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

(72) Inventors: **KAMBLE, Vikas Shivaji**; Lupin Limited (Re-
search Park), 46A / 47A, Village Nande, Taluka Mulshi,
Maharashtra, Pune 412115 (IN). **KULKARNI, Akshay,**
Sanjay; Lupin Limited (Research Park), 46A / 47A, Vil-
lage Nande, Taluka Mulshi, Maharashtra, Pune 412115
(IN). **RANANAWARE, Umesh, Babanrao**; Lupin Lim-
ited (Research Park), 46A / 47A, Village Nande, Taluka
Mulshi, Maharashtra, Pune 412115 (IN). **GODBOLE, Hi-**
manshu, Madhav; Lupin Limited (Research Park), 46A /
47A, Village Nande, Taluka Mulshi, Maharashtra, Pune
412115 (IN). **SINGH, Girij, Pal**; Lupin Limited (Research
Park), 46A / 47A, Village Nande, Taluka Mulshi, Maha-
rashtra, Pune 412115 (IN).

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

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(54) Title: PREMIX OF DAPAGLIFLOZIN AND PROCESS FOR THE PREPARATION THEREOF

(57) Abstract: The present invention relates to a premix of dapagliflozin with lactose, processes for its preparation, and pharmaceut-
ical composition thereof. The invention also relates to a process for the preparation of an amorphous dapagliflozin and crystalline
dapagliflozin propanediol hydrate.



WO 2017/118945 A1

**PREMIX OF DAPAGLIFLOZIN AND PROCESS FOR
THE PREPARATION THEREOF**

FIELD OF THE INVENTION

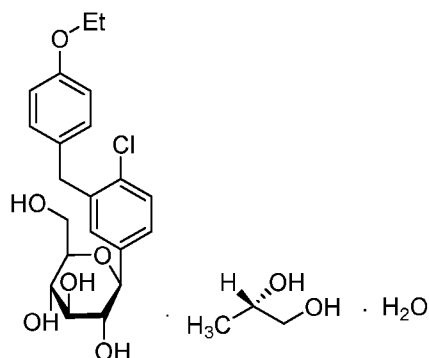
5 The present invention relates to premix of dapagliflozin with lactose and process for the preparation thereof. Further, the invention also relates to pharmaceutical composition comprising premix of dapagliflozin with lactose together with one or more pharmaceutically acceptable excipients and process for the preparation thereof. The invention also relates to a process for the preparation of an amorphous form of
10 dapagliflozin. The invention also relates to a process for the preparation of crystalline dapagliflozin propanediol hydrate.

BACKGROUND OF THE INVENTION

Diabetes is a global epidemic affecting more than 200 million people worldwide.
15 The incidence of this disease is growing fast. Each year more than 4 million people die from complications of diabetes including heart diseases, strokes & kidney failure.

Sodium glucose cotransporter-2 (SGLT-2) has been discovered to be a new target for treating diabetes in recent years. SGLT-2 is mainly distributed in renal proximal
20 tubules. It was responsible for atleast 90% of the glucose reabsorption in the kidney.

Dapagliflozin propanediol monohydrate (also designated as FARXIGA[®]) is inhibitor of sodium dependent glucose transporter-2 which is chemically represented as (2*S*, 3*R*, 4*R*, 5*S*,6*R*)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-
25 (hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol, (2*S*)-propane-1,2-diol (1:1) monohydrate and is also known as D-glucitol, 1,5-anhydro-1-*C*-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-(1*S*)-compounded with (2*S*)-1,2-propanediol hydrate (1:1:1) having structural formula as represented by



US patent No. 6,515,117 discloses dapagliflozin or a pharmaceutically acceptably salts, a stereoisomer thereof or a prodrug ester thereof. Dapagliflozin in the form of a non-crystalline solid is disclosed in US'117 patent.

WO 2008/002824, WO 2014/178040, WO 2015/011113 & WO 2015/104658 disclose various crystalline forms, solvates, co-crystals and solid dispersion of dapagliflozin.

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The glass transition temperature of an amorphous dapagliflozin is very low and it is hygroscopic in nature, which results semisolid or gel like consistency. The amorphous solids in general having low glass transition temperature not only create complications during formulation but also has stability related problem on storage. Hence, there is a need to develop premix of dapagliflozin which is suitable for pharmaceutical preparation and pharmaceutical composition comprising same.

Though, there are processes available in the literature for the preparation of crystalline dapagliflozin propanediol hydrate, still there remains a need for the cost effective and industrially applicable process for the preparation of crystalline dapagliflozin propanediol hydrate.

20

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a premix of dapagliflozin with lactose and process for the preparation thereof.

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In another aspect, the present invention provides a process for the preparation of an amorphous form of dapagliflozin.

5 In yet another aspect, the present invention provides a process for the preparation of crystalline dapagliflozin propanediol hydrate.

In yet another aspect, the present invention provides D-P complex of dapagliflozin and process for the preparation thereof.

10

In yet another aspect, the present invention provides flozin-amino acid complex and process for the preparation thereof.

In yet another aspect, the present invention provides pharmaceutical composition
15 comprising premix of dapagliflozin with lactose together with one or more pharmaceutically acceptable excipients and process for the preparation thereof.

BRIEF DESCRIPTION OF THE FIGURE

20 Fig. 1: depicts the X-ray powder diffraction pattern of premix of dapagliflozin with lactose.

Fig. 2: depicts the differential scanning calorimetry pattern of premix of dapagliflozin with lactose.

Fig. 3: depicts the thermogravimetric analysis pattern of premix of dapagliflozin with
25 lactose.

Fig. 4: depicts the X-ray powder diffraction pattern of lactose (upper) compared with dapagliflozin-lactose premix (lower).

Fig. 5: depicts the X-ray powder diffraction pattern of an amorphous dapagliflozin.

Fig. 6: depicts the X-ray powder diffraction pattern of D-P_A complex of formula (II_A).

30 Fig. 7: depicts the differential scanning calorimetry pattern of D-P_A complex of formula (II_A).

Fig. 8: depicts the thermogravimetric analysis pattern of D-P_A complex of formula (II_A).

Fig. 9: depicts the X-ray powder diffraction pattern of D-P_B complex of formula (II_B).

Fig. 10: depicts the differential scanning calorimetry pattern of D-P_B complex of formula (II_B).

Fig. 11: depicts the thermogravimetric analysis pattern of D-P_B complex of formula (II_B).

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DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the present invention provides a premix of dapagliflozin with lactose.

10 In another aspect, the present invention provides a premix of dapagliflozin with lactose, wherein the weight ratio of dapagliflozin to the lactose is from about 1:0.01 to 1:100, preferably 1:0.1 to 1:10.

In one embodiment, a premix of dapagliflozin with lactose characterized by one or
15 more of the following:

- (i) X-ray powder diffraction pattern as depicted in Figure 1;
- (ii) differential scanning calorimetry pattern as depicted in Figure 2; and
- (iii) thermogravimetric analysis pattern as depicted in Figure 3.

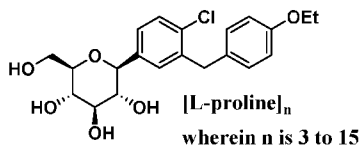
20 In another embodiment, premix of dapagliflozin with lactose having same X-ray powder diffraction pattern as depicted in Figure 1, which shows crystalline nature of lactose, while dapagliflozin remains as amorphous in premix.

In yet another embodiment, a premix of dapagliflozin with lactose; wherein, the
25 premix contains amorphous dapagliflozin in stable form.

In yet another aspect, the invention provides a process for the preparation of the premix of dapagliflozin with lactose comprising the steps of:

(a) providing solution of crude dapagliflozin in suitable solvent or mixtures
30 thereof;

(b) preparing D-P complex of dapagliflozin of formula (II) by treating solution of crude dapagliflozin with 3 to 15 molar equivalents of L-proline;



D-P complex of formula (II)

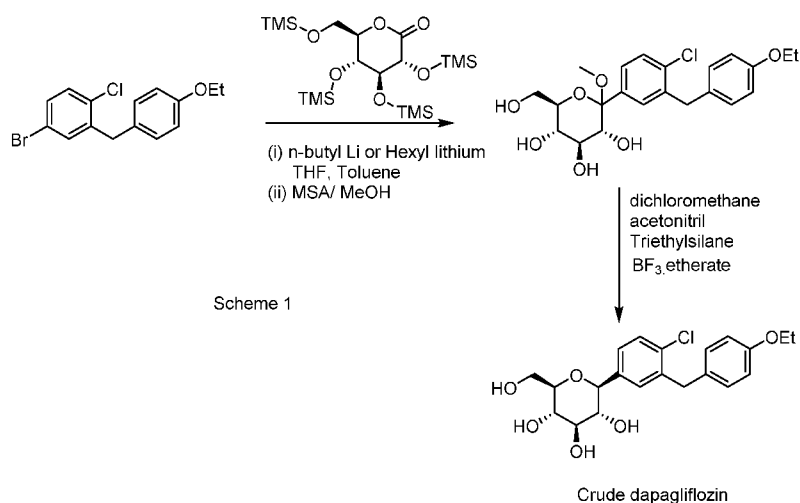
(c) converting D-P complex of dapagliflozin of formula (II) into dapagliflozin, by treating the solution of D-P complex of formula (II) in suitable solvent or mixtures thereof with water;

- 5 (d) providing solution of dapagliflozin obtained in step (c);
 (e) adding the solution of step (d) into an antisolvent and lactose or vice versa;
 (f) isolating premix of dapagliflozin with lactose.

Providing solution of crude dapagliflozin in step (a) includes:

- 10 (i) direct use of reaction mixture containing dapagliflozin that is obtained during its synthesis; or
 (ii) dissolving dapagliflozin in suitable solvent or mixtures thereof.

Crude dapagliflozin that may be used as the input for the process of the invention
 15 may be obtained by any process including the process described in the art. For example, crude dapagliflozin may be prepared by the process schematically represented as follows in scheme 1:



Suitable solvents that may be used in step (a) is selected from the group comprising of alcohol, ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, water, nitrile and mixtures thereof in any suitable proportion. Particularly, preferred solvent is selected from the group comprising of methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, acetone, butanone, 2-pentanone, 3-pentanone, methylbutyl ketone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, dichloromethane, ethylene dichloride, acetonitrile, toluene, xylene, water, methyl tert-butyl ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether and mixtures thereof in any suitable proportion. More preferably dichloromethane, isopropyl alcohol or mixtures thereof may be used as suitable solvent.

D-P complex of dapagliflozin of formula (II) may be obtained by adding appropriate amount of L-proline into the solution of dapagliflozin obtained in step (a). The ratio of dapagliflozin to L-proline will depend on amount of amino acid used in complex formation. While developing the process, the inventors come across by increasing the amount of L-proline in the reaction which results higher yield of the product. D-P complex of dapagliflozin of formula (II) may be obtained by adding 3 to 15 molar equivalents of L-proline into the solution of dapagliflozin obtained in step (a). The process for the preparation of D-P complex of dapagliflozin with L-proline may be carried out at temperature of room temperature to reflux temperature; preferably reaction mixture may be heated at 35-50°C for a period of 1 to 5 hours. The D-P complex of dapagliflozin may be optionally isolated from the reaction mixture by suitable techniques such as filtration, evaporation, distillation, vacuum drying, centrifugation and the like. The isolated D-P complex may be dried at suitable temperature, preferably at 45-50°C for a period of about 5 hour to about 6 hours.

The obtained D-P complex of dapagliflozin of formula (II) may be converted into dapagliflozin in step (c) by using conventional techniques known in the art. Preferably, dapagliflozin may be obtained by treating the solution of D-P complex of dapagliflozin of formula (II) with water; at lower, ambient, or elevated temperature. Suitable solvents that may be used in step (c) for preparing solution of D-P complex of dapagliflozin is selected

from the group comprising of alcohol, ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, nitrile and mixtures thereof in any suitable proportion. Particularly preferred solvent is selected from the group comprising of methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, acetone, butanone, 2-pentanone, 3-pentanone, methylbutyl ketone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, dichloromethane, ethylene dichloride, acetonitrile, toluene, xylene, methyl tert-butyl ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether and mixtures thereof in any suitable proportion. More preferably isopropyl acetate, ethyl acetate, dichloromethane or mixtures thereof may be used as suitable solvent.

More preferably D-P complex of dapagliflozin of formula (II) may be converted into dapagliflozin by comprising the steps of :

- (i) dissolving D-P complex of dapagliflozin of formula (II) in suitable solvent or mixture thereof;
- (ii) adding water into the solution of step (i);
- (iii) optionally heating the reaction mixture;
- (iv) separating the organic layer; and
- (v) optionally isolated the product.

The dapagliflozin obtained in step (c) is optionally isolated from the reaction mixture by suitable techniques known in the art such as filtration, evaporation, distillation, vacuum drying, centrifugation and the like. Dapagliflozin may optionally be further dried. Drying may be suitably carried out in equipment such as tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer and the like.

