of step (ii); and

(iv) isolating amorphous dapagliflozin.

15 9. A process for the preparation of D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, 2,3,4,6-tetraacetate, (1*S*)-, a compound of formula VIII, in a purity of $\geq 99.6\%$ and wherein the level of impurity G and impurity H is less than 0.15%,



20 the process comprising:

(a) treating the compound of formula VIII with an ether solvent to form a reaction mass;

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

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

(d) obtaining the compound of formula VIII from the reaction mass of step (c);

25 (e) optionally, crystallizing the compound of formula VIII obtained in step (d) with an alcohol solvent; and

(f) isolating the compound of formula VIII with a purity of $\geq 99.6\%$ and wherein the level of impurity G and impurity H is less than 0.15%.

10. The process of claim 9, wherein the ether solvent is selected from the group consisting of diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran, dioxane.
- 5 11. The process of claim 9, wherein the alcohol solvent is selected from the group consisting of methanol, ethanol, n-propyl alcohol, isopropyl alcohol.
12. The process of claim 9, further comprising converting the compound of formula VIII to amorphous dapagliflozin.
- 10 13. The use of the compound of formula VIII, as obtained by the process of claim 9, in the preparation of dapagliflozin.
14. A crystalline 2,3-butanediol solvate of dapagliflozin characterized by an X-ray powder diffraction (XRPD) spectrum having peak reflections at about 3.7, 9.6, 14.7, 16.7 and 18.4 ± 0.2 degrees 2 theta.
- 15 15. The solvate of claim 14, characterized by a TGA thermogram, showing a weight loss of about 18 weight% to 26 weight% up to 250°C determined over the temperature range of 0°C to 350°C.
- 20 16. The solvate of claim 14, characterized by a proton NMR spectrum having peak positions at 7.40-7.25 (m,2H), 7.25-7.18 (d,1H), 7.12-7.00 (d,2H), 6.81-6.75 (d,2H), 4.97 (brs,2H), 4.84 (brs,1H), 4.46 (brs,1H), 4.32 (brs,2H), 4.10-3.90 (m,4H), 3.80-3.60 (m,1H), 3.55-3.05 (m,8H), 1.29 (t,3H), 1.05-0.85 (m,6H) ppm.
- 25 17. The solvate of claim 14, which is in the form of a hydrate.
18. A process for the preparation of crystalline 2,3-butanediol solvate of dapagliflozin, the process comprising:
- 30 (a) treating dapagliflozin with 2,3-butanediol, optionally in the presence of a solvent, to form a solution;
- (b) obtaining crystalline 2,3-butanediol solvate of dapagliflozin from the solution of step (a); and

(c) isolating the crystalline 2,3-butanediol solvate of dapagliflozin.

19. The process of claim 18, wherein the step (b) of obtaining 2,3-butanediol solvate of dapagliflozin comprises:

- 5 (i) optionally cooling and stirring the solution obtained in step (a); or
(ii) removing the solvent from the solution obtained in step (a); or
(iii) treating the solution of step (a) with an anti-solvent to form a mixture and optionally, cooling and stirring the obtained mixture.

10 20. A process for the preparation of dapagliflozin in amorphous form, the process comprising:

- (a) dissolving 2,3-butanediol solvate of dapagliflozin in a solvent to form a solution; and
(b) recovering dapagliflozin in amorphous form from the solution of step (a).

15 21. The process of claim 20, wherein the solvent is selected from the group consisting of haloalkanes, ketones, alcohols, ethers, esters, hydrocarbons, water, or mixtures thereof.

22. The process of claim 20, wherein the step (b) of recovering dapagliflozin in amorphous form comprises:

- 20 (i) removing the solvent from the solution obtained in step (a); or
(ii) treating the solution of step (a) with an anti-solvent.

