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(54) Title: DAPAGLIFLOZIN PREMIXES

(57) Abstract: The present invention relates to novel premixes of dapagliflozin, processes for the preparation of such premixes, pharmaceutical compositions comprising the same and their use in medicine.

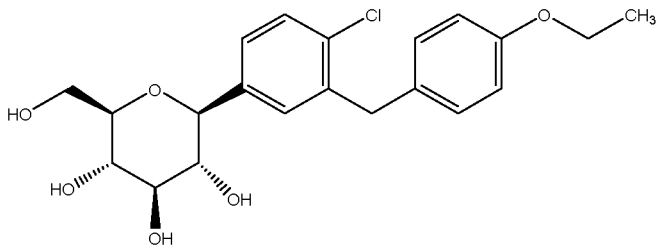
Dapagliflozin premixes

FIELD OF INVENTION:

The present invention relates to novel premixes of dapagliflozin, processes for the preparation of such premixes, pharmaceutical compositions comprising the same and their use in medicine.

BACKGROUND OF INVENTION:

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



Formula I

US 6515117 specifically discloses dapagliflozin and its pharmaceutically acceptable salts, a method for treating diabetes and related diseases employing dapagliflozin alone or in combination with another antidiabetic agent or other therapeutic agent.

WO 2008/002824 describes crystalline forms and solvates of (1 S)-1, 5-anhydro-1-C-(3-((phenyl)methyl)phenyl)-D-glucitol derivatives and their complexes with amino acids.

WO 2008/116179 refers to pharmaceutical formulations which include crystalline dapagliflozin propylene glycol hydrate.

WO 2012/163546 discloses pharmaceutical compositions comprising dapagliflozin and cyclodextrin, which compositions are in the form of inclusion bodies.

WO 2014/178040 relates to novel crystalline forms of dapagliflozin, namely a dapagliflozin lactose co-crystal and a dapagliflozin asparagine co-crystal, to pharmaceutical compositions comprising same, methods for their preparation and uses thereof for treating type 2 diabetes.

WO 2015/011113 relates to pharmaceutical compositions containing amorphous dapagliflozin, in particular in the form of solid dispersions and adsorbates, and a process for preparing the same.

WO 2015/104658 discloses a process for the preparation of amorphous dapagliflozin, amorphous solid dispersion of dapagliflozin together with one or more pharmaceutically acceptable carriers, process for its preparation and pharmaceutical compositions thereof.

It is a well-known fact that different polymorphic forms of the same drug may have substantial differences in certain pharmaceutically important properties. The amorphous form of a drug may exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to crystalline forms. Further, amorphous and crystalline forms of a drug may have different handling properties, dissolution rates, solubility and stability.

Although several solid forms of dapagliflozin are known in the art, finding a better form having good physicochemical properties, desirable bioavailability, and advantageous pharmaceutical parameters remains a challenge.

OBJECTS OF THE INVENTION:

Therefore, it is an object of the present invention to provide premixes of dapagliflozin with a view to providing dapagliflozin with increased bioavailability.

An object of the present invention to provide a novel dapagliflozin-crospovidone premix.

Another object of the present invention is to provide industrially advantageous, cost effective and environmentally friendly processes for the preparation of a dapagliflozin-crospovidone premix.

Yet another object of the invention is to provide a pharmaceutical composition comprising a therapeutically effective amount of a dapagliflozin-crospovidone premix.

An object of the present invention to provide a novel dapagliflozin-microcrystalline cellulose premix.

Another object of the present invention is to provide industrially advantageous, cost effective and environmentally friendly processes for the preparation of a dapagliflozin-microcrystalline cellulose premix.

Yet another object of the invention is to provide a pharmaceutical composition comprising a therapeutically effective amount of a dapagliflozin-microcrystalline cellulose premix.

An object of the present invention to provide a novel dapagliflozin-microcrystalline cellulose and mannitol premix.

Another object of the present invention is to provide industrially advantageous, cost effective and environmentally friendly processes for the preparation of a dapagliflozin-microcrystalline cellulose and mannitol premix.

Yet another objection of the invention is to provide a pharmaceutical composition comprising a therapeutically effective amount of a dapagliflozin-microcrystalline cellulose and mannitol premix.

SUMMARY OF THE INVENTION:

In line with the above objectives, the present invention provides dapagliflozin premixes.

The present invention provides a dapagliflozin-crospovidone premix.

The present invention provides a dapagliflozin-crospovidone premix which is stable and amorphous in nature.

The present invention provides a process for the preparation of dapagliflozin-crospovidone premix.

The present invention provides a dapagliflozin-microcrystalline cellulose premix.

The present invention provides a dapagliflozin-microcrystalline cellulose premix which is stable and amorphous in nature.

The present invention provides a process for the preparation of dapagliflozin-microcrystalline cellulose premix.

The present invention provides a dapagliflozin-microcrystalline cellulose-mannitol premix which is stable.

The present invention also provides a process for the preparation of dapagliflozin-microcrystalline cellulose and mannitol premix.

The advantages of the process include simplicity of manufacturing, eco-friendliness and suitability for commercial use.

BRIEF DESCRIPTION OF THE DRAWINGS:

Figure 1: Depicts an X-ray powder diffractogram of a dapagliflozin-crospovidone premix of the present invention.

Figure 2: Depicts an X-ray powder diffractogram of a dapagliflozin-microcrystalline cellulose premix of the present invention.

Figure 3: Depicts an X-ray powder diffractogram of a dapagliflozin-microcrystalline cellulose premix prepared following the methodology given in Example 8 herein.

Figure 4: Depicts an X-ray powder diffractogram of dapagliflozin tablets prepared using a dapagliflozin-microcrystalline cellulose premix of the present invention. In this Figure, there is included a diffractogram pattern of a placebo tablet (i.e. containing no dapagliflozin) for comparative purposes.

Figure 5: Depicts an X-ray powder diffractogram of a dapagliflozin-metformin tablet containing a dapagliflozin-microcrystalline cellulose premix of the present invention. In this Figure, there is included a diffractogram pattern of a placebo tablet (i.e. containing no dapagliflozin) for comparative purposes.

DETAILED DESCRIPTION OF THE INVENTION:

The invention will now be described in detail in connection with certain preferred and optional aspects, so that various aspects thereof may be more fully understood and appreciated.

Dapagliflozin free base is amorphous in nature and has low intrinsic bioavailability. This presents practical difficulties when administering the drug orally. The drug is available

commercially under the trade name Forxiga® in which it is formulated as a film coated tablet containing dapagliflozin propanediol monohydrate. The present invention provides dapagliflozin premixes with a view to improving the bioavailability of dapagliflozin.

As used herein the term "premix" means two or more components combined to form an admixture. Preferably, the term is used to describe an admixture comprising dapagliflozin and at least one other pharmaceutically acceptable excipient including, but not limited to, crospovidone, microcrystalline cellulose and mannitol.

As used herein, the term "premixing agent" means a component, preferably a pharmaceutically acceptable excipient, which is used to form a premix with dapagliflozin. It will be appreciated that more than one premixing agent may be used to form a premix with dapagliflozin in accordance with the present invention.

Crospovidone is a synthetic, water-insoluble, cross-linked homopolymer N-vinyl-2-pyrrolidone. Crospovidone has been developed as a drug carrier and is widely used as a disintegrant agent, tablet excipient (disintegrant and binder) and solubilising excipient in oral solid dosage pharmaceutical formulations.