Providing solution of dapagliflozin in step (d) includes:

- (i) direct use of reaction mixture containing dapagliflozin that is obtained during its synthesis in step (c); or
- (ii) dissolving dapagliflozin of step (c) in suitable solvent or mixtures thereof.

Suitable solvents that may be used in step (d) is selected from the group comprising of alcohol, hydrocarbon, ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, nitrile and mixtures thereof in any suitable proportion. Particularly preferred solvent is selected from the group comprising of methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, ethylene glycol, glycerol, acetone, butanone, 2-pentanone, 3-pentanone, methylbutyl ketone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, toluene, xylene, dichloromethane, ethylene dichloride, chlorobenzene, acetonitrile, tetrahydrofuran, methyl tert-butyl ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether, 1,2-dimethoxy ethane and mixtures thereof in any suitable proportion. More preferably ethyl acetate, isopropyl acetate, methyl tert-butyl ether (MTBE) or mixtures thereof may be used in any suitable proportion.

Optionally, the solution obtained above may be filtered to remove any insoluble particles. The solution may optionally be treated with carbon, hyflow or any other suitable material to remove colour and/or to clarify the solution.

The anti-solvent for step (e) is selected from the group comprising of n-hexane, n-heptane, n-pentane, cyclohexane, methylcyclohexane, and mixtures thereof in any suitable proportion. More preferably n-heptane may be used as anti-solvent.

The treatment with the antisolvent may be carried out, for example, by adding the solution of dapagliflozin into the antisolvent or vice versa at temperature about -25°C to 10°C, preferably at -25°C to 0°C. The treatment with antisolvent may be followed by stirring the reaction mixture for about 1 hour to about 5 hours.

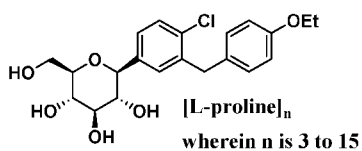
The premix of dapagliflozin with Lactose may be prepared by treating lactose with precipitate obtained in step (e). The obtained premix may be isolated using conventional techniques known in the art. One skilled in the art may appreciate that there are many ways to separate a solid from the mixture, for example it may be separated by using any techniques such as filtration, centrifugation, decantation and the like. After separation, the solid may optionally be washed with a suitable solvent.

Alternatively, the premix of dapagliflozin with Lactose may be prepared by treating the solution of dapagliflozin of step (d) with the suspension or slurry of antisolvent and lactose or vice versa at temperature about -25°C to about 10°C, preferably at -25°C to 0°C. The treatment with antisolvent may be followed by stirring the reaction mixture for about 1 hour to 5 hours. The obtained premix may be isolated using conventional techniques known in the art. One skilled in the art may appreciate that there are many ways to separate a solid from the mixture, for example it may be separated by using any techniques such as filtration, centrifugation, decantation and the like. After separation, the solid may optionally be washed with a suitable solvent. The premix may optionally be further dried. Drying may be suitably carried out in equipment such as tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer and the like. The drying may be carried out at suitable temperature, preferably at about 45°C to about 60°C, optionally under reduced pressure. The drying may be carried out for any time periods necessary for obtaining a product with desired purity.

In one embodiment, the invention provides a process for the preparation of the premix of dapagliflozin with lactose comprising the steps of:

(a) providing solution of crude dapagliflozin in the mixture of dichloromethane and isopropanol;

(b) preparing D-P complex of dapagliflozin of formula (II) by treating solution of crude dapagliflozin of step (a) with 3 to 15 molar equivalents of L-proline;



D-P complex of formula (II)

(c) converting D-P complex of dapagliflozin of formula (II) into dapagliflozin, by treating the solution of D-P complex of formula (II) in isopropyl acetate with water;

(d) providing solution of dapagliflozin obtained in step (c);

(e) distilling off the solvent till 0.5 to 1.0 volumes of solvent remains behind;

(f) adding methyl *tert*-butyl ether into the reaction mixture;

(g) adding the solution of step (f) into the slurry or suspension of n-heptane and lactose or vice versa;

(h) isolating premix of dapagliflozin with lactose.

5 Providing solution of crude dapagliflozin in step (a) includes:

(i) direct use of reaction mixture containing dapagliflozin that is obtained during its synthesis; or

(ii) dissolving dapagliflozin in the mixture of dichloromethane and isopropanol.

10

Crude dapagliflozin that may be used as the input for the process of the invention may be obtained by any process including the process described in the art. D-P complex of dapagliflozin of formula (II) may be obtained by adding 3 to 15 molar equivalents of L-proline into the solution of Dapagliflozin obtained in step (a). The process for the preparation of D-P complex of dapagliflozin with L-proline may be carried out at temperature of room temperature to reflux temperature for few minutes; preferably reaction mixture may be heated at 35-50°C for a period of 1 to 5 hours. The D-P complex of dapagliflozin is optionally isolated from the reaction mixture by suitable techniques such as filtration, evaporation, distillation, vacuum drying, centrifugation and the like.

15 The isolated D-P complex may be dried at suitable temperature, preferably at 45°C to 50°C for a period of about 5 hours to about 6 hours.

The obtained D-P complex of dapagliflozin of formula (II) may be converted into dapagliflozin in step (c) by using conventional techniques known in the art; at lower, ambient, or elevated temperature. Preferably, dapagliflozin may be obtained by treating the solution of D-P complex of dapagliflozin of formula (II) in isopropyl acetate with water.

25 More preferably D-P complex of dapagliflozin of formula (II) may be converted into dapagliflozin by comprising the steps of:

(i) dissolving D-P complex of dapagliflozin of formula (II) in isopropyl acetate;

- (ii) adding water into the solution of step (i);
- (iii) optionally heating the reaction mixture;
- (iv) separating the organic layer;
- (v) optionally isolated the product.

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The dapagliflozin obtained in step (c) may be optionally isolated from the reaction mixture by suitable techniques known in the art such as filtration, evaporation, distillation, vacuum drying, centrifugation and the like. Dapagliflozin may optionally be further dried. Drying may be suitably carried out in equipment such as tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer and the like.

10

Providing solution of dapagliflozin in step (d) includes:

- (i) direct use of reaction mixture containing dapagliflozin that is obtained during its synthesis in step (c); or
- (ii) dissolving dapagliflozin of step (c) in isopropyl acetate.

15

Optionally, the solution obtained above may be filtered to remove any insoluble particles. The solution may optionally be treated with carbon, hyflow or any other suitable material to remove colour and/or to clarify the solution.

20

The reaction mixture may be distilled out till 0.5 to 1.0 volumes of solvent remains behind. Optionally, the solution obtained after addition of methyl *tert* butyl ether in step (f) may be filtered to remove any insoluble particles. The solution may optionally be treated with carbon, hyflow or any other suitable material to remove colour and/or to clarify the solution.

25

The premix of dapagliflozin with lactose may be prepared by adding the solution of dapagliflozin of step (f) into the suspension or slurry of n-heptane and lactose at temperature about -25°C to 10°C, preferably at -25°C to -10°C. The resultant mixture may be further stirring for a time period of about 2-3 hours.

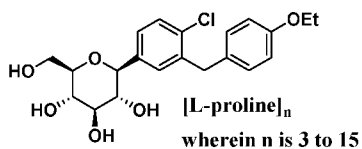
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The obtained precipitate may be isolated using conventional techniques known in the art. One skilled in the art may appreciate that there are many ways to separate a solid from the mixture, for example it may be separated by using any techniques such as filtration, centrifugation, decantation and the like. After separation, the solid may optionally be washed with a suitable solvent. The premix may optionally be further dried. Drying may be suitably carried out in equipment such as tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer and the like. The drying may be carried out at suitable temperature, preferably at about 45°C to about 60°C, optionally under reduced pressure. The drying may be carried out for any time periods necessary for obtaining a product with desired purity.

In yet another aspect, the invention provides a process for the preparation of amorphous dapagliflozin comprising the steps of:

(a) providing solution of crude dapagliflozin in suitable solvent or mixtures thereof;

(b) preparing D-P complex of dapagliflozin of formula (II) by treating solution of crude dapagliflozin with 3 to 15 molar equivalents of L-proline;



D-P complex of formula (II)

(c) converting D-P complex of dapagliflozin of formula (II) into dapagliflozin, by treating the solution of D-P complex of formula (II) in suitable solvent or mixtures thereof with water;

(d) providing solution of dapagliflozin obtained in step (c);

(e) treating the solution of step (d) with an antisolvent;

(f) isolating amorphous dapagliflozin.

Providing solution of crude dapagliflozin in step (a) includes:

(i) direct use of reaction mixture containing dapagliflozin that is obtained during its synthesis; or

(ii) dissolving dapagliflozin in suitable solvent or mixtures thereof.

Crude dapagliflozin that may be used as the input for the process of the invention may be obtained by any process including the process described in the art.

5

Suitable solvents that may be used in step (a) is selected from the group comprising of alcohol, ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, water, nitrile and mixtures thereof in any suitable proportion. Particularly, preferred solvent is selected from the group comprising of methanol, ethanol, isopropanol, 2-propanol, 1-
10 butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, acetone, butanone, 2-pentanone, 3-pentanone, methylbutyl ketone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, dichloromethane, ethylene dichloride, acetonitrile, toluene, xylene, water, methyl tert-butyl ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether and mixtures thereof in any
15 suitable proportion. More preferably dichloromethane, isopropyl alcohol or mixtures thereof may be used as suitable solvent.

D-P complex of dapagliflozin of formula (II) may be obtained by adding 3 to 15 molar equivalents of L-proline into the solution of dapagliflozin obtained in step (a). The
20 process for the preparation of D-P complex of dapagliflozin with L-proline may be carried out at temperature of room temperature to reflux temperature; preferably reaction mixture may be heated at 35-50°C for a period of 1 to 5 hours. The D-P complex of dapagliflozin may be optionally isolated from the reaction mixture by suitable techniques such as filtration, evaporation, distillation, vacuum drying, centrifugation and the like.
25 The isolated D-P complex may be dried at suitable temperature, preferably at 45-50°C for a time 5-6 hours.

The obtained D-P complex of dapagliflozin of formula (II) may be converted into dapagliflozin in step (c) by using conventional techniques known in the art. Preferably,
30 dapagliflozin may be obtained by treating the solution of D-P complex of dapagliflozin of formula (II) with water; at lower, ambient, or elevated temperature. Suitable solvents that may be used in step (c) for preparing solution of D-P complex of dapagliflozin is selected

from the group comprising of alcohol, ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, nitrile and mixtures thereof in any suitable proportion. Particularly, preferred solvent is selected from the group comprising of methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, acetone, butanone, 2-pentanone, 3-pentanone, methylbutyl ketone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, dichloromethane, ethylene dichloride, acetonitrile, toluene, xylene, methyl tert-butyl ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether and mixtures thereof in any suitable proportion. More preferably isopropyl acetate, ethyl acetate, dichloromethane or mixtures thereof may be used as suitable solvent.

More preferably D-P complex of dapagliflozin of formula (II) may be converted into dapagliflozin by comprising the steps of:

- (i) dissolving D-P complex of dapagliflozin of formula (II) in suitable solvent or mixture thereof;
- (ii) adding water into the solution of step (i);
- (iii) optionally heating the reaction mixture;
- (iv) separating the organic layer; and
- (v) optionally isolated the product.

The dapagliflozin obtained in step (c) is optionally isolated from the reaction mixture by suitable techniques known in the art such as filtration, evaporation, distillation, vacuum drying, centrifugation and the like. The obtained dapagliflozin may optionally be further dried. Drying may be suitably carried out in equipment such as tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer and the like.

Providing solution of dapagliflozin in step (d) includes:

- (i) direct use of reaction mixture containing dapagliflozin that is obtained during its synthesis in step (c); or
- (ii) dissolving dapagliflozin of step (c) in suitable solvent or mixtures thereof.

Suitable solvents that may be used in step (d) is selected from the group comprising of alcohol, hydrocarbon, ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, nitrile and mixtures thereof in any suitable proportion. Particularly, preferred solvent is selected from the group comprising of methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, ethylene glycol, glycerol, acetone, butanone, 2-pentanone, 3-pentanone, methylbutyl ketone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, toluene, xylene, dichloromethane, ethylene dichloride, chlorobenzene, acetonitrile, tetrahydrofuran, methyl tert-butyl ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether, 1,2-dimethoxy ethane and mixtures thereof in any suitable proportion. More preferably ethyl acetate, isopropyl acetate, methyl tert-butyl ether (MTBE) or mixtures thereof may be used in any suitable proportion.

15

Optionally, the solution obtained above may be filtered to remove any insoluble particles. The solution may optionally be treated with carbon, hyflow or any other suitable material to remove colour and/or to clarify the solution.

20 The anti-solvent for step (e) is selected from the group comprising of n-hexane, n-heptane, n-pentane, cyclohexane, methylcyclohexane, and mixtures thereof in any suitable proportion. More preferably n-heptane may be used as anti-solvent.