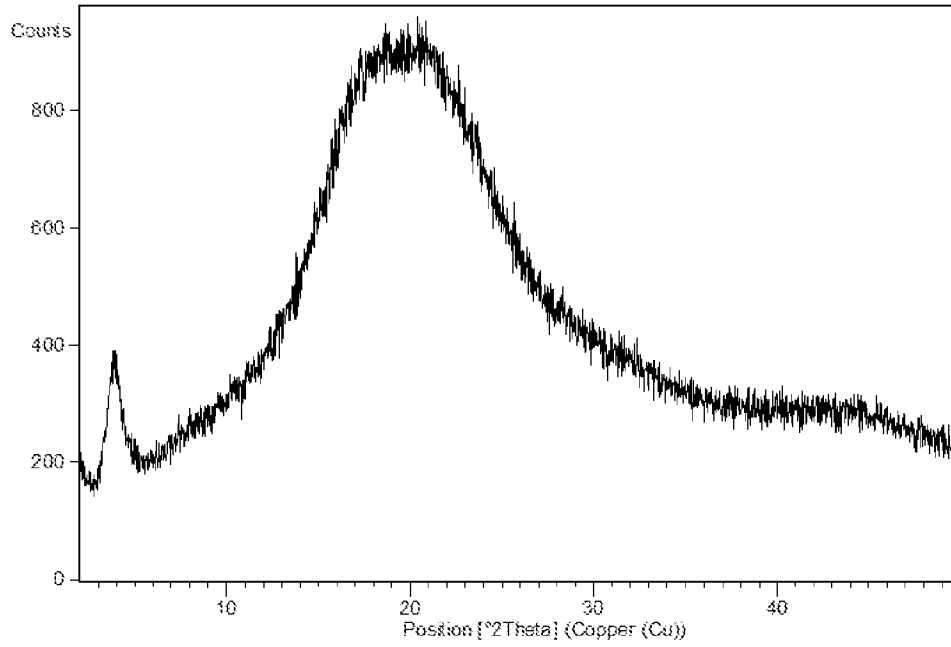
23. The process of claim 22, wherein the solvent is removed from the solution by concentrating the solution, or completely evaporating the solvent, or removing the
25 solvent by lyophilisation, freeze-drying, spray drying, fluid bed drying, flash drying, spin flash drying, thin-film drying.

24. The use of 2,3-butanediol solvate of dapagliflozin in the preparation of amorphous dapagliflozin.

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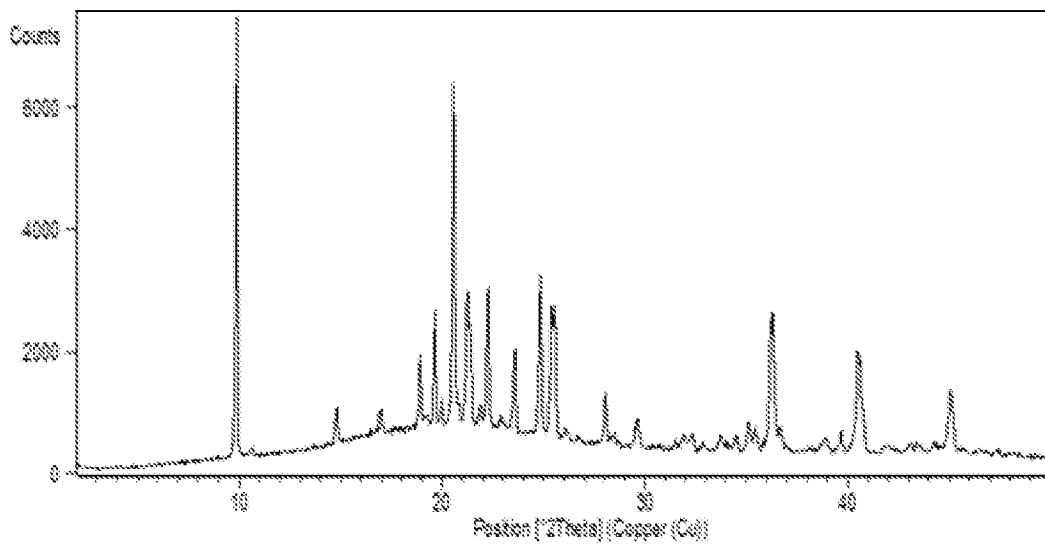
Glenmark Pharmaceuticals Limited