In accordance with the above, in one preferred aspect, the present invention provides a novel premix of dapagliflozin, comprising crospovidone as a premixing agent, i.e. a dapagliflozin-crospovidone premix.

The present invention further provides a process for the preparation of a premix of dapagliflozin-crospovidone. In one aspect, the process for the preparation of a premix of dapagliflozin-crospovidone premix comprises the steps of:

(a) dissolving dapagliflozin in one or more suitable first solvent(s);

(b) adding crospovidone to the solution obtained in step (a);

(c) removing the first solvent(s) from the solution obtained in step (b);

(d) adding one or more second solvent(s) to the solid obtained in step (c); and optionally thereafter,

(e) isolating the premix of dapagliflozin-crospovidone so formed.

In one aspect, as depicted in step (a), the first solvent is one or more organic solvents, preferably selected from the group consisting of polar solvents such as C_1-C_4 alcohols; esters such as ethyl acetate; polar aprotic solvents such as dimethyl formamide, dimethyl sulfoxide, tetrahydrofuran, 1,4-dioxane, trioxane, N-methyl pyrrolidone, dimethyl acetamide; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone, methyl vinyl ketone; nitriles such as acetonitrile, propionitrile; chlorinated organic solvents such as chloroform, dichloromethane, ethylene dichloride, hydrocarbons such as toluene, xylene, heptane, cyclohexane and the like or any combination thereof. More preferably, the first solvent is is a C_1-C_4 alcohol, such as methanol, ethanol, isopropyl alcohol or butanol, particularly methanol.

In one aspect, as depicted in step (a), the dapagliflozin can be prepared by any method known in the art. Further, the dapagliflozin employed may be in any solid state form, such as an amorphous, crystalline, semi-crystalline, or solvated form.

In one aspect, as depicted in step (a), the dissolution temperature may range from about 10 °C to about the reflux temperature of the solvent(s), depending on the solvent(s) used for dissolution. The dissolution temperature may range from about 10 °C to about 120 °C or from about 10 °C to about 80 °C, or from about 10 °C to about 65 °C. In a preferred aspect, the dissolution temperature is from about 60 °C to about 70 °C.

In one aspect, as depicted in step (b), the crospovidone can be any commercially available form and may be selected based upon a desired particle size. Different types of crospovidone are commercially available, depending on the particle size, such as Type A- particle structure of normal crospovidone and Type B - particle structure of micronized crospovidone and the like.

In one aspect, as depicted in step (b), the weight ratio of dapagliflozin to crospovidone is from about 1:10 to about 10: 1. Preferably, the weight ratio of dapagliflozin to crospovidone is 1:1, 1:0.5 or 1:0.3.

In one aspect, as depicted in step (c), removing the first solvent(s) from the solution obtained in step (b), is undertaken by distillation of the solvent under vacuum.

In one aspect, as depicted in step (d), the suitable second solvent is an one or more organic solvents, preferably selected from the group consisting of polar solvents such as C_1-C_4 alcohols; esters such as ethyl acetate; polar aprotic solvents such as dimethyl formamide, dimethyl sulfoxide, tetrahydrofuran, 1,4-dioxane, trioxane, N-methyl pyrrolidone, dimethyl acetamide; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone, methyl vinyl ketone; nitriles such as acetonitrile, propionitrile; chlorinated organic solvents such as chloroform, dichloromethane, ethylene dichloride, hydrocarbons such as toluene, xylene, heptane, cycloheptane, cyclohexane and the like or any combination thereof. Preferably, the second solvent is cycloheptane or cyclohexane.

Step (e) comprises isolating and drying the dapagliflozin-containing premix into a solid form. Any suitable techniques known in the art may be used, for example, filtering and then drying under vacuum.

In one aspect, the dapagliflozin-crospovidone premix of the present invention is characterized by powder x-ray diffraction (XRD) as illustrated by Fig.1.

In one aspect, the dapagliflozin-crospovidone premix of the present invention is characterized by a glass transition temperature in the range from about 20 °C to about 40 °C, preferably from about 30 °C to about 40 °C and most preferably from about 36 °C to about 39 °C, when measured by an appropriate analytical technique such as Differential Scanning Calorimetry.

In one aspect, the dapagliflozin-crospovidone of the present invention is amorphous in nature and stable. The amorphous form of dapagliflozin-crospovidone premix provided according to the invention is thermodynamically stable, and is expected to have higher dissolution, solubility and hence bioavailability than the free base of dapagliflozin per se.

Dapagliflozin-containing premixes can also be prepared using other suitable premixing agents in accordance with the present invention. Suitable premixing agents include one or more pharmaceutically acceptable excipients which, when admixed with dapagliflozin, result in the formation of a premix having improved solubility compared to dapagliflozin. Preferred premixing agents include, but are not limited to, microcrystalline cellulose (MCC), mannitol, silicon dioxide, Silicified MCC, magnesium aluminometasilicate (MAS) and the like thereof or any combination thereof.

In accordance with the above, there is provided, as a further aspect of the present invention, a novel premix of dapagliflozin-microcrystalline cellulose as a premixing agent, i.e. a dapagliflozin-microcrystalline cellulose premix.

The present invention further provides a process for the preparation of a premix of dapagliflozin-microcrystalline cellulose. In one aspect, the process for the preparation of a dapagliflozin-microcrystalline cellulose premix comprises the steps of:

(a) dissolving dapagliflozin in one or more suitable first solvent(s);
(b) adding microcrystalline cellulose to the solution obtained in step (a);
(c) removing first solvent(s) from the solution obtained in step (b);
(d) adding one or more second solvent(s) to the solid obtained in step (c); and optionally thereafter,
(e) isolating the premix of dapagliflozin- microcrystalline cellulose so formed.

In one aspect, as depicted in step (a), the first solvent is one or more organic solvents, preferably selected from the group consisting of polar solvents such as C_1-C_4 alcohols; esters

such as ethyl acetate; polar aprotic solvents such as dimethyl formamide, dimethyl sulfoxide, tetrahydrofuran, 1,4-dioxane, trioxane, N-methyl pyrrolidone, dimethyl acetamide; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone, methyl vinyl ketone; nitriles such as acetonitrile, propionitrile; chlorinated organic solvents such as chloroform, dichloromethane, ethylene dichloride, hydrocarbons such as toluene, xylene, heptane, cyclohexane and the like or any combination thereof. More preferably, the first solvent is a C_1-C_4 alcohol, such as methanol, ethanol, isopropyl alcohol or butanol, particularly methanol.

In one aspect, as depicted in step (a), the dapagliflozin can be prepared by any method known in the art. Further, the dapagliflozin employed may be in any solid state form, such as an amorphous, crystalline, semi-crystalline or solvated form.

In one aspect, as depicted in step (a), the dissolution temperatures may range from about 10 °C to about reflux temperature of the solvent, depending on the solvent used for dissolution.

In one aspect, as depicted in step (b), the weight ratio of dapagliflozin and microcrystalline cellulose is from 1:10 to 10:1. Preferably, the weight ratio of dapagliflozin and microcrystalline cellulose is 1:1 or 1:0.5.

In one aspect, as depicted in step (c), removing the first solvent from the solution obtained in step (b), is undertaken by distillation of the solvent under vacuum.