The treatment with the antisolvent may be carried out, for example, by adding the solution of dapagliflozin into the antisolvent or vice versa at temperature about -25°C to 30°C, preferably at -25°C to 0°C. The treatment with antisolvent may be followed by stirring the mixture for about 1-5 hours.

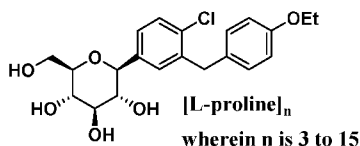
30 The obtained amorphous dapagliflozin may be isolated using conventional techniques known in the art. One skilled in the art may appreciate that there are many ways to separate a solid from the mixture, for example it may be separated by using any techniques such as filtration, centrifugation, decantation and the like. After separation, the

solid may optionally be washed with a suitable solvent. The drying may be carried out at suitable temperature, optionally under reduced pressure. The drying may be carried out for any time periods necessary for obtaining a product with desired purity.

5 In yet another embodiment, the invention provides a process for the preparation of amorphous dapagliflozin comprising the steps of:

(a) providing solution of crude dapagliflozin in the mixture of chlorinated hydrocarbon and alcohol solvent;

10 (b) preparing D-P complex of dapagliflozin of formula (II) by treating solution of crude dapagliflozin of step (a) with 3 to 15 molar equivalents of L-proline;



D-P complex of formula (II)

(c) converting D-P complex of dapagliflozin of formula (II) into dapagliflozin, by treating the solution of D-P complex of formula (II) in ester with water;

(d) adding ether solvent into the reaction mixture;

15 (e) adding the solution of step (e) into the antisolvent or vice versa;

(f) isolating amorphous dapagliflozin.

Providing solution of crude dapagliflozin in step (a) includes:

20 (i) direct use of reaction mixture containing dapagliflozin that is obtained during its synthesis; or

(ii) dissolving dapagliflozin in mixture of hydrocarbon and alcohol solvent.

25 Crude dapagliflozin that may be used as the input for the process of the invention may be obtained by any process including the process described in the art. Chlorinated hydrocarbon & alcohol solvent used in step (a) is selected from the group comprising of methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, dichloromethane, ethylene dichloride, toluene and xylene.

D-P complex of dapagliflozin of formula (II) may be obtained by adding 3 to 15 molar equivalents of L-proline into the solution of Dapagliflozin obtained in step (a). The process for the preparation of D-P complex of dapagliflozin with L-proline may be carried out at temperature of room temperature to reflux temperature; preferably reaction mixture may be heated at 35-50°C for a period of 1 to 5 hours. The D-P complex of dapagliflozin may be optionally isolated from the reaction mixture by suitable techniques such as filtration, evaporation, distillation, vacuum drying, centrifugation and the like. The isolated D-P complex may be dried at suitable temperature, preferably at 45°C to 50°C for a time 5-6 hours.

The obtained D-P complex of dapagliflozin of formula (II) may be converted into dapagliflozin in step (c) by using conventional techniques known in the art; at lower, ambient, or elevated temperature. Preferably, dapagliflozin may be obtained by treating the solution of D-P complex of dapagliflozin of formula (II) in ester solvent with water. Ester solvent used herein is selected from the group comprising of ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, and mixtures thereof.

More preferably D-P complex of dapagliflozin of formula (II) may be converted into dapagliflozin by comprising the steps of:

- (i) dissolving D-P complex of dapagliflozin of formula (II) in isopropyl acetate;
- (ii) adding water into the solution of step (i);
- (iii) optionally heating the reaction mixture;
- (iv) separating the organic layer;
- (v) optionally isolated the product.

The dapagliflozin obtained in step (c) may be optionally isolated from the reaction mixture by suitable techniques known in the art such as filtration, evaporation, distillation, vacuum drying, centrifugation and the like. Dapagliflozin may optionally be

further dried. Drying may be suitably carried out in equipment such as tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer and the like.

Providing solution of dapagliflozin in step (d) includes:

- 5 (i) direct use of reaction mixture containing dapagliflozin that is obtained during its synthesis in step (c); or
- (ii) dissolving dapagliflozin of step (c) in suitable solvent or mixtures thereof.

- 10 Optionally, the solution obtained above may be filtered to remove any insoluble particles. The solution may optionally be treated with carbon, hyflow or any other suitable material to remove colour and/or to clarify the solution.

15 The reaction mixture may be distilled out till 0.5 to 1.0 volumes of solvent remains behind. Optionally, the solution obtained after addition of ester solvent in step (d) may be filtered to remove any insoluble particles. The solution may optionally be treated with carbon, hyflow or any other suitable material to remove colour and/or to clarify the solution. Ether solvent used in step (d) is selected from the group comprising of methyl tert-butyl ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether and mixtures thereof.

20 The amorphous dapagliflozin may be prepared by adding the solution of dapagliflozin of step (d) into the suitable antisolvent at temperature about -25°C to 30°C, preferably at -25°C to -10°C. The resultant mixture may be further stirring for about 2-3 hours. The anti-solvent for step (e) is selected from the group comprising of n-hexane, n-heptane, n-pentane, cyclohexane, methylcyclohexane, and mixtures thereof in any

25 suitable proportion. More preferably n-heptane may be used as anti-solvent.

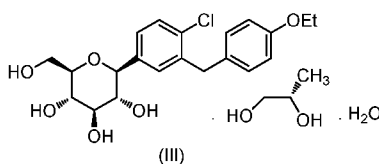
 The treatment with the antisolvent may be carried out, for example, by adding the solution of dapagliflozin of step (d) into the suitable antisolvent or vice versa at

30 temperature about -25°C to about 30°C, preferably at -25°C to -10°C. The treatment with antisolvent may be followed by stirring the reaction mixture for about 10 minutes to 20

hours, preferably about 1 hour to 5 hours. The stirring may be carried out at about -30°C to about 50°C, preferably at -15°C to 10°C.

The obtained precipitate may be isolated using conventional techniques known in the art. One skilled in the art may appreciate that there are many ways to separate a solid from the mixture, for example it may be separated by using any techniques such as filtration, centrifugation, decantation and the like. After separation, the solid may optionally be washed with a suitable solvent. The amorphous dapagliflozin may optionally be further dried. Drying may be suitably carried out in equipment such as tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer and the like. The drying may be carried out at suitable temperature, optionally under reduced pressure. The drying may be carried out for any time periods necessary for obtaining a product with desired purity. Amorphous dapagliflozin obtained by above process of the invention is characterized by X-ray powder diffraction pattern. The powder X-ray powder diffraction pattern (Fig.5) shows product to be in amorphous form.

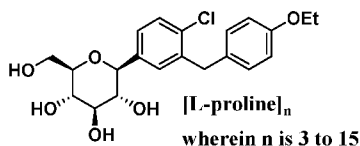
In yet another aspect, the invention provides a process for the preparation of the crystalline dapagliflozin propanediol hydrate of formula (III)



comprising the steps of:

(a) providing solution of crude dapagliflozin in suitable solvent or mixtures thereof;

(b) preparing D-P complex of dapagliflozin of formula (II) by treating solution of crude dapagliflozin with 3 to 15 molar equivalents of L-proline;



D-P complex of formula (II)

(c) converting D-P complex of formula (II) into dapagliflozin, by treating the solution of D-P complex of formula (II) in suitable solvent or mixtures thereof with water;

(d) providing solution of dapagliflozin obtained in step (c);

5 (e) adding (S)- propylene glycol;

(f) optionally seeded with previously prepared compound of formula (III);

(g) isolating crystalline dapagliflozin propanediol hydrate of formula (III).

Providing solution of crude dapagliflozin in step (a) includes:

10 (i) direct use of reaction mixture containing dapagliflozin that is obtained during its synthesis; or

(ii) dissolving dapagliflozin in suitable solvent or mixtures thereof.

Crude dapagliflozin that may be used as the input for the process of the invention
15 may be obtained by any process including the process described in the art.

Suitable solvents that may be used in step (a) is selected from the group comprising of alcohol, ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, water, nitrile and mixtures thereof in any suitable proportion. Particularly preferred solvent is
20 selected from the group comprising of methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, acetone, butanone, 2-pentanone, 3-pentanone, methylbutyl ketone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, dichloromethane, ethylene dichloride, acetonitrile, toluene, xylene, water, methyl tert-
25 butyl ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether and mixtures thereof in any suitable proportion. More preferably dichloromethane, isopropyl alcohol or mixtures thereof may be used as suitable solvent.

D-P complex of dapagliflozin of formula (II) may be obtained by adding 3 to 15
30 molar equivalents of L-proline into the solution of Dapagliflozin obtained in step (a). The process for the preparation of D-P complex of dapagliflozin with L-proline may be

carried out at temperature of room temperature to reflux temperature; preferably reaction mixture may be heated at 35-50°C for a period of 1 to 5 hours. The D-P complex of dapagliflozin may be optionally isolated from the reaction mixture by suitable techniques such as filtration, evaporation, distillation, vacuum drying, centrifugation and the like.

- 5 The isolated D-P complex may be dried at suitable temperature, preferably at 45-50°C for a time 5-6 hours.

The obtained D-P complex of dapagliflozin of formula (II) may be converted into dapagliflozin in step (c) by using conventional techniques known in the art. Preferably,
10 dapagliflozin may be obtained by treating the solution of D-P complex of dapagliflozin of formula (II) with water; at lower, ambient, or elevated temperature. Suitable solvents that may be used in step (c) for preparing solution of D-P complex is selected from the group comprising of alcohol, ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, nitrile and mixtures thereof in any suitable proportion. Particularly preferred solvent is selected
15 from the group comprising of methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, acetone, butanone, 2-pentanone, 3-pentanone, methylbutyl ketone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, dichloromethane, ethylene dichloride, acetonitrile, toluene, xylene, methyl tert-butyl
20 ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether and mixtures thereof in any suitable proportion. More preferably isopropyl acetate, methyl acetate, butyl acetate, ethyl acetate, dichloromethane or mixtures thereof may be used as suitable solvent.

More preferably D-P complex of dapagliflozin of formula (II) may be converted
25 into dapagliflozin by comprising the steps of :

- (i) dissolving D-P complex of dapagliflozin of formula (II) in suitable solvent or mixture thereof;
- (ii) adding water into the solution of step (i);
- (iii) optionally heating the reaction mixture;
- 30 (iv) separating the organic layer; and
- (v) optionally isolated the product.

The dapagliflozin obtained in step (c) is optionally isolated from the reaction mixture by suitable techniques known in the art such as filtration, evaporation, distillation, vacuum drying, centrifugation and the like. Dapagliflozin may optionally be further dried. Drying may be suitably carried out in equipment such as tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer and the like.

Providing solution of dapagliflozin in step (d) includes:

- (i) direct use of reaction mixture containing dapagliflozin that is obtained during its synthesis in step (c); or
- (ii) dissolving dapagliflozin of step (c) in suitable solvent or mixtures thereof.

Suitable solvents that may be used in step (d) is selected from the group comprising of alcohol, hydrocarbon, ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, nitrile, water and mixtures thereof in any suitable proportion. Particularly preferred solvent is selected from the group comprising of methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, ethylene glycol, glycerol, acetone, butanone, 2-pentanone, 3-pentanone, methylbutyl ketone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, toluene, xylene, dichloromethane, ethylene dichloride, chlorobenzene, acetonitrile, tetrahydrofuran, methyl tert-butyl ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether, 1,2-dimethoxy ethane, water and mixtures thereof in any suitable proportion. More preferably ethyl acetate, methyl acetate, butyl acetate, isopropyl acetate, methyl tert-butyl ether (MTBE) or mixtures thereof may be used in any suitable proportion.

Optionally, the solution obtained above may be filtered to remove any insoluble particles. The solution may optionally be treated with carbon, hyflow or any other suitable material to remove colour and/or to clarify the solution.

The treatment with the (S)-propylene glycol may be carried out, for example, by adding the (S)-propylene glycol into the solution of dapagliflozin or vice versa at

temperature about -10°C to about 50°C, preferably at 25°C to 30°C. The treatment with (S)-propylene glycol may be followed by stirring the mixture for about 1 to 5 hours. The crystalline dapagliflozin propanediol hydrate of formula (III) may be separated from the slurry using conventional techniques known in the art. For example, the slurry of

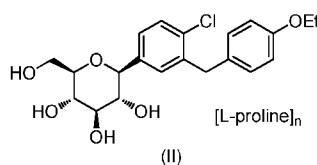
5 compound of formula (III) may be treated with suitable solvents such as n-hexane, n-heptane, n-pentane, cyclohexane, methylcyclohexane, iso-octane or mixtures thereof in any suitable proportion. The obtained crystalline dapagliflozin propanediol hydrate of formula (III) may be isolated using conventional techniques known in the art. One skilled in the art may appreciate that there are many ways to separate a solid from the mixture,

10 for example it may be separated by using any techniques such as filtration, centrifugation, decantation and the like. After separation, the solid may optionally be washed with a suitable solvent. The crystalline dapagliflozin propanediol hydrate of formula (III) may optionally be further dried. Drying may be suitably carried out in equipment such as tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer and the

15 like. The drying may be carried out at suitable temperature, preferably at about 45°C to about 60°C, optionally under reduced pressure. The drying may be carried out for any time periods necessary for obtaining a product with desired purity.