Figure 1



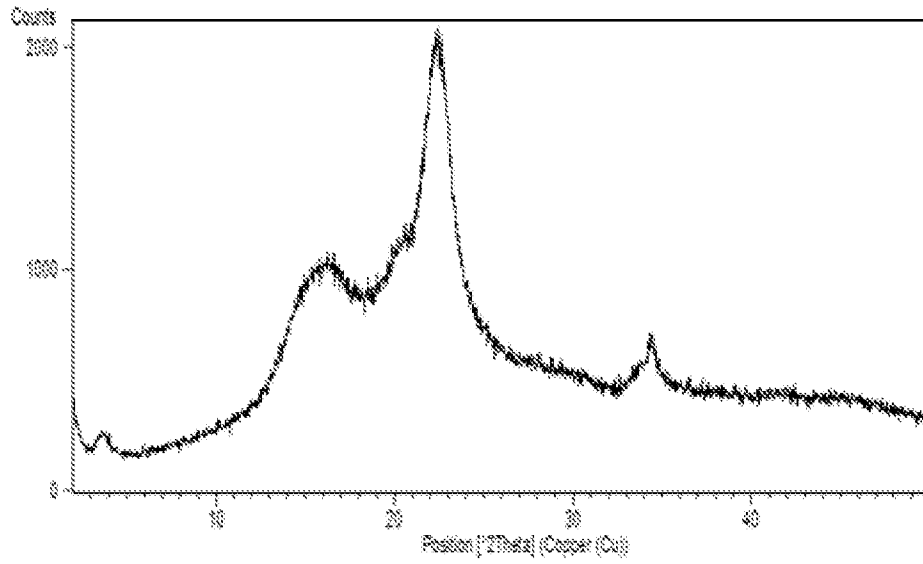
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Figure 2



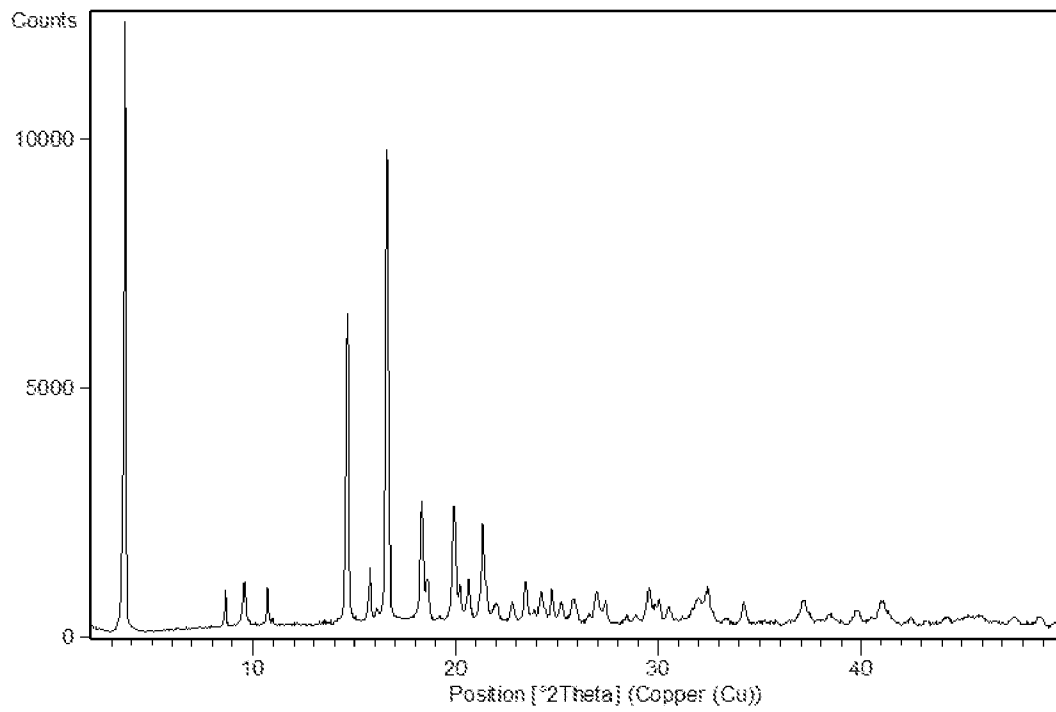
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Figure 3