In one aspect, as depicted in step (d), the second solvent is one or more organic solvents, preferably selected from the group consisting of polar solvents such as C_1-C_4 alcohols; esters such as ethyl acetate; polar aprotic solvents such as dimethyl formamide, dimethyl sulfoxide, tetrahydrofuran, 1,4-dioxane, trioxane, N-methyl pyrrolidone, dimethyl acetamide; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone, methyl vinyl ketone; nitriles such as acetonitrile, propionitrile; chlorinated organic solvents such as chloroform, dichloromethane, ethylene dichloride, hydrocarbons such as toluene, xylene, heptane,

cycloheptane, cyclohexane and the like or any combination thereof. Preferably, the second solvent is cycloheptane or cyclohexane.

Step (e) comprises isolating and drying the dapagliflozin-containing premix into a solid form. Any suitable techniques known in the art may be used, for example filtering and then drying under vacuum.

In one aspect, the dapagliflozin-microcrystalline cellulose premix of the present invention is characterized by XRD as illustrated by Fig.2.

In one aspect, the dapagliflozin-microcrystalline cellulose premix of the present invention is amorphous in nature and stable. The amorphous forms are generally readily soluble than their crystalline counter parts and therefore, the amorphous form of dapagliflozin- microcrystalline cellulose premix provided according to the invention is stable and is expected to have higher dissolution, solubility and hence bioavailability than the free base of dapagliflozin per se.

In a further aspect of the present invention, there is provided a novel dapagliflozin-microcrystalline cellulose-mannitol premix.

In one aspect, the weight ratio of dapagliflozin to microcrystalline cellulose and mannitol is from about 1:20 to about 10:1. Preferably, the weight ratio of dapagliflozin to microcrystalline cellulose and mannitol is from about 1:20 to about 1:30.

The dapagliflozin-microcrystalline cellulose-mannitol premix of the present invention is stable. The dapagliflozin-microcrystalline cellulose-mannitol premix provided according to the invention is expected to have higher dissolution, solubility and hence bioavailability than the free base of dapagliflozin per se.

In one aspect, there is provided a further process for the preparation of dapagliflozin premix comprising the steps of:

(i) preparing a solution of dapagliflozin and a pharmaceutically acceptable first excipient in one or more suitable solvents;

(ii) adsorbing the solution obtained in step (i) onto a pharmaceutically acceptable second excipient or combination of second excipients;

(iii) granulating the mixture obtained in step (ii); and optionally thereafter

(iv) drying the premix so formed.

In one aspect, as depicted in step (ii), the dapagliflozin can be prepared by any method known in art. Further, the dapagliflozin employed may be in any solid state form, such as an amorphous, crystalline, semi-crystalline or solvated form.

In one aspect, as depicted in step (i), the solvent employed may be one or more organic solvents selected from polar solvents such as C_1-C_4 alcohols water, halogenated hydrocarbon, ketone, organic the group consisting of ether, organic ester and the like or a combination thereof. Preferably, the solvent is isopropyl alcohol.

In one aspect, as depicted in step (i), the pharmaceutically acceptable first excipient may be polyvinyl pyrrolidone (Povidone), polyvinyl alcohol, copolymers of vinylpyrrolidone with other vinylderivatives (Copovidone), hydroxypropyl methylcellulose, methylcellulose, hydroxypropylcellulose, powdered acacia, gelatin, guar gum, carbomer such as carbopol, polymethacrylates and pregelatinized starch and more preferably copovidone NF (Plasdone S-630).

In one aspect, as depicted in step (i), preparing a solution of dapagliflozin and a pharmaceutically acceptable first excipient in in a suitable solvent, may be undertaken at a temperature in the range from about 0 °C to about reflux temperature of the solvent used, such as from about 0 °C to about 100 °C. In a preferred aspect, the temperature is from about 75 °C to about 85 °C.

In one aspect, as depicted in step (ii), the solution obtained in step (i) is adsorbed onto one or more pharmaceutically acceptable second excipient(s). Suitable pharmaceutically acceptable excipient(s) include, but are not limited to, pregelatinized starches, lactose, powdered celluloses, microcrystalline celluloses, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar, crospovidone and the like or a combination thereof. Preferably, the second pharmaceutically acceptable excipient is mannitol.

In one aspect, as depicted in step (ii), the pharmaceutically acceptable second excipient or the mixture thereof is preheated to a temperature in the range from about 25 °C to about 70 °C.

In one aspect, as depicted in step (ii), adsorption of the solution obtained in step (i) onto pharmaceutically acceptable second excipient is carried out at a temperature in the range from about 30 °C to about 35 °C.

In one aspect, as depicted in step (iii), granulating the mixture obtained in step (ii) is carried out by spray drying or dispersing the solution obtained in step (ii) or by other methods known in the art.

On completion of the granulation step, the obtained granules of premix are preferably dried by maintaining them at a temperature in the range from about 20 to about 75 °C until the level on drying (LOD) reaches between about 0.5-2.0% w/w.

In another aspect, the present invention also provides a process for the preparation of a pharmaceutical composition comprising a dapagliflozin premix, said process comprising the steps of:

(1) providing a dapagliflozin premix in granulate form in accordance with the processes of the present invention;

(2) blending the dapagliflozin premix with one or more further pharmaceutically acceptable excipients; and thereafter,

(3) drying the mixture so formed and optionally performing a micronisation step.

In one aspect, as depicted in step (2), the further pharmaceutically acceptable excipient is selected from the group consisting of fillers, disintegrants, binders, lubricants, and surfactants or any combination thereof.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a dapagliflozin premix and one or more pharmaceutically acceptable excipients.

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

The dapagliflozin premixes of the present invention may be in the form of a powder, granules or the like. Suitable oral dosages of dapagliflozin include 5 mg and 10 mg, preferably administered once or twice daily.

The dapagliflozin premixes of the present invention may be used in combination with the other types of therapeutic agents. Examples of such therapeutic agents include, but are not

limited to, SGLT2 inhibitors, anti-obesity agents, antihypertensive agents, antiplatelet agents, antiatherosclerotic agents and/or lipid lowering agents. Particularly preferred therapeutic agents for use in combination with the dapagliflozin premixes of the present invention include metformin or a pharmaceutically acceptable salt of solvate thereof, such as metformin hydrochloride and saxagliptin or a pharmaceutically acceptable salt or solvate thereof, such as saxagliptin hydrochloride. A suitable oral dosage of metformin is 850 mg. A suitable oral dosage of saxagliptin include is 5 mg.

In another aspect of the present invention there is a dapagliflozin premix for use in medicine, preferably for the treatment, prophylaxis or management of type 2 diabetes mellitus.

In another aspect of the present invention there is provided the use of a dapagliflozin premix in the manufacture of a medicament for the treatment, prophylaxis or management of type 2 diabetes mellitus.

The following examples, which include preferred aspects, will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purpose of illustrative discussion of preferred aspects of the invention.

Powder X-ray Diffraction data were collected on a Rigaku MiniFlex-II X-ray diffractometer using a Cu K-α radiation source under standard operating conditions.