In yet another aspect, the invention provides D-P complex of dapagliflozin of

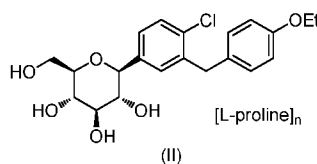
20 formula (II)



wherein n is 3 to 15.

In yet another aspect, the invention provides a process for the preparation of D-P

25 complex of dapagliflozin of formula (II)



wherein n is 3 to 15;

comprising the steps of:

- (a) providing solution of dapagliflozin in suitable solvent or mixtures thereof;
- (b) treating with 3 to 15 molar equivalents of L-proline;
- (c) isolating D-P complex of dapagliflozin of formula (II).

5

Providing solution of crude dapagliflozin in step (a) includes:

- (i) direct use of reaction mixture containing dapagliflozin that is obtained during its synthesis; or
- (ii) dissolving dapagliflozin in suitable solvent or mixtures thereof.

10

Crude dapagliflozin that may be used as the input for the process of the invention may be obtained by any process including the process described in the art.

Suitable solvents that may be used in step (a) is selected from the group comprising of alcohol, ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, water, nitrile and mixtures thereof in any suitable proportion. Particularly preferred solvent is selected from the group comprising of methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, acetone, butanone, 2-pentanone, 3-pentanone, methylbutyl ketone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, dichloromethane, ethylene dichloride, acetonitrile, toluene, xylene, water, methyl tert-butyl ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether and mixtures thereof in any suitable proportion. More preferably dichloromethane, isopropyl alcohol or mixtures thereof may be used as suitable solvent.

25

D-P complex of dapagliflozin of formula (II) may be obtained by adding 3 to 15 molar equivalents of L-proline into the solution of Dapagliflozin obtained in step (a). The process for the preparation of D-P complex of dapagliflozin with L-proline may be carried out at temperature of room temperature to reflux temperature; preferably reaction mixture may be heated at 35-50°C for a period of 1 to 5 hours. The D-P complex of dapagliflozin may be optionally isolated from the reaction mixture by suitable techniques such as filtration, evaporation, distillation, vacuum drying, centrifugation and the like.

30

Drying may be suitably carried out in equipment such as tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer and the like. The drying may be carried out at suitable temperature, optionally under reduced pressure. The drying may be carried out for any time periods necessary for obtaining a product with desired purity.

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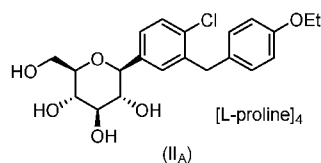
In yet another aspect, use of D-P complex of dapagliflozin of formula (II) of the invention can be utilized for the preparation of premix of dapagliflozin with lactose.

10 In yet another aspect, use of D-P complex of dapagliflozin of formula (II) of the invention can be utilized for the preparation of an amorphous form of dapagliflozin.

In yet another aspect, use of D-P complex of dapagliflozin of formula (II) of the invention can be utilized for the preparation of crystalline dapagliflozin propanediol hydrate.

15

In yet another embodiment, the invention provides D-P_A complex of dapagliflozin of formula (II_A).



20 In another embodiment, the D-P_A complex of dapagliflozin of formula (II_A) is characterized by any one of the following:

- (i) X-ray powder diffraction pattern as depicted in Fig. 6;
- (ii) differential scanning calorimetry pattern as depicted in Fig. 7; and
- (iii) thermogravimetric analysis pattern as depicted in Fig. 8.

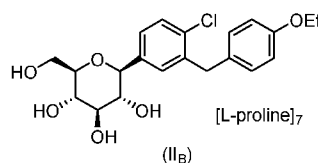
25

In yet another embodiment, the D-P_A complex of dapagliflozin of formula (II_A) is characterized by X-ray powder diffraction pattern comprising the following 2θ values at 4.43, 6.30, 13.26, 14.36, 15.18, and 16.07 +/- 0. 2.

In yet another embodiment, the D-P_A complex of dapagliflozin of formula (II_A) may further be characterized by X-ray powder diffraction peaks having 2θ values at 4.43, 6.30, 6.72, 8.61, 13.26, 14.36, 15.18, 16.07, 18.07, 18.30, 18.79, 18.99, 19.16, 19.56, 19.88, 20.10, 20.51, 24.59 and 24.81+/- 0. 2.

5

In yet another embodiment, the invention provides D-P_B complex of dapagliflozin of formula (II_B)



The D-P_B complex of dapagliflozin of formula (II_B) is characterized by any one of the following:

- (i) X-ray powder diffraction pattern as depicted in Fig. 9;
- (ii) differential scanning calorimetry pattern as depicted in Fig. 10;
- (iii) thermogravimetric analysis pattern as depicted in Fig. 11.

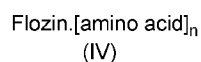
In yet another embodiment, the D-P_B complex of dapagliflozin of formula (II_B) is characterized by X-ray powder diffraction pattern comprising the following 2θ values at 4.41, 6.28, 14.34, 15.16, 18.05, 18.27 and 19.54 +/- 0.2.

In yet another embodiment, use of D-P_A and D-P_B complex of dapagliflozin of the invention can be utilized for the preparation of premix of dapagliflozin with lactose.

In yet another embodiment, use of D-P_A and D-P_B complex of dapagliflozin of the invention can be utilized for the preparation of an amorphous form of dapagliflozin.

In yet another embodiment, use of D-P_A and D-P_B complex of dapagliflozin of the invention can be utilized for the preparation of crystalline dapagliflozin propanediol hydrate.

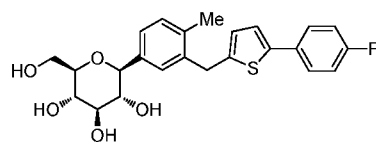
In yet another aspect, the invention provides flozin-amino acid complex of formula (IV)



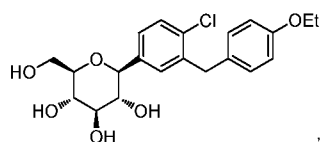
wherein,

5 n is 3 to 15;

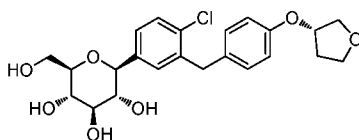
flozin compound is selected from the group comprising of:



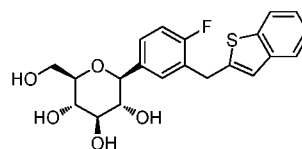
Canagliflozin



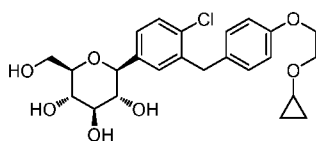
Dapagliflozin



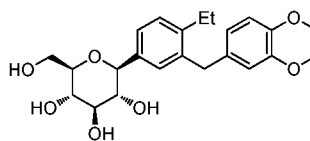
Empagliflozin



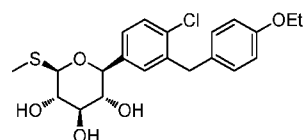
Ipragliflozin



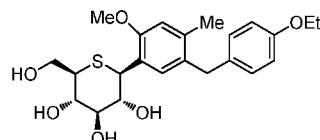
Bexagliflozin



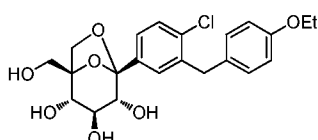
LIK-066



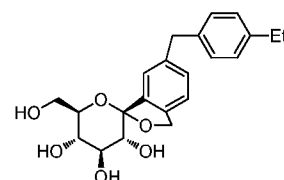
Sotagliflozin



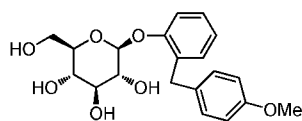
Luseogliflozin



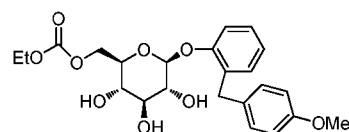
Ertugliflozin



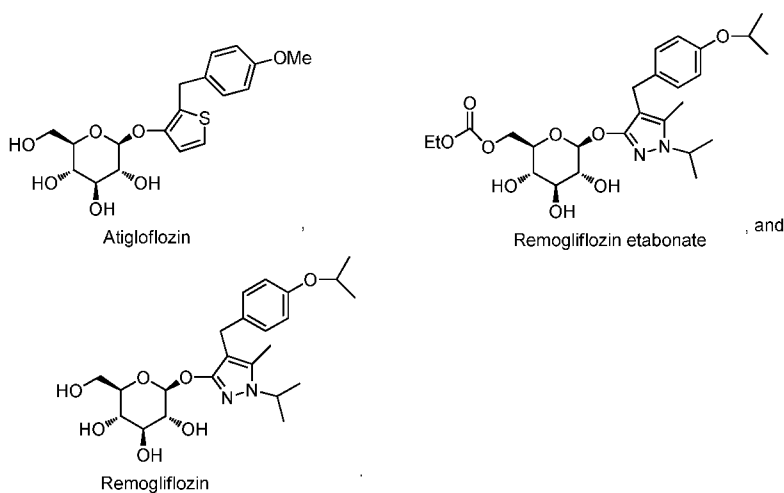
Tofogliflozin



Sergliflozin

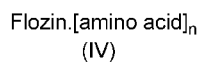


Sergliflozin etabonate



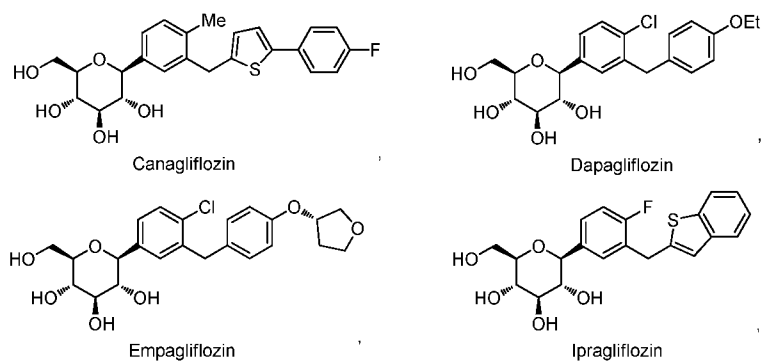
Suitable amino acid that may be used includes alanine, proline, phenylalanine, aspartamine, valine, leucine, isoleucine, tryptophan, methionine, glycine, serine, 5 threonine, cysteine, tyrosine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid or glutamic acid. The amino acid used may be either optically active or racemic form. The optically active amino acid may have either L or D configuration.

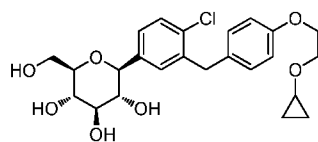
In yet another aspect, the invention provides a process for the preparation of 10 flozin-amino acid complex of formula (IV)



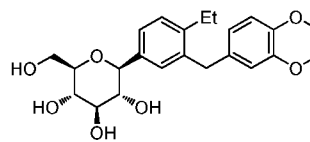
wherein, n is 3 to 15;

flozin compound is selected from the group comprising of:

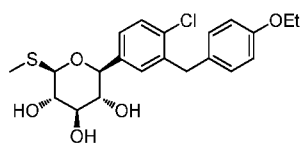




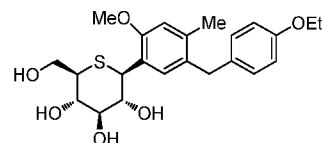
Bexagliflozin



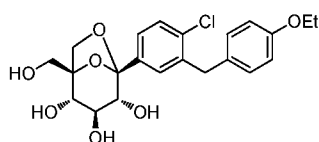
LIK-066



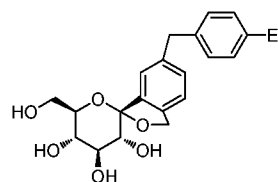
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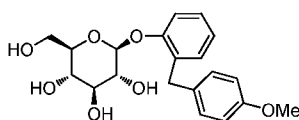
Luseogliflozin



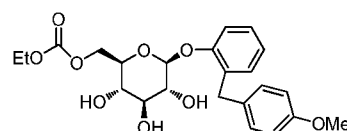
Ertugliflozin



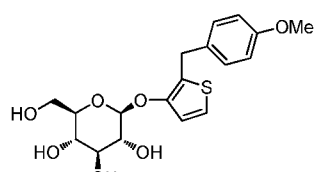
Tofogliflozin



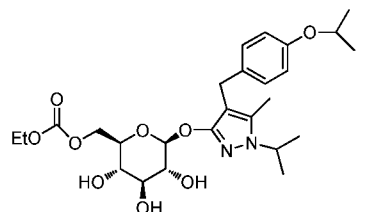
Sergliflozin



Sergliflozin etabonate

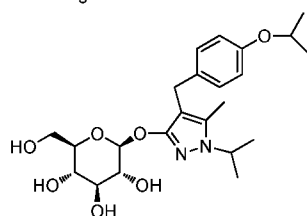


Atigloflozin



Remogliflozin etabonate

, and



Remogliflozin

Suitable amino acid that may be used includes alanine, proline, phenylalanine, aspartamine, valine, leucine, isoleucine, tryptophan, methionine, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, lysine, arginine, histidine, aspartic acid or glutamic acid. The amino acid used may be either optically active or racemic form. The optically active amino acid may have either L or D configuration; comprising the steps of:

- (a) providing solution of flozin compound in suitable solvent or mixtures thereof;
- (b) treating with 3 to 15 molar equivalents of L-proline;
- (c) isolating flozin-amino acid complex of formula (IV).