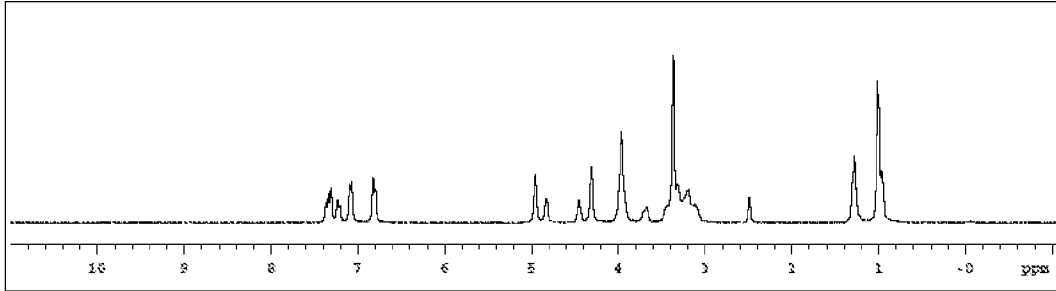
Glenmark Pharmaceuticals Limited

Figure 4



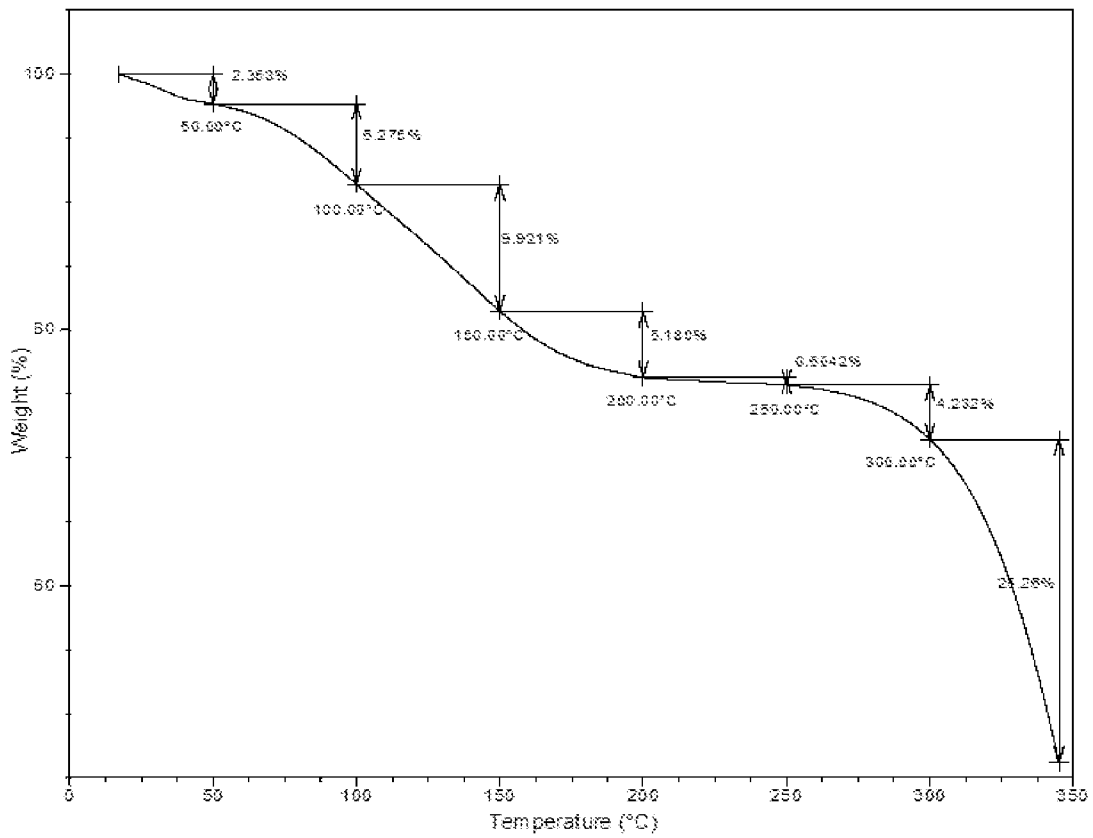
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Figure 5