Glass transition temperatures were obtained by Differential Scanning Calorimetry (DSC) using a TA Waters Q2000 differential scanning calorimeter under the following operating conditions:

Heating Range: -50°C to 150°C

Isothermal at -50°C for 5 min

Modulation Temperature: ± 0.70°C every 60sec

Heating Rate: 2.00°C/min

Examples:

Example 1: Preparation of Dapagliflozin-Crospovidone premix

To a slurry of Dapagliflozin (10gm) in methanol (100ml) was added (10gm) crospovidone at 25-30°C. The content was stirred for 1hr at 25-30°C. Methanol was distilled out under vacuum at 50-55 °C. The solid obtained was further degassed for 1hr under vacuum at 50-55 °C. To the solid was added 80ml of cyclohexane at 25-30°C and further stirred for 1hr at 25-30 °C. The solid obtained was subjected to filtration and further washed with 20ml of cyclohexane. Wet solid was further dried under vacuum at 45-50 °C to afford 19gm of Dapagliflozin-crospovidone premix having the glass transition temperature as 37.58°C. The Dapagliflozin-crospovidone premix thus obtained was subjected to XRD (Figure 1) and found to be amorphous in nature.

Example 2: Preparation of Dapagliflozin-Crospovidone premix

To a slurry of Dapagliflozin (10gm) in methanol (100ml) was added (5gm) crospovidone at 25-30°C. The content was stirred for 1hr at 25-30°C. Methanol was distilled out under vacuum at 50-55 °C. The solid obtained was further degassed for 1hr under vacuum at 50-55 °C. To the solid was added 80 ml of cyclohexane at 25-30°C and further stirred for 1hr at 25-30 °C. The solid obtained was subjected to filtration and further washed with 20ml of cyclohexane. Wet solid was further dried under vacuum at 45-50 °C to afford 14gm of Dapagliflozin-crospovidone premix having a glass transition temperature of 38.78°C.

Example 3: Preparation of Dapagliflozin-Crospovidone premix

To a slurry of Dapagliflozin (10gm) in methanol (100ml) was added (3gm) crospovidone at 25-30°C. The content was stirred for 1hr at 25-30°C. Methanol was distilled out under vacuum at 50-55 °C. The solid obtained was further degassed for 1hr under vacuum at 50-55 °C. To the solid was added 80 ml of cyclohexane at 25-30°C and further stirred for 1hr at 25-

30 °C. The solid obtained was subjected to filtration and further washed with 20ml of cyclohexane. Wet solid was further dried under vacuum at 45-50 °C to afford 13gm of Dapagliflozin-crospovidone premix having a glass transition temperature of 24.88°C.

Example 4: Preparation of Dapagliflozin-Crospovidone premix

To a slurry of (13.5gm) dapagliflozin (propanediol) solvate in (270ml) water was added (170ml) dichloromethane at 25-30°C. Organic layer was separated. Organic layer was washed with 2x270ml of water followed by drying over sodium sulphate, further subjected to distillation under vacuum. To the solid foam obtained was added (100ml) methanol followed by addition of (10gm) of crospovidone at 25-30°C. The content was stirred for 1hr at 25-30°C. Methanol was distilled out under vacuum at 50-55 °C. The solid obtained was further degassed for 1hr under vacuum at 50-55°C. To the solid was added 80 ml of cyclohexane at 25-30°C and further stirred for 1hr at 25-30 °C. The solid obtained was subjected to filtration and further washed with 20ml of cyclohexane. Wet solid was further dried under vacuum at 45-50°C to afford 19gm of Dapagliflozin-crospovidone premix having a glass transition temperature of 36.54°C.

Example 5: Preparation of Dapagliflozin-Crospovidone premix

To a slurry of (17gm) acetylated dapagliflozin in (170ml) methanol, cooled to 15-20°C, was added (0.82gm) sodium methoxide. The reaction mixture was stirred for 2hr. On completion of reaction, pH was adjusted to pH 6-7 by addition of IPA.HCl. The reaction mixture was allowed to attain room temperature. Further reaction mixture was distilled under vacuum until 10 volumes of methanol remains in the mixture. To the mixture was added (3gm) of crospovidone at 25-30°C. The content was stirred for 1hr at 25-30°C. Methanol was distilled out under vacuum at 50-55 °C. The solid obtained was further degassed for 1hr under vacuum at 50-55 °C. To the solid was added 80 ml of cyclohexane at 25-30°C and further stirred for 1hr at 25-30 °C. The solid obtained was subjected to filtration and further washed with 20ml of cyclohexane. Wet solid was further dried under vacuum at 45-50°C to afford 19

gm of Dapagliflozin-crospovidone premix having the glass transition temperature as 36.54°C.

Example 6: Preparation of Dapagliflozin-microcrystalline cellulose premix

To a slurry of Dapagliflozin (10gm) in methanol (100ml) was added (10gm) microcrystalline cellulose at 25-30°C. The content was stirred for 1hr at 25-30°C. Methanol was distilled out under vacuum at 50-55 °C. The solid obtained was further degassed for 1hr under vacuum at 50-55 °C. To the solid was added 80ml of cyclohexane at 25-30°C and further stirred for 1hr at 25-30 °C. The solid obtained was subjected to filtration and further washed with 20ml of cyclohexane. Wet solid was further dried under vacuum at 45-50 °C to afford 19gm of Dapagliflozin-microcrystalline cellulose premix.

Example 7: Preparation of Dapagliflozin-microcrystalline cellulose-mannitol premix

To a slurry of Dapagliflozin (10gm) in methanol (100ml) was added (5gm) microcrystalline cellulose and (5gm) mannitol at 25-30°C. The content was stirred for 1hr at 25-30°C. Methanol was distilled out under vacuum at 50-55 °C. The solid obtained was further degassed for 1hr under vacuum at 50-55 °C. To the solid was added 80ml of cyclohexane at 25-30°C and further stirred for 1hr at 25-30 °C. The solid obtained was subjected to filtration and further washed with 20ml of cyclohexane. Wet solid was further dried under vacuum at 45-50 °C to afford 19gm of Dapagliflozin-microcrystalline cellulose-mannitol premix.

Example 8: Preparation of Dapagliflozin-microcrystalline cellulose premix

23302gm of microcrystalline cellulose (MCC) was pre-heated maintaining temperature 25-70°C. When the temperature reached in the range 30-35°C, granulation was achieved by spraying the clear solution obtained by dissolving 1125gm of copovidone, 1845gm of Dapagliflozin propanediol solvate in 36 litre of isopropyl alcohol over pre-heated MCC. On completion of spraying, the obtained granules were dried at 20-75°C to yield 26273 gm of dapagliflozin-microcrystalline cellulose premix in form of granules as depicted by XRD represented in Figure 3.

Example 9: Preparation of Dapagliflozin-microcrystalline cellulose-mannitol premix

9585 gm of microcrystalline cellulose (MCC) and 8400gm of mannitol mixture was pre-heated maintaining temperature 25-70°C. When the temperature reached in the range 30-35°C, granulation was achieved by spraying the clear solution obtained by dissolving 750gm of copovidone, 615gm of Dapagliflozin (propanediol) solvate in 20 litre of isopropyl alcohol. On completion of spraying, the obtained granules were dried at 20-75°C to yield 19350 gm of dapagliflozin-microcrystalline cellulose-mannitol premix in the form of granules.

Claims

1. A premix comprising dapagliflozin and one or more pharmaceutically acceptable excipients.

2. A premix according to claim 1, wherein the pharmaceutically acceptable excipient is selected from the group consisting of crospovidone, microcrystalline cellulose, silicon dioxide, silicified microcrystalline cellulose, magnesium aluminosilicate and mannitol or any combination thereof.