5 Providing solution of crude flozin compound in step (a) includes:

- (i) direct use of reaction mixture containing flozin compound that is obtained during its synthesis; or
- (ii) dissolving flozin compound in suitable solvent or mixtures thereof.

10 Flozin compound that may be used as the input for the process of the invention may be obtained by any process including the process described in the art. Suitable solvent that may be used in step (a) is selected from the group comprising of alcohol, ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, water, nitrile and mixtures thereof in any suitable proportion. Particularly preferred solvent is selected from the
15 group comprising of methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, acetone, butanone, 2-pentanone, 3-pentanone, methylbutyl ketone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, dichloromethane, ethylene dichloride, acetonitrile, toluene, xylene, methyl tert-butyl
20 ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether and mixtures thereof in any suitable proportion.

The flozin-amino acid complex of formula (IV) may be obtained by adding amino acid into the solution of flozin compound obtained in step (a). The process for the
25 preparation of flozin-amino acid complex of formula (IV) may be carried out at temperature of room temperature to reflux temperature for few minutes to few hours. The flozin-amino acid complex of formula (IV) is isolated from the reaction mixture by suitable techniques such as filtration, evaporation, distillation, vacuum drying, centrifugation and the like. The isolated flozin-amino acid complex of formula (IV)
30 obtained in step (c) is optionally be further dried. Drying may be suitably carried out in equipment such as tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer and the like. The drying may be carried out at suitable temperature,

optionally under reduced pressure. The drying may be carried out for any time periods necessary for obtaining a product with desired purity. The obtained flozin-amino acid complex of formula (IV) may be optionally further converted into flozin by using conventional techniques known in the art.

5

In an aspect of the invention, dapagliflozin-lactose premix prepared according to the processes of the application can be substantially pure having a chemical purity greater than about 99% or greater than about 99.5% by weight when measured by high performance liquid chromatography. The obtained dapagliflozin-lactose premix is stable

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In an aspect of the invention, amorphous dapagliflozin prepared according to the processes of the application can be substantially pure having a chemical purity greater than about 99% or greater than about 99.5% by weight when measured by high

15

In an aspect of the invention, crystalline dapagliflozin propanediol hydrate prepared according to the processes of the application can be substantially pure having a chemical purity greater than about 99% or greater than about 99.5% by weight when

20

In another aspect, the present invention provides pharmaceutical composition comprising premix of dapagliflozin with lactose together with one or more pharmaceutically acceptable excipients for use in treating or preventing diabetes. The

pharmaceuticals can be safely administered orally or non-orally. Routes of administration include, but are not limited to, oral, topical, mucosal, nasal, parenteral, gastrointestinal, intraspinal, intraperitoneal, intramuscular, intravenous, intrauterine, intraocular, intradermal, intracranial, intratracheal, intravaginal, intracerebroventricular, intracerebral, subcutaneous, ophthalmic, transdermal, rectal, buccal, epidural and sublingual.

25
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The pharmaceutical composition can be formulated as solid oral dosage forms such as, but are not limited to, powders, granules, pellets, tablets (single layered tablets,

multilayered tablets, mini tablets, bioadhesive tablets, caplets, matrix tablets, tablet within a tablet, mucoadhesive tablets, immediate release tablets, sustained release tablet, extended release tablet, modified release tablets, pulsatile release tablets, and timed release tablets), beads, granules, sustained release formulations, capsules, microcapsules, 5 tablets in capsules, microspheres, matrix formulations, microencapsulation, or capsules; liquid oral dosage forms such as, but are not limited to, syrups, suspensions, dispersions, or emulsions; or injectable preparations such as, but not limited to, solutions, dispersions, or freeze dried compositions.

10 The term “pharmaceutically acceptable excipients” used in the pharmaceutical composition of invention comprise but are not limited to diluents, binders, pH stabilizing agents, disintegrants, surfactants, glidants and lubricants known in the art.

 The amount of excipient employed will depend upon how much active agent is to 15 be used. One excipient(s) can perform more than one function.

 In another aspect, pharmaceutical composition of present inventions can be used for the treatment or prevention of diabetes.

20 In another aspect, the present invention further provides pharmaceutical composition comprising premix of dapagliflozin with lactose in combination therapy with one or more other active ingredients in a single pharmaceutical composition or separate pharmaceutical compositions.

25 In yet another aspect, the one or more active ingredients which optionally employed in combination therapy may include, but are not limited to other type of antidiabetic agents and/or other types of therapeutic agents.

 The other type of antidiabetic agent which optionally employed in combination 30 may include, but are not limited one or more antidiabetic agents or antihyperglycemic agents including insulin secretagogues or insulin sensitizers, or other antidiabetic agents preferably having a mechanism of action different from SGLT2 inhibition and may

include biguanides, sulfonyl ureas, glucosidase inhibitors, PPAR γ agonists such as thiazolidinediones, α 2 inhibitors, PPAR α/γ dual agonists, dipeptidyl peptidase IV (DP4) inhibitors, and/or meglitinides, as well as insulin, glucagon-like peptide-1 (GLP-1), PTPIB inhibitors, glycogen phosphorylase inhibitors and/or glucos-6-phosphatase inhibitors.

The other types of therapeutic agents which optionally employed in combination may include, but are not limited anti-obesity agents, antihypertensive agents, antiplatelet agents, antiatherosclerotic agents and/or lipid lowering agents.

One skilled in the art will recognize that additional starting compounds and/or reagents are commercially available or may be easily prepared according to conventional methods well known to these skilled in the art.

Analytical Methods:

(1) Powder X-ray Diffraction:

Powder X-ray diffraction can be obtained under following conditions: XRPD pattern is made using Cu K- α 1 radiation at a voltage 40 mA & 45 kV. XRPD pattern was observed at 25°C and scanned from 3.5 to 40 two theta values.

(2) Differential Scanning Calorimetry:

Differential Scanning Calorimetry was performed using a Diamond DSC PERKIN ELMER differential instrument. 2-3 mg samples were placed in crimped aluminum pans and heated from 20°C to 250°C in a dry nitrogen atmosphere at a heating rate of 10°C/minute.

(3) Thermogravimetric analysis:

Thermogravimetric analysis was performed using a Pyris 1 TGA PERKIN ELMER measurement unit. 2-5 mg samples were placed in open Platinum pans and heated from 25°C to 300°C in a dry nitrogen atmosphere at a heating rate of 10°C/min.

EXAMPLES

Following examples are set forth to aid in the understanding of the invention, and are not intended and should not be interpreted as a limitation thereon. Modifications to reaction conditions, for example, temperature, duration of the reaction or combination thereof, are envisioned as part of the invention.

Example 1

2,3,4,6-tetra-O-trimethylsilyl- β -D-glucolactone

Solution of D-glucolactone (1 Kg, 0.0056 mol) and N-methylmorpholine (4.23 Kg, 0.0418 mol) in THF (5 L) was cooled to -20°C to -10°C. Trimethylsilyl chloride (3.17 Kg, 0.029 mol) was added to the reaction mixture. After stirring for 1 hr, the mixture was heated to 40-50°C for 5 to 6 hours whereupon it was allowed to cool to 0-10°C. After dilution with toluene, water was slowly added. The layers were separated and the organic phases washed with aqueous potassium dihydrogen phosphate solution followed by water. The organic layer was dried over sodium sulphate and after concentration to yield oily residue (yield: 2.5 kg).

Example 2

Preparation of D-P_B complex of Dapagliflozin

Hexyl lithium (1.71 L, 6.14 mol) was slowly added to a stirred solution of 4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene (1 kg, 3.07 mol) in THF (4 L) and toluene (4 L) at -100°C to -80°C. After stirring for 60 to 90 minutes at same temperature, solution of 2,3,4,6-tetra-O-trimethylsilyl- β -D-glucolactone (1.93 kg, 4.14 mol) in toluene was slowly added by maintaining the reaction at -105°C to -80°C and mixture was stirred for 2-3 hours at same temperature. Subsequently, a solution of methane sulphonic acid (0.885 Kg) in methanol (3 L) was added to the reaction mixture at -100°C to -50°C and stirred for 1 hour at same temperature. The reaction mixture was further stirred for 2 hours at room temperature. Water was added to the resultant mixture followed by addition of aqueous Na₂CO₃. After phase separation, the organic layer was washed with brine solution, and after concentration to yield oily mass. The obtained oily mass added in to dichloromethane (4.5 L) and acetonitrile; and resultant mass was stirred under nitrogen atmosphere at room temperature. The reaction mixture was cooled at -35°C to -25°C. To this stirred solution was added triethylsilane (1.07 kg, 9.21 mol) followed by addition of

BF₃Et₂O (1 L). Approximately 30 minutes after addition was complete; the resulting mixture was stirred at room temperature. After completion of reaction, the mixture was cooled at 0-10°C and further quenched by the addition of aqueous NaHCO₃ solution. After phase separation, L-proline (1.41 kg) in isopropanol (5 L) was added into the organic layer containing product. The reaction mixture was heated at 35-40°C for 1-2 hours. The reaction mixture was cooled at room temperature and further stirred for 1 hour. The resultant precipitate was filtered and dried to obtain title compound (yield: 2.0 Kg).

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Example 3

Preparation of premix of Dapagliflozin with lactose

To a stirred solution of D-P_B complex of dapagliflozin (1 kg, 1.90 mol) in isopropyl acetate (5 L) was added water (5 L). The reaction mixture was stirred at room temperature for 30 to 60 minutes. After phase separation, the organic layer was distilled out till 0.5 to 1.0 volumes of solvent remains behind. Methyl tert-butyl ether (3L) was added and resultant mixture was heated at 40-50°C. The resultant solution was added to the pre-chilled solution of n-heptane (12.5 L) at 0 to -10°C; the solid precipitated and lactose was added and the resultant mass was stirred for 1-2 hours at 0-10°C. The reaction mixture was filtered, washed with n-heptane and further dried to obtain dapagliflozin-lactose premix (yield: 0.580 Kg).

20

Example 4

Preparation of amorphous Dapagliflozin

To a stirred solution of D-P_B complex of dapagliflozin (1 Kg) in isopropyl acetate (5L) was added water (5L). The reaction mixture was stirred at room temperature for 30 to 60 minutes. After phase separation, the organic layer was distilled out till 0.5 to 1.0 volumes of solvent remains behind. Methyl tert-butyl ether (3 L) was added and resultant mixture was heated at 40-50°C. The resultant solution was added to the pre-chilled solution of n-heptane (12.5 L) at 0 to -10°C. The solid precipitated was filtered and dried to obtain amorphous dapagliflozin (yield: 0.420 gm).

30

Example 5

Preparation of D-P_A complex of Dapagliflozin

Hexyl lithium (1.71 L, 6.14 mol) was slowly added to a stirred solution of 4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene (1 kg, 3.07 mol) in THF (4 L) and toluene (4 L) at -100°C to -80°C. After stirring for 60 to 90 minutes at same temperature, solution of 2,3,4,6-tetra-O-trimethylsilyl-β-D-glucolactone (1.93 kg, 4.14 mol) in toluene was slowly added by maintaining the reaction at -100°C to -80°C and mixture was stirred for 2-3 hours at same temperature. Subsequently, a solution of methane sulphonic acid (0.885 Kg) in methanol (3 L) was added to the reaction mixture at -100°C to -50°C and stirred for 1 hour at same temperature. The reaction mixture was further stirred for 2 hours at room temperature. Water was added to the resultant mixture followed by addition of aqueous Na₂CO₃. After phase separation, the organic layer was washed with brine solution, and after concentration to yield oily mass. The obtained oily mass added in to dichloromethane (4.5 L) and resultant mass was stirred under nitrogen atmosphere at room temperature. The reaction mixture was cooled at -35°C to -25°C. To this stirred solution was added triethylsilane (1.07 kg, 9.21 mol) followed by addition of BF₃Et₂O (1 L). Approximately 30 minutes after addition was complete; the resulting mixture was stirred at room temperature. After completion of reaction, the mixture was cooled at 0-10°C and further quenched by the addition of aqueous NaHCO₃ solution. After phase separation, L-proline (1.06 kg) in isopropanol (5 L) was added into the organic layer containing product. The reaction mixture was heated at 35-40°C for 1-2 hours. The reaction mixture was cooled at room temperature and further stirred for 1 hour. The resultant precipitate was filtered and dried to yield title compound.