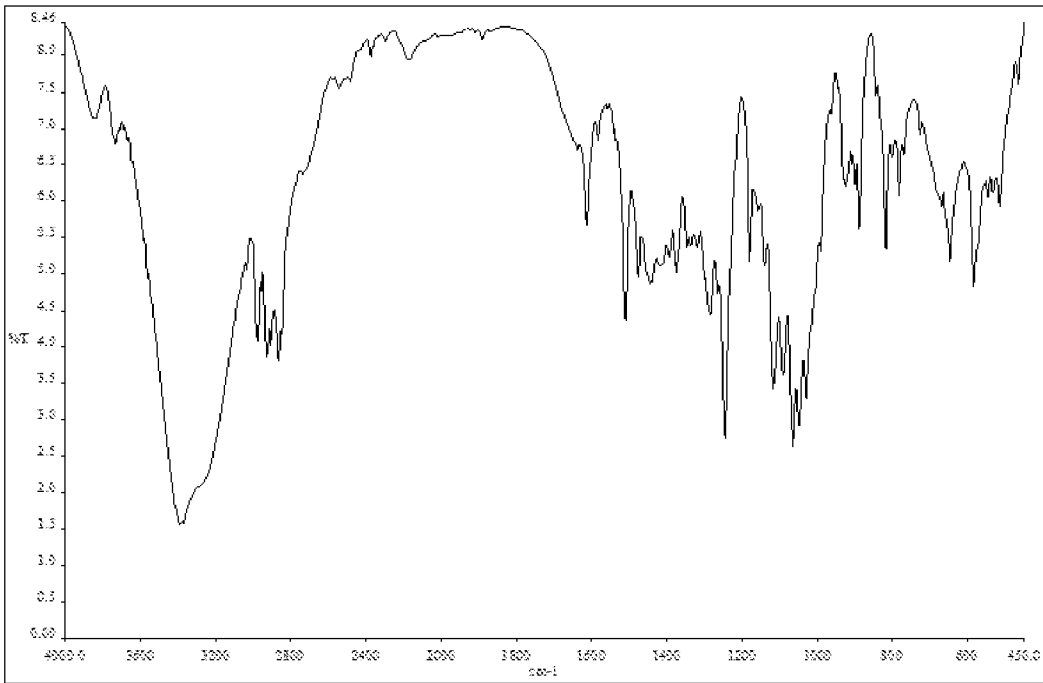
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Figure 6