3. A premix according to claim 2 wherein the pharmaceutically acceptable excipient is selected from the group consisting of crospovidone, microcrystalline cellulose and mannitol or any combination thereof.

4. A premix according to any one of claims 1 to 3 which is amorphous.

5. A premix according to any one of claims 1 to 4 comprising dapagliflozin and crospovidone.

6. A premix according to claim 5, wherein the weight ratio of dapagliflozin to crospovidone is 1:1, 1:0.5 or 1:0.3.

7. A premix according to claim 5 or claim 6 having an XRD pattern as shown in Figure 1.

8. A premix according to any one of claims 5 to 7 having a glass transition temperature in the range from about 30 °C to about 40 °C.

9. A premix according to any one of claims 1 to 4 comprising dapagliflozin and microcrystalline cellulose.

10. A premix according to claim 9 wherein the weight ratio of dapagliflozin to microcrystalline cellulose is 1:1 or 1:0.5.

11. A premix according to claim 9 or claim 10 having an XRD pattern as shown in Figure 2.

12. A premix according to any one of claims 1 to 3, comprising dapagliflozin, microcrystalline cellulose and mannitol.

13. A premix according to claim 12 wherein the weight ratio of dapagliflozin to microcrystalline cellulose and mannitol is from about 1:20 to about 1:30.

14. A process for preparing a premix according to any one of claims 1 to 13 comprising the steps of:

(a) dissolving dapagliflozin in one or more suitable first solvent(s);
(b) adding one or more pharmaceutically acceptable excipients to the solution obtained in step (a);
(c) removing the first solvent(s) from the solution obtained in step (b);
(d) adding one or more second solvent(s) to the solid obtained in step (c); and optionally thereafter,
(e) isolating the premix so formed.

15. A process according to claim 14 wherein the one or more pharmaceutically acceptable excipients are selected from the group consisting of crospovidone, microcrystalline cellulose and mannitol or any combination thereof.

16. A process according to claim 14 or claim 15 wherein the first and second solvents are selected from the group consisting of a C_1-C_4 alcohol, dimethyl formamide, dimethyl sulfoxide, tetrahydrofuran, 1, 4-dioxane, a trioxane, N-methyl pyrrolidone, dimethyl acetamide, acetone, ethyl methyl ketone, methyl isobutyl ketone, methyl vinyl ketone, acetonitrile, propionitrile, chloroform, dichloromethane, ethylene dichloride, toluene, xylene, heptane, cyclohexane or any combination thereof.

17. A process according to any of claims 14 to 16 wherein the first solvent is methanol.

18. A process according to any one of claims 14 to 17 wherein the second solvent is cyclohexane.

19. A process according to any one of claims 14 to 18 wherein dapagliflozin is in an amorphous, crystalline, semi-crystalline or solvated form.

20. A process according to any one of claims 14 to 19, wherein the dissolution temperature in step (a) ranges from about 10 °C to about the reflux temperature of the first solvent.

21. A process according to any one of claims 14 to 20 wherein the weight ratio of dapagliflozin to at least one excipient in step (b) is from about 1:10 to about 10:1.

22. A process for preparing a premix according to any of claims 1 to 13 comprising the steps of:

(i) preparing a solution of dapagliflozin and a pharmaceutically acceptable first excipient in one or more suitable solvents;

(ii) adsorbing the solution obtained in step (i) onto a pharmaceutically acceptable second excipient or combination of second excipients;

(iii) granulating the mixture obtained in step (ii); and optionally thereafter

(iv) drying the premix so formed.

23. A process according to claim 22, wherein dapagliflozin is in an amorphous, crystalline, semi-crystalline or solvated form.

24. A process according to claim 22 or claim 23 wherein the solvent employed in step (i) is selected from the group consisting of a C_1-C_4 alcohol, water, a halogenated hydrocarbon, a ketone, an organic ether, an organic ester or any combination thereof.

25. A process according to claim 24 wherein the solvent is isopropyl alcohol.

26. A process according to any one of claims 22 to 25 wherein the pharmaceutically acceptable first excipient employed in step (i) is selected from the group consisting of polyvinyl pyrrolidone (PVP), polyvinyl alcohol, copolymers of vinylpyrrolidone with other vinylderivatives, copovidone NF, hydroxypropyl methylcellulose, methylcellulose, hydroxypropylcellulose, powdered acacia, gelatin, guar gum, carbomer such as carbopol, polymethacrylates and pregelatinized starch or any combination thereof.

27. A process according to claim 26, wherein the pharmaceutically acceptable first excipient is copovidone NF.

28. A process according to any one of claims 22 to 27 wherein the solution in step (i) is maintained at a temperature ranging from about 0 °C to about reflux temperature of the solvent used.

29. A process according to any one of claims 22 to 28 wherein the pharmaceutically acceptable second excipient employed in step (ii) is selected from the group

consisting of pregelatinized starch, lactose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar, crospovidone or any combination thereof.

30. A process according to claim 29 wherein the second excipient is a combination of mannitol and microcrystalline cellulose.

31. A process according to any one of claims 22 to 30 wherein the second excipient or the mixture thereof is preheated to a temperature in the range of about 25 °C to about 70 °C.

32. A process according to any one of claims 22 to 31 wherein in step (ii) is carried out at a temperature in the range from about 30 °C to about 35 °C.

33. A process according to any one of claims 22 to 32 wherein the granulating step (iii) comprises spray drying or dispersing the solution obtained in step (ii).

34. A process according to any one of claims 22 to 33 wherein the drying step (v) is carried out a temperature in the range from about 20 °C to about 75 °C.

35. A premix according to any of claims 1 to 13 for use in the treatment, prophylaxis or management of type II diabetes mellitus.

36. Use of a premix according to any one of claims 1 to 13 in the manufacture of a medicament for the treatment, prophylaxis or management of type II diabetes mellitus.

37. A pharmaceutical composition comprising a premix according to any of claims 1 to 13.

38. A pharmaceutical composition according to claim 37 further comprising one or more further therapeutic agents.

39. A pharmaceutical composition according to claim 38 wherein the additional therapeutic agent is selected from the group consisting of SGLT2 inhibitors, anti-obesity agents, antihypertensive agents, antiplatelet agents, antiatherosclerotic agents and/or lipid lowering agents.

40. A pharmaceutical composition according to claim 38 or claim 39 wherein the additional therapeutic agent is metformin hydrochloride or saxagliptin hydrochloride.

41. A process for preparing a pharmaceutical composition according to any one of claims 37 to 40 comprising the steps of:

(i) preparing a premix according to any one of claims 14 to 34;

(ii) granulating the premix so formed;

(iii) optionally blending the resulting granules with one or more further pharmaceutically acceptable excipients and/or one or more further therapeutic agents;

(iv) drying the resulting mixture; and optionally

(v) micronizing the product so formed.

42. A process according to claim 41, wherein the one or more further pharmaceutically acceptable excipients are selected from the group consisting of fillers, disintegrants, binders, lubricants and surfactants or any combination thereof.