Example 6

Preparation of premix of Dapagliflozin with lactose

To a stirred solution of D-P complex of dapagliflozin (1 kg, 1.90 mol) in isopropyl acetate (5 L) was added water. The reaction mixture was stirred at room temperature for 30 to 60 minutes. After phase separation, the organic layer was distilled out till 0.5 to 1.0 volumes of solvent remains behind. Methyl tert-butyl ether (2 L) was added and resultant mixture was heated at 40-50°C. The reaction mixture was filtered through micron assembly. The resultant solution was added to the pre-chilled suspension of n-heptane

(12.5 L) and anhydrous lactose at -25 to 0°C; the solid precipitated and Lactose was added and the resultant mass was stirred for 1-2 hours at 0-10°C. The reaction mixture was filtered, washed with n-heptane and further dried to obtain dapagliflozin-lactose premix (yield: 0.58 Kg).

5

Example 7

Preparation of crystalline dapagliflozin propanediol hydrate

To a stirred solution of D-P complex of dapagliflozin (250 gm) in isopropyl acetate (1250 ml) was added water (1250 ml). The reaction mixture was stirred at room temperature for 30 to 60 minutes and organic layer was separated. (S)-1,2-propanediol was added into the organic layer and resultant mixture was stirred at room temperature for 10 to 20 minutes. The resultant mixture was seeded with previously prepared crystalline dapagliflozin propanediol hydrate and further stirred at room temperature for 1 to 2 hours. n-heptane (1250 ml) was added to the resultant mixture and further cooled to from room temperature to 5°C. The mixture was stirred at same temperature for 2 hours to 3 hours. The solid precipitated was filtered, washed with n-heptane and dried to obtain crystalline dapagliflozin propanediol hydrate (yield: 119.2 gm).

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CLAIMS

1. A premix of dapagliflozin with lactose, wherein the weight ratio of dapagliflozin to the lactose is from about 1:0.1 to 1:10.

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2. The premix according to claim 1, characterized by one or more of the following:

- (i) X-ray powder diffraction pattern as depicted in Figure 1;
- (ii) differential scanning calorimetry pattern as depicted in Figure 2; and
- (iii) thermogravimetric analysis pattern as depicted in Figure 3.

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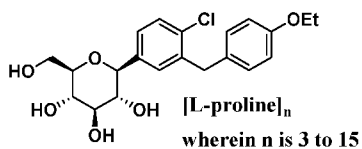
3. The premix according to claim 1; wherein the premix contains amorphous dapagliflozin in stable form.

4. A process for the preparation of premix of dapagliflozin with lactose comprising the steps of:

15

(a) providing solution of crude dapagliflozin in suitable solvent or mixtures thereof;

(b) preparing D-P complex of dapagliflozin of formula (II) by treating solution of crude dapagliflozin with 3 to 15 molar equivalents of L-proline;



20

D-P complex of formula (II)

(c) converting D-P complex of dapagliflozin of formula (II) into dapagliflozin, by treating the solution of D-P complex of formula (II) in suitable solvent or mixtures thereof with water;

(d) providing solution of dapagliflozin obtained in step (c);

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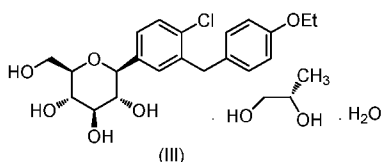
(e) adding the solution of step (d) into an antisolvent and lactose or vice versa;

(f) isolating premix of dapagliflozin with lactose.

5. The process according to claim 4, wherein the suitable solvent used in step (a) is selected from the group comprising of alcohol, ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, nitrile and mixtures thereof.
- 5 6. The process according to claim 4, wherein the suitable solvent in step (a) is a mixture of chlorinated hydrocarbon and alcohol.
7. The process according to claim 4, wherein the suitable solvent used in step (c) for preparing solution of D-P complex of formula (II) is selected from the group comprising
10 of ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, nitrile and mixtures thereof.
8. The process according to claim 4, wherein ester solvent used in step (c) for preparing solution of D-P complex of formula (II) is selected from the group comprising of ethyl
15 acetate, methyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, and mixtures thereof.
9. The process according to claim 4, wherein the suitable solvent used in step (d) is selected from the group comprising of alcohol, hydrocarbon, chlorinated hydrocarbon,
20 ketone, ester, ether, hydrocarbon, nitrile, and mixtures thereof.
10. The process according to claim 4, wherein ether solvent used in step (d) is selected from the group comprising of methyl tert-butyl ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether and mixtures thereof.
25
11. The process according to claim 4, wherein anti-solvent for step (e) is selected from the group comprising of n-hexane, n-heptane, n-pentane, cyclohexane, methylcyclohexane, and mixtures thereof.
- 30 12. The process according to claim 4, wherein mixture of dichloromethane and isopropanol is used as a suitable solvent in step (a); isopropyl acetate is used as a suitable

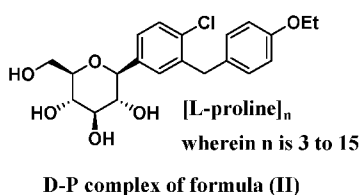
solvent in step (c); methyl tert-butyl ether is used as a suitable solvent in step (d); and n-heptane is used as antisolvent in step (e).

13. A process for the preparation of the crystalline dapagliflozin propanediol hydrate of formula (III)



comprising the steps of:

- (a) providing solution of crude dapagliflozin in suitable solvent or mixtures thereof;
- (b) preparing D-P complex of dapagliflozin of formula (II) by treating solution of crude dapagliflozin with 3 to 15 molar equivalents of L-proline;



- (c) converting D-P complex of formula (II) into dapagliflozin, by treating the solution of D-P complex of formula (II) in suitable solvent or mixtures thereof with water;
- (d) providing solution of dapagliflozin obtained in step (c);
- (e) adding (S)- propylene glycol;
- (f) optionally seeded with previously prepared compound of formula (III);
- (g) isolating crystalline dapagliflozin propanediol hydrate of formula (III).

14. The process according to claim 13, wherein the suitable solvent used in step (a) is selected from the group comprising of alcohol, ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, nitrile and mixtures thereof.

15. The process according to claim 13, wherein the suitable solvent in step (a) is a mixture of chlorinated hydrocarbon and alcohol.

16. The process according to claim 13, wherein the suitable solvent used in step (c) for preparing solution of D-P complex of formula (II) is selected from the group comprising of ketone, ester, ether, hydrocarbon, chlorinated hydrocarbon, nitrile and mixtures thereof.

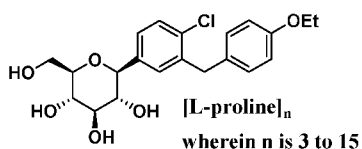
17. The process according to claim 13, wherein ester solvent used in step (c) for preparing solution of D-P complex of formula (II) is selected from the group comprising of ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, and mixtures thereof.

18. The process according to claim 13, wherein mixture of dichloromethane and isopropanol is used as a suitable solvent in step (a); and isopropyl acetate is used as a suitable solvent in step (c).

19. A process for the preparation of amorphous dapagliflozin comprising the steps of:

(a) providing solution of crude dapagliflozin in the mixture of chlorinated hydrocarbon and alcohol solvent;

(b) preparing D-P complex of dapagliflozin of formula (II) by treating solution of crude dapagliflozin of step (a) with 3 to 15 molar equivalents of L-proline;



(c) converting D-P complex of dapagliflozin of formula (II) into dapagliflozin, by treating the solution of D-P complex of formula (II) in ester solvent with water;

(d) adding ether solvent into the dapagliflozin obtained in step (c);

(e) adding the solution of step (d) into the antisolvent or vice versa;

(f) isolating amorphous dapagliflozin.

20. The process according to claim 19, wherein chlorinated hydrocarbon, & alcohol solvent is selected from the group comprising of methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, dichloromethane and ethylene dichloride.

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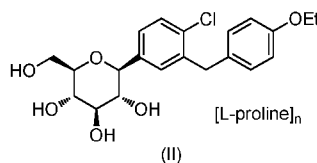
21. The process according to claim 19, wherein ester solvent used in step (c) is selected from the group comprising of ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, t-butyl acetate, isobutyl acetate, and mixtures thereof.

10 22. The process according to claim 19, wherein the ether solvent used in step (d) is selected from the group comprising of methyl tert-butyl ether, ethyl tert-butyl ether, ethyl ether, isopropyl ether and mixtures thereof.

15 23. The process according to claim 19, wherein anti-solvent for step (e) selected from the group comprising of n-hexane, n-heptane, n-pentane, cyclohexane, methylcyclohexane, and mixtures thereof.

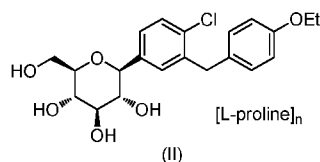
24. The process according to claim 19, wherein mixture of dichloromethane and isopropanol is used as a suitable solvent in step (a); isopropyl acetate is used as a suitable solvent in step (c); methyl tert-butyl ether is used in step (d); and n-heptane is used as antisolvent in step (e).

25. D-P complex of dapagliflozin of formula (II)



25 wherein, n is 3 to 15.

26. A process for the preparation of D-P complex of dapagliflozin of formula (II)



wherein n is 3 to 15;

comprising the steps of:

- (a) providing solution of dapagliflozin in suitable solvent or mixtures thereof;
- 5 (b) treating with 3 to 15 molar equivalents of L-proline;
- (c) isolating D-P complex of dapagliflozin of formula (II).

27. The process according to claim 26, wherein the suitable solvent used in step (a) for preparing the solution is selected from the group comprising of alcohol, ketone, ester,
 10 ether, hydrocarbon, chlorinated hydrocarbon, nitrile and mixtures thereof.

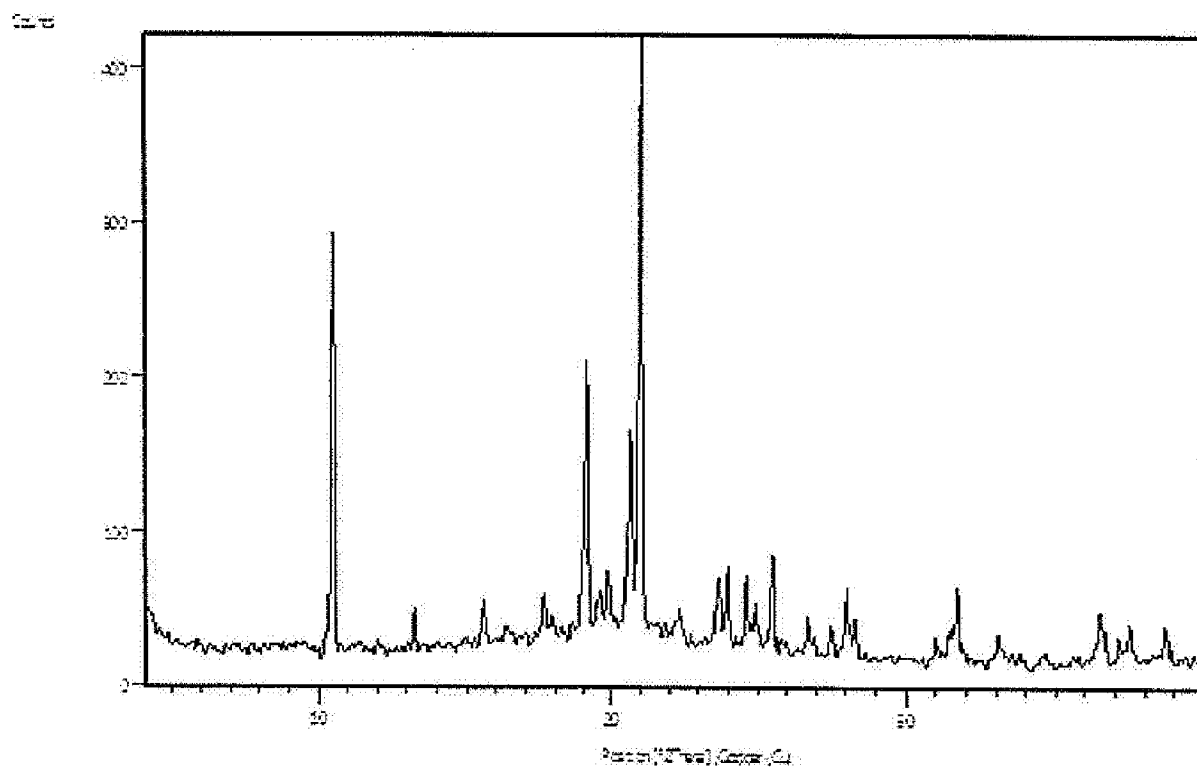
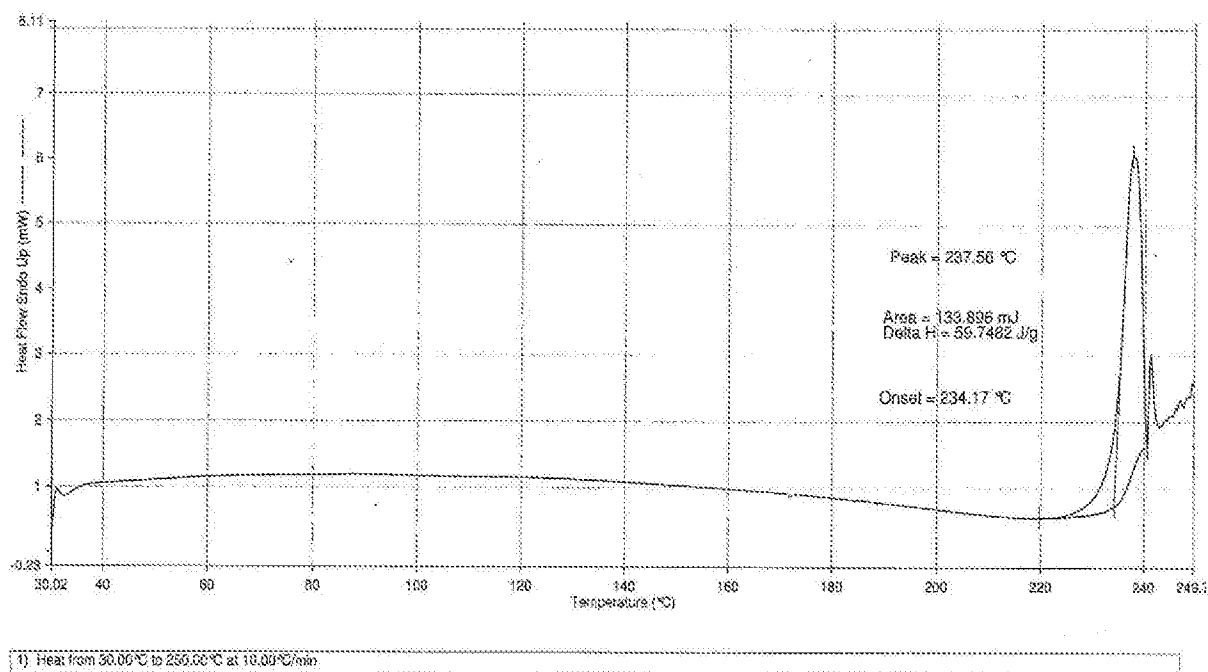
Figure 1:**Figure 2:**