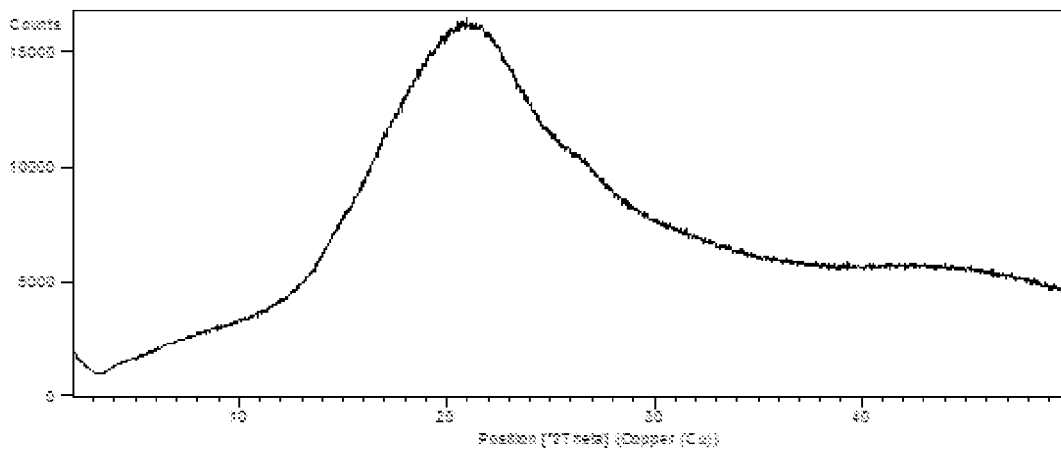
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Figure 7



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Figure 8



INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2016/052527

A. CLASSIFICATION OF SUBJECT MATTER		
C07D 309/10(2006.01)i; A61K 31/351(2006.01)i; A61P 3/10(2006.01)i		
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) C07D309/-; A61K31/-; A61P3/-		
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) CNPAT,CNKI,CA,DWPI,VEN,STN(REG. CASREACT,CAPLUS):amorphous, dapagliflozin, butanediol, +diol, hexamethyldisilazane,acetyl+ ,HMDS,diabete.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004063209 A2 (SQUIBB BRISTOL MYERS CO ET AL.) 29 July 2004 (2004-07-29) examples 16-17, 19-21	1-7
X	WO 2004063209 A2 (SQUIBB BRISTOL MYERS CO ET AL.) 29 July 2004 (2004-07-29) example 20	8-13
Y	CN 104478839 A (SUZHOU JONATHAN NEW MATERIAL TECHNOLOGY) 01 April 2015 (2015-04-01) claims 1-6, examples 1-5	1-7
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X	CN 1653075 A (BRISTOL-MYERS SQUIBB COMPANY) 10 August 2005 (2005-08-10) example	8-13
A	WO 2010022313 A2 (THERACOS INC ET AL.) 25 February 2010 (2010-02-25) the whole document	1-24
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
“A”	document defining the general state of the art which is not considered to be of particular relevance	“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
“E”	earlier application or patent but published on or after the international filing date	“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
“L”	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
“O”	document referring to an oral disclosure, use, exhibition or other means	“&” document member of the same patent family
“P”	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search	Date of mailing of the international search report	
29 August 2016	08 September 2016	
Name and mailing address of the ISA/CN	Authorized officer	
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA 6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China	Ma Liangxiao	
Facsimile No. (86-10)62019451	Telephone No. (86-10)62086312	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2016/052527

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008002824 A1 (SQUIBB BRISTOL MYERS CO ET AL.) 03 January 2008 (2008-01-03) the whole document	1-24
.....		

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- [1] 1. Claims 1-7 relate to a process for the preparation of dapagliclozin.
- [2] 2. Claim 8 relates to another process for the preparation of dapagliclozin.
- [3] 3. Claims 9-12 relate to a process for the preparation of compound of formula VIII.
- [4] 4. Claim 13 relates to the use of compound of formula VIII.
- [5] 5. Claims 14-24 relate to the crystalline 2,3-butanediol solvate of dapagliflozin, preparation method and the use thereof.
- [6] The common technical feature of the five inventions described above is dapagliclozin or compound of formula VIII, however, dapagliclozin and compound of formula VIII are known compounds. Thus this common feature cannot be considered as a special technical feature within the meaning of Rule 13.2 PCT. Therefore the five inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/IB2016/052527

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Information on patent family members

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International application No.

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