43. A premix obtainable by a process according to any one of claims 14 to 34.

44. A premix substantially as hereinbefore described with reference to any one of the Examples.

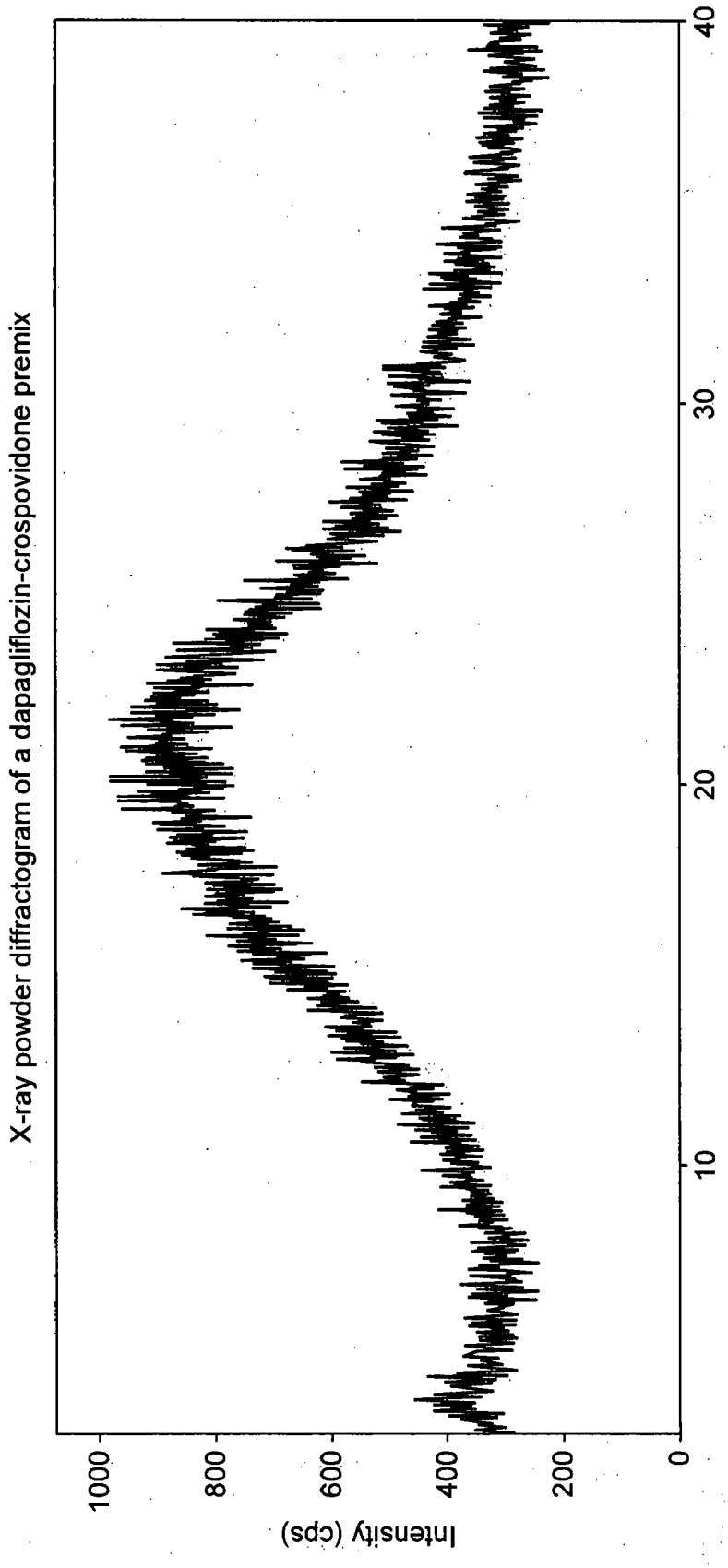

X-ray powder diffractogram of a dapagliflozin-crospovidone premix
Intensity (cps)
0
200
400
600
800
1000
2-theta (deg)
10
20
30
40

FIG. 1

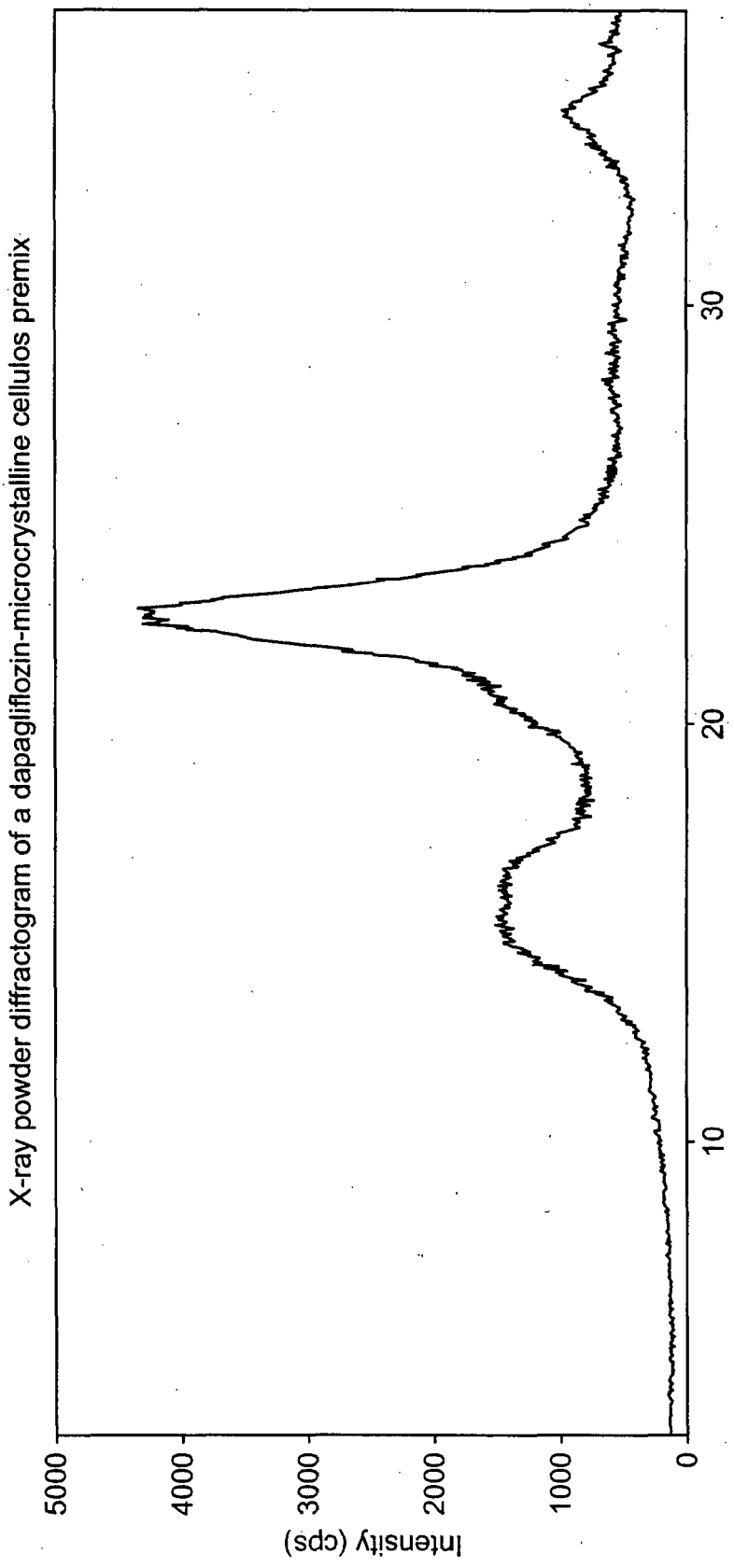

X-ray powder diffractogram of a dapagliflozin-microcrystalline cellulos premix
Intensity (cps)
5000
4000
3000
2000
1000
0
10
20
30
2-theta (deg)