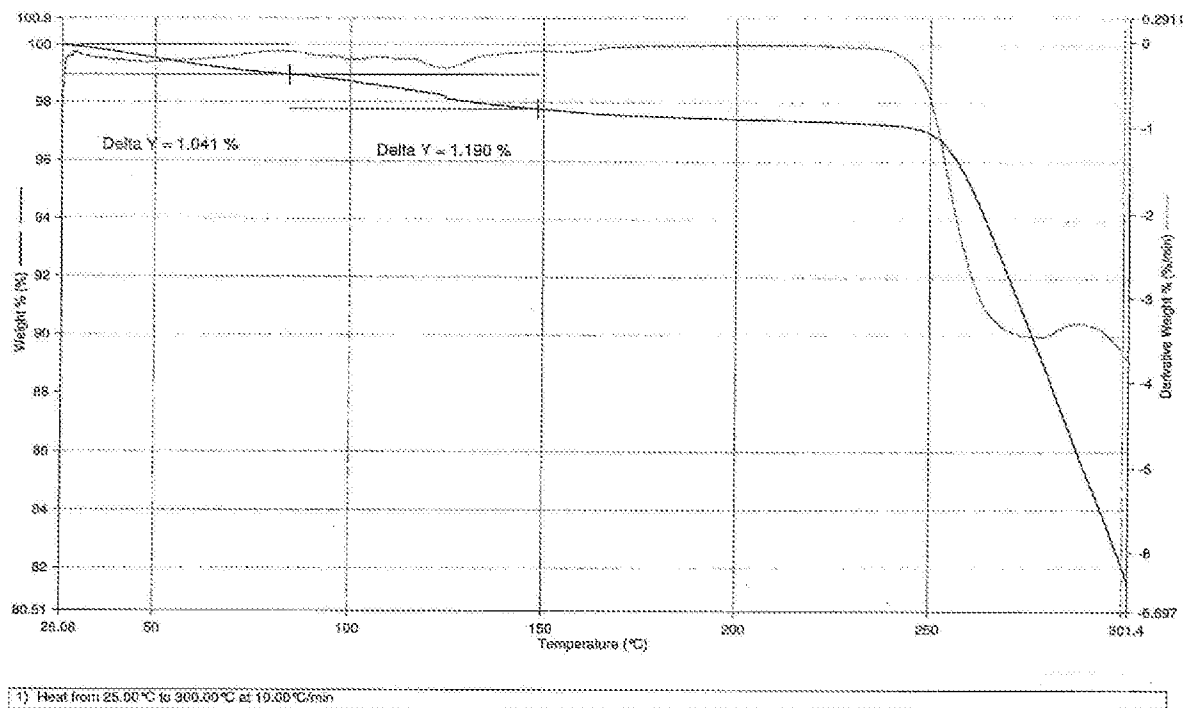
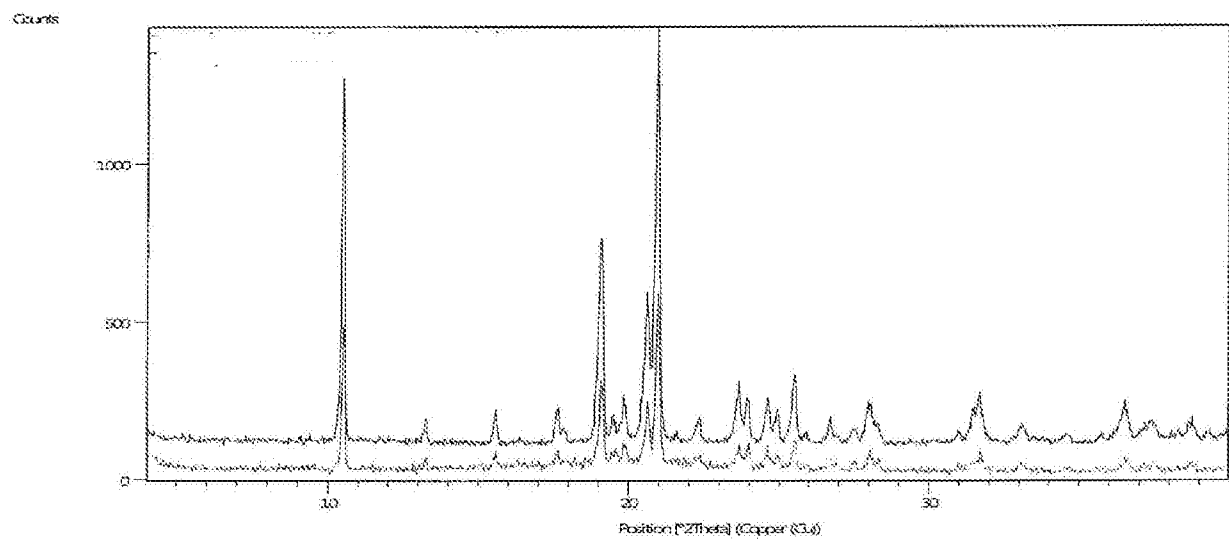
Figure 3:**Figure 4:**

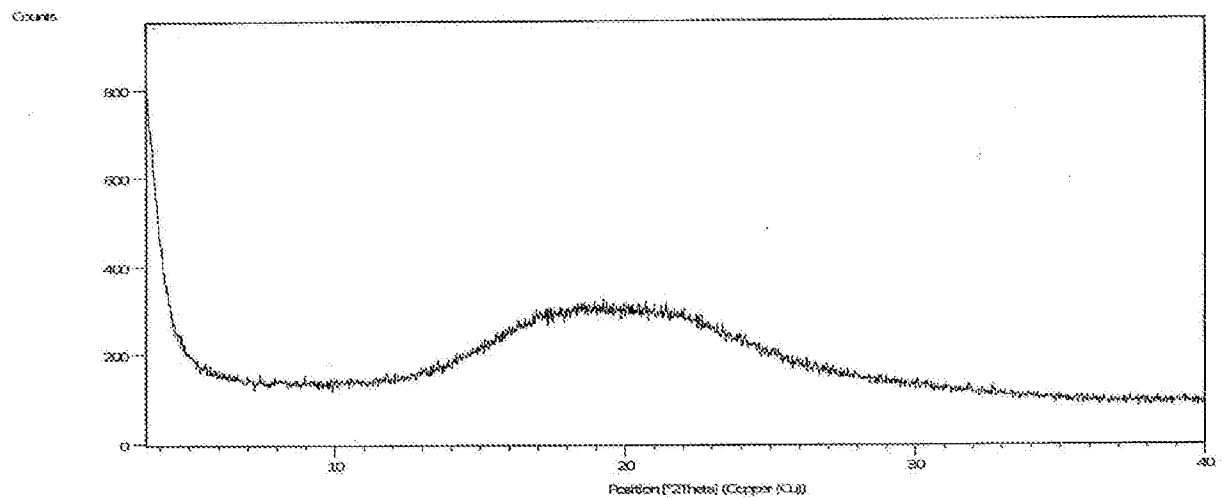
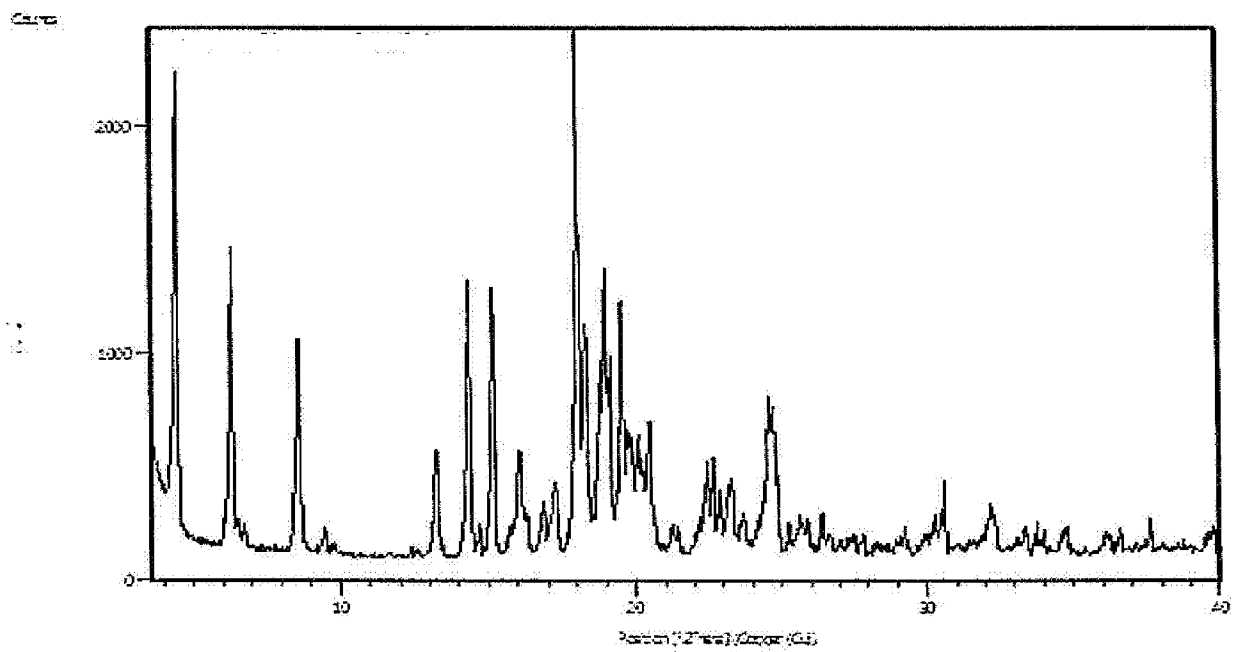
Figure 5:**Figure 6:**