FIG. 2

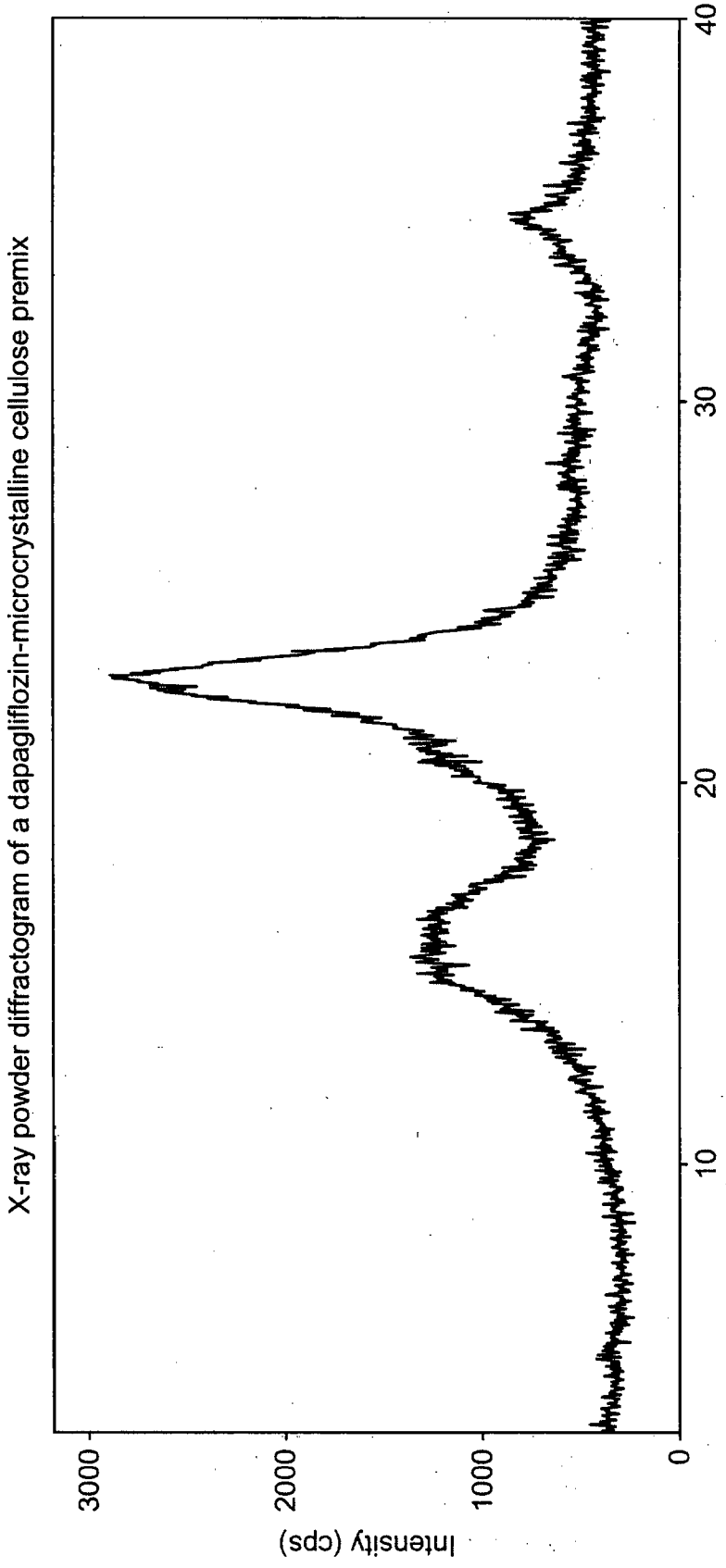

X-ray powder diffractogram of a dapagliflozin-microcrystalline cellulose premix
Intensity (cps)
3000
2000
1000
0
10
20
30
40
2-theta (deg)

FIG. 3

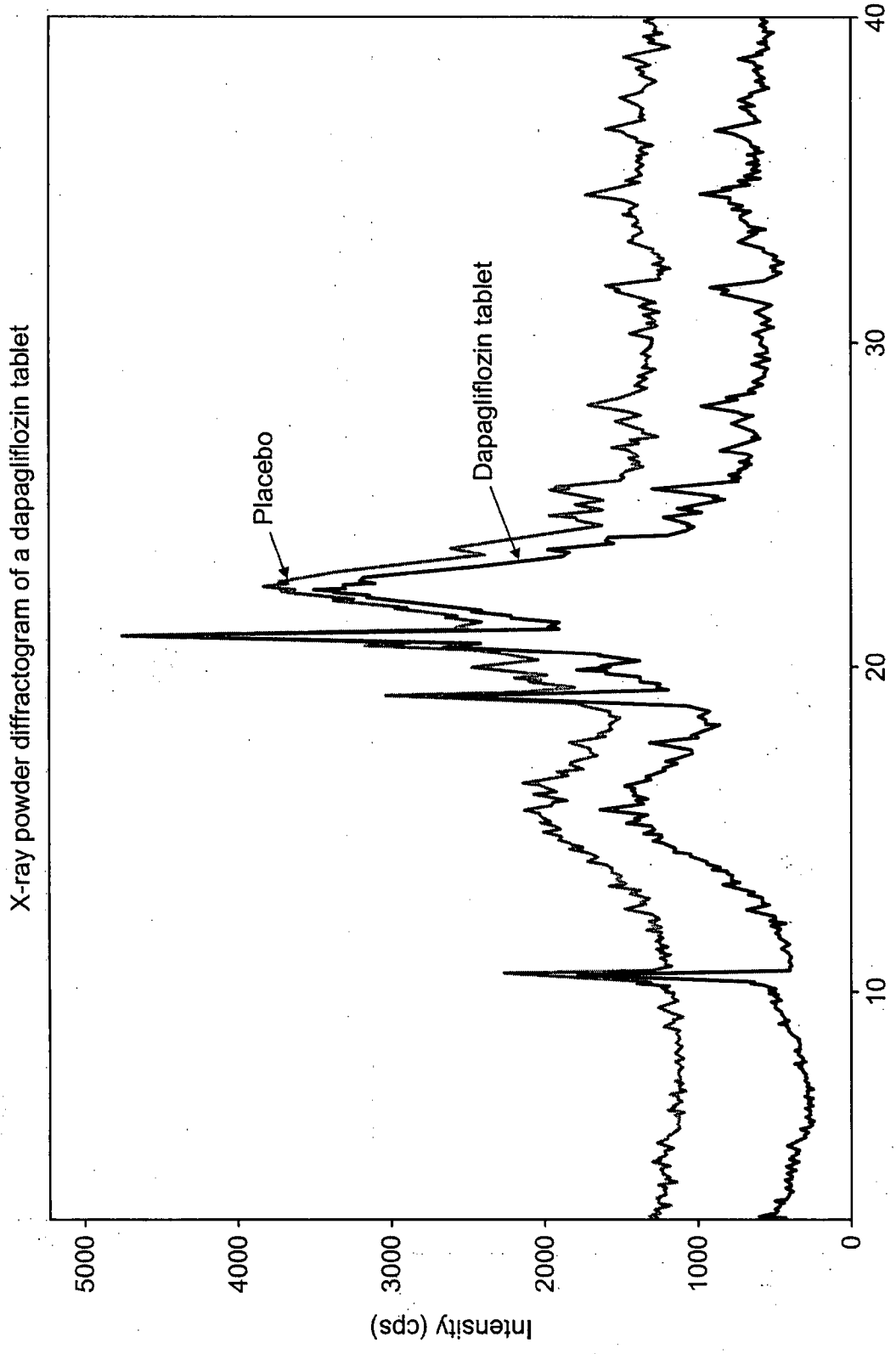

X-ray powder diffractogram of a dapagliflozin tablet
Placebo
Dapagliflozin tablet
Intensity (cps)
5000
4000
3000
2000
1000
0
10
20
30
40
2-theta (deg)

FIG. 4

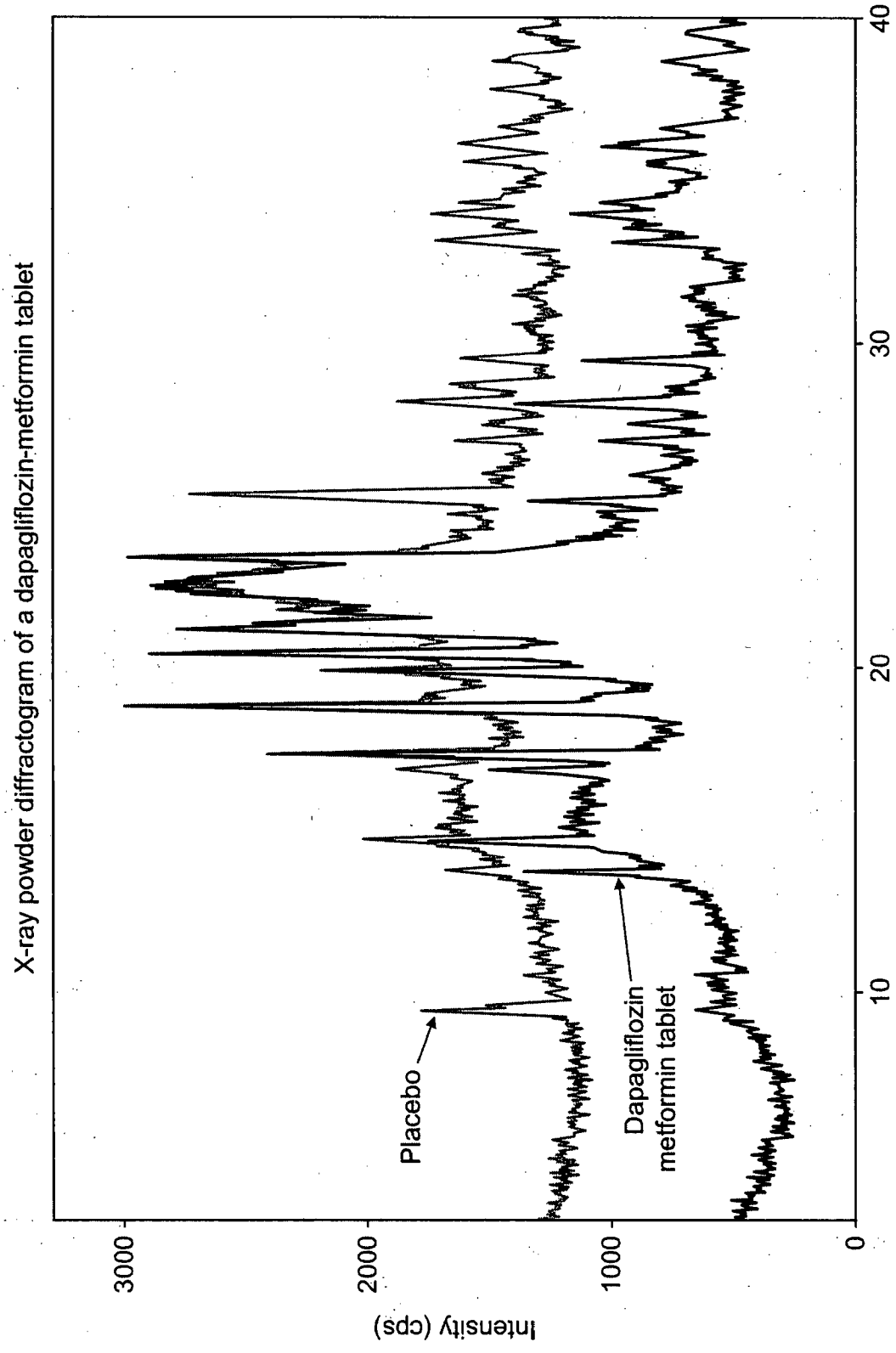

X-ray powder diffractogram of a dapagliflozin-metformin tablet
Intensity (cps)
3000
2000
1000
0
10
20
30
40
2-theta (deg)
Placebo
Dapagliflozin metformin tablet

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2017/051434

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K45/06 A61K31/155 A61K31/403 A61K31/70 A61P3/10
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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, CHEM ABS Data, 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	EP 2 508 188 A1 (SQUIBB BRISTOL MYERS CO [US]) 10 October 2012 (2012-10-10) examples 8,9 paragraph [0040] claims 1,16-18 -----	1-8, 35-37

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 August 2017	16/10/2017

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2017/051434

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.:

1-8, 35-37(all partially)

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: 1-8, 35-37(all partially)

   A premix comprising dapagliflozin and one or more pharmaceutically acceptable excipients, wherein the pharmaceutically acceptable excipient is crospovidone or any combination thereof, wherein the weight ratio of dapagliflozin to crospovidone is 1:1

   ---

2. claims: 1-8, 35-37(all partially)

   A premix comprising dapagliflozin and one or more pharmaceutically acceptable excipients, wherein the pharmaceutically acceptable excipient is crospovidone or any combination thereof, wherein the weight ratio of dapagliflozin to crospovidone is 1:0.5

   ---

3. claims: 1-8, 35-37(all partially)

   A premix comprising dapagliflozin and one or more pharmaceutically acceptable excipients, wherein the pharmaceutically acceptable excipient is crospovidone or any combination thereof, wherein the weight ratio of dapagliflozin to crospovidone is 1:0.3

   ---

4. claims: 9-11(completely); 1-4, 12, 13, 35-37(partially)

   A premix comprising dapagliflozin and one or more pharmaceutically acceptable excipients, wherein the pharmaceutically acceptable excipient is microcrystalline cellulose or any combination thereof

   ---

5. claims: 1, 2, 35-37(all partially)

   A premix comprising dapagliflozin and one or more pharmaceutically acceptable excipients, wherein the pharmaceutically acceptable excipient is silicon dioxide, silicified microcrystalline cellulose, magnesium aluminosilicate or any combination thereof

   ---

6. claims: 1, 2, 12, 13, 35-37(all partially)

   A premix comprising dapagliflozin and one or more pharmaceutically acceptable excipients, wherein the pharmaceutically acceptable excipient is mannitol or any combination thereof

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. claims: 14-34, 41-44

A process according to claim 14 or 22, a premix according to claim 43 obtainable by a process according to any of claims 14-34; a process according to claim 41

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8. claims: 38-40(completely); 1, 35-37(partially)

A pharmaceutical composition according to claim 37 comprising a premix comprising dapagliflozin and one or more pharmaceutically acceptable excipients further comprising one or more further therapeutic agents

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2017/051434

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