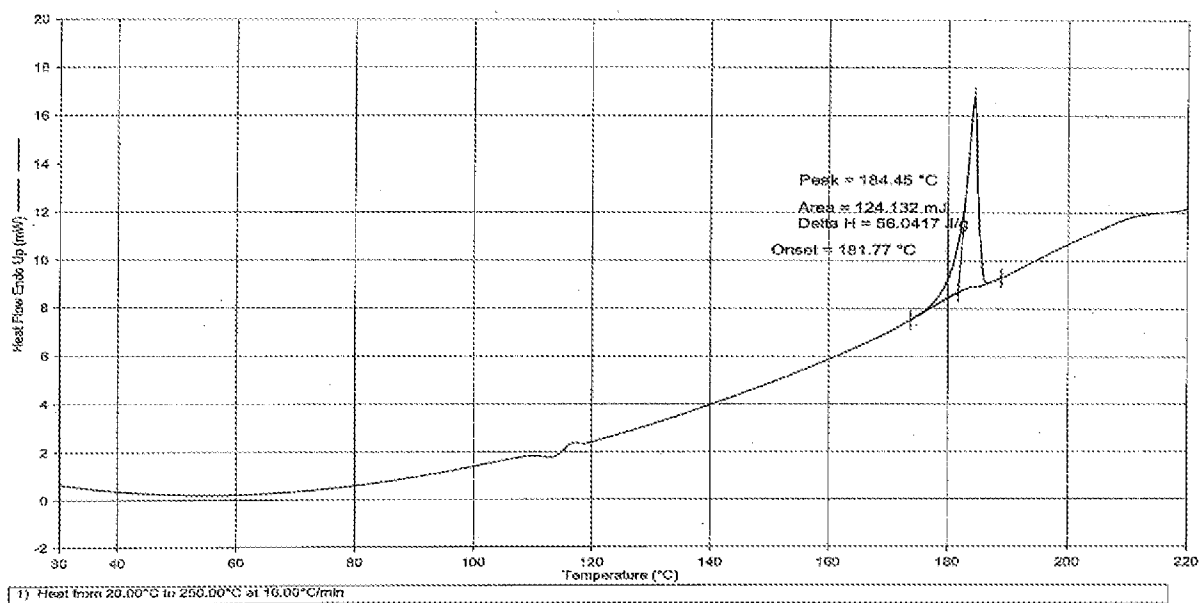
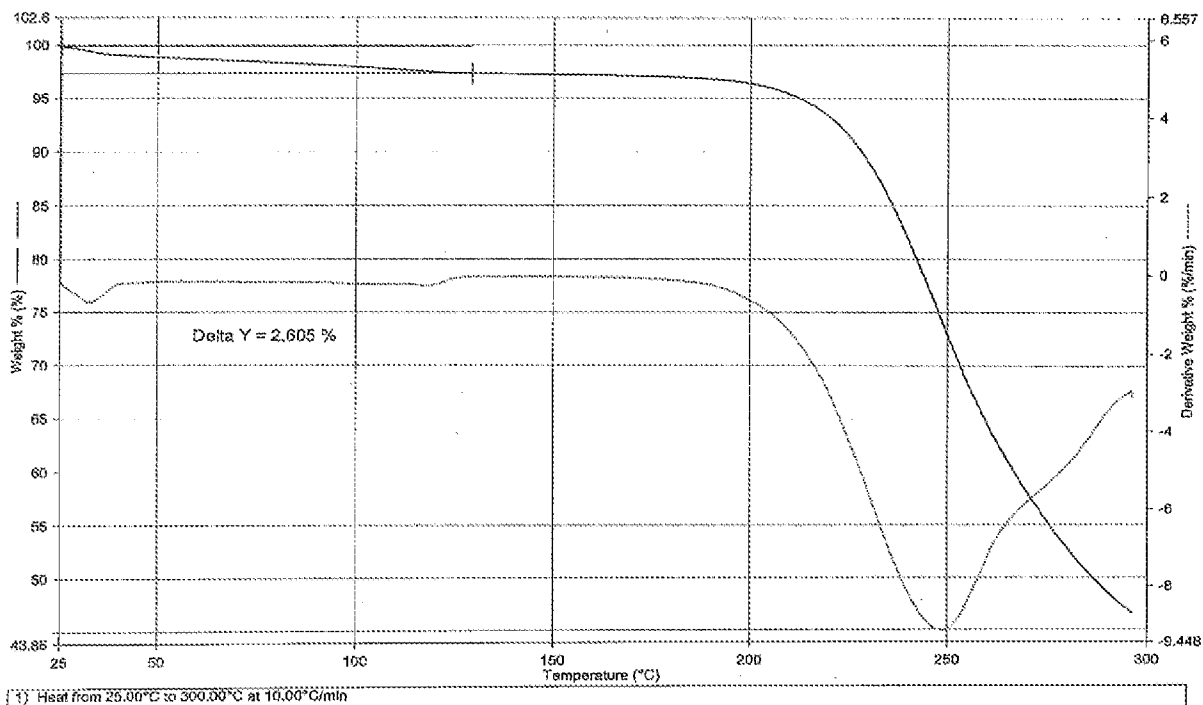
Figure 7:**Figure 8:**

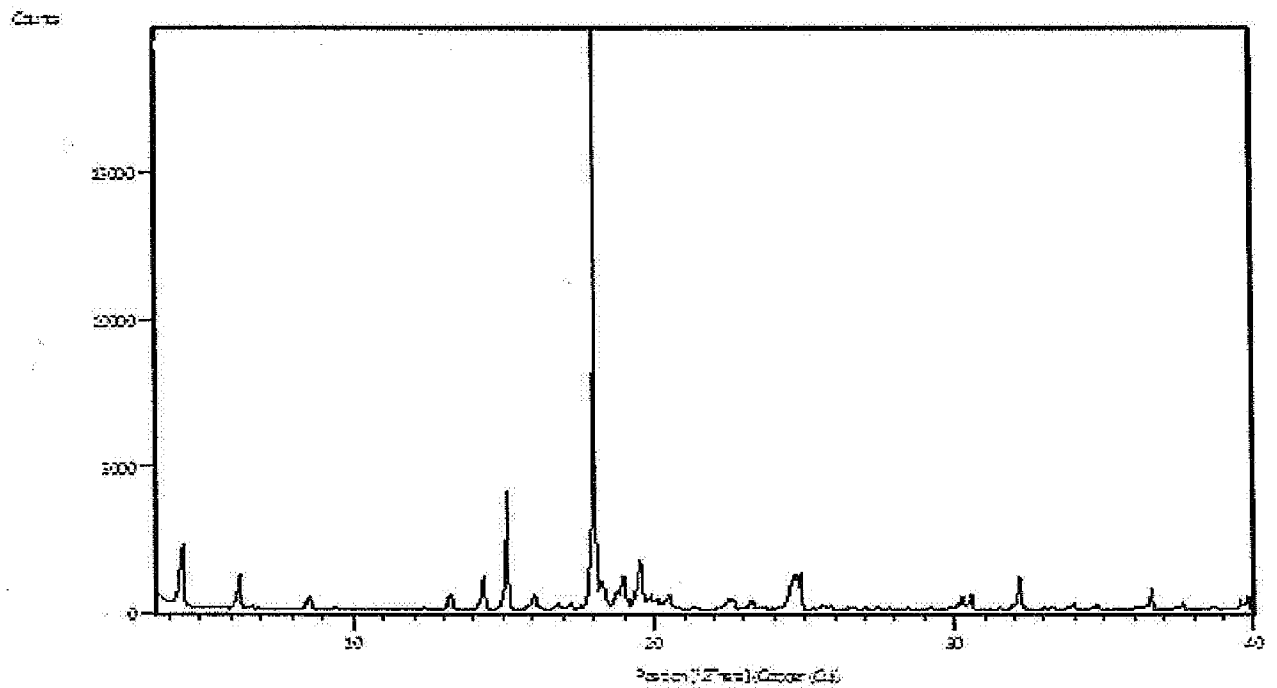
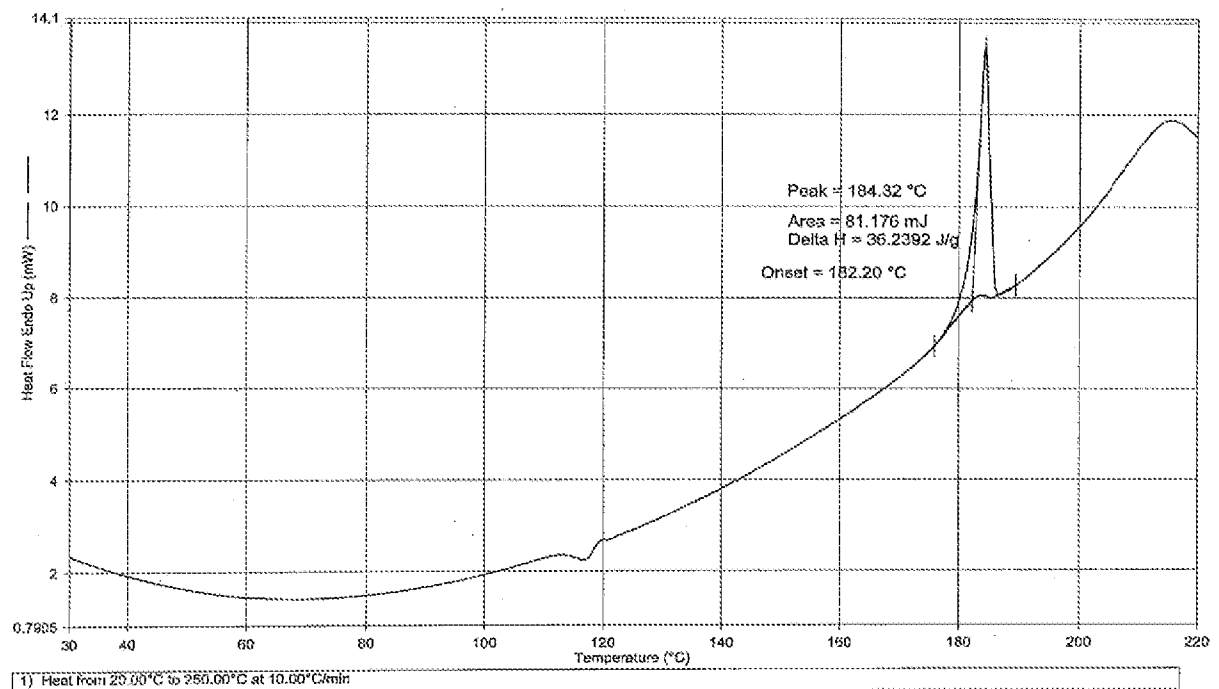
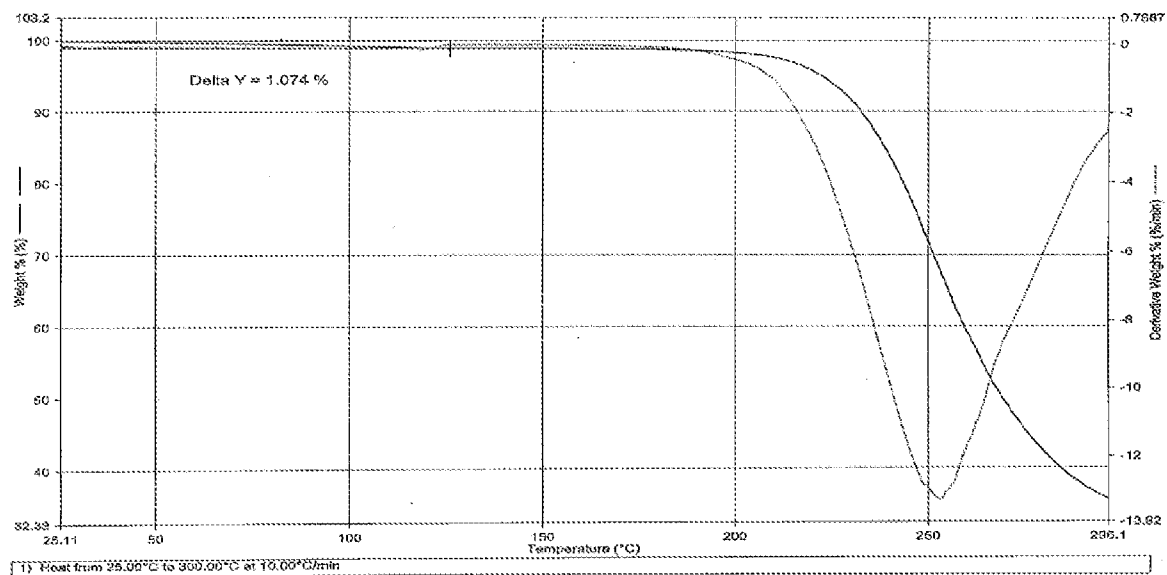
Figure 9:**Figure 10:**

Figure 11:

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/050057

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D309/10
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

EP0-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/178040 A1 (MAPI PHARMA LTD [IL]) 6 November 2014 (2014-11-06) cited in the application page 6, line 19 - line 23; figure 1A -----	1-3

☐

Further documents are listed in the continuation of Box C.

☒

See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 March 2017

Date of mailing of the international search report

24/05/2017

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Bissmire, Stewart

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2017/050057

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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:

see additional sheet

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 an 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.:

1-3

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3

A premix of dapagliflozin and lactose

2. claims: 4-27

Processes for the preparation of various forms of dapagliflozin involving the use of proline complexes of dapagliflozin, said proline complexes and processes for their preparation

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2017/050057

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014178040 A1	06-11-2014	EP 2991999 A1	09-03-2016
		US 2014343010 A1	20-11-2014
		WO 2014178040 A1	06-11-2014
