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(54) Title: PHARMACEUTICAL COMPOSITION OF DAPAGLIFLOZIN CO-CRYSTAL

(57) Abstract: The present disclosure relates to oral pharmaceutical compositions comprising dapagliflozin citric acid co-crystal and one or more pharmaceutically acceptable excipients, and processes for their preparation. It further relates to a method of treating diabetes using said pharmaceutical compositions.



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PHARMACEUTICAL COMPOSITION OF DAPAGLIFLOZIN CO-CRYSTAL

Field of the Invention

The present disclosure relates to oral pharmaceutical compositions comprising dapagliflozin citric acid co-crystal and one or more pharmaceutically acceptable
5 excipients, and processes for their preparation. The disclosure further relates to methods of treating diabetes using said pharmaceutical compositions.

Background of the Invention

Dapagliflozin is a SGLT2 inhibitor, chemically known as (2*S*,3*R*,4*R*,5*S*,6*R*)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol.
10 Current commercially available formulations of dapagliflozin contain a propanediol (propylene glycol) monohydrate solvate of dapagliflozin as the active ingredient. The commercially available dapagliflozin is crystalline in nature. In contrast, dapagliflozin base can exist in amorphous form.

U.S. Patent No. 6,515,117 reports the compound dapagliflozin. U.S. Patent No.
15 7,919,598 reports a (S)-propylene glycol solvate of dapagliflozin and processes of preparation thereof.

U.S. Patent Nos. 7,851,502, 8,221,786, and 8,361,972 reports pharmaceutical compositions comprising dapagliflozin or dapagliflozin propylene glycol hydrate and specific excipients in given amounts. U.S. Patent No. 8,221,786 further reports
20 pharmaceutical compositions in the form of a stock granulation comprising dapagliflozin propylene glycol hydrate and excipients.

PCT Publication No. WO 2012/163546 reports pharmaceutical compositions comprising cyclodextrin and dapagliflozin, in some embodiments as an inclusion complex.

PCT Publication No. WO 2015/011113 reports pharmaceutical compositions
25 comprising amorphous solid dispersions of dapagliflozin or adsorbates of dapagliflozin with one or more pharmaceutically acceptable excipients.

PCT Publication No. WO 2015/104658 reports an amorphous form of dapagliflozin and a solid dispersion comprising the same.

A novel co-crystal of dapagliflozin with citric acid was reported in PCT
30 Publication no. WO 2015/198227, which is hereby incorporated by reference in its

entirety. Such co-crystals were reported to have higher solubility, good storage stability, and better handling and processing ability due to their non-hygroscopic nature when compared to other polymorphic forms. Such co-crystals were reported to be useful in the treatment of patients with diabetes.

5

Summary of the Invention

The present disclosure relates to oral pharmaceutical compositions comprising dapagliflozin citric acid co-crystal and one or more pharmaceutically acceptable excipients. In some embodiments, the dapagliflozin citric acid co-crystal is present in an amount of from about 0.5% to about 25% in weight of the active moiety, based on the total
10 weight of the composition. In some embodiments, the oral pharmaceutical composition of the present invention is prepared by a wet granulation process or by a dry process, such as direct compression and dry granulation.

Detailed Description of the Invention

The present disclosure provides oral pharmaceutical formulations comprising
15 dapagliflozin citric acid co-crystal, especially a solid oral dosage form, such that the therapeutic benefits of the dapagliflozin may be delivered to a patient in need thereof. In some embodiments, the present invention provides a stable oral pharmaceutical formulation which is easy to manufacture, provides an acceptable dose uniformity, and provides a rapid dissolution profile. In some embodiments, the disclosure provides an oral
20 pharmaceutical composition comprising dapagliflozin citric acid co-crystal and one or more pharmaceutically acceptable excipients.

According to some embodiments, the dapagliflozin citric acid co-crystal is from about 0.5% to about 25%, about 1% to about 20%, about 2% to about 15%, about 3% to about 10%, or about 4% to about 8% by weight of the total weight of the composition.
25 According to some embodiments, the dapagliflozin citric acid co-crystal is from about 0.5% to about 25% by weight of the total weight of the composition. In some embodiments, the dapagliflozin citric acid co-crystal is from about 4% to about 8% by weight of the total weight of the composition. Unless indicated otherwise, “%” and “percentage” when referring to amounts of active agent or excipients (e.g., diluents, disintegrants, lubricants, glidants, etc.) refers to wt%, e.g., the weight of the active agent
30 or excipient relative to the weight of the total composition.

According to some embodiments, the dapagliflozin citric acid co-crystal is present in an amount of from about 1 mg to about 100 mg, about 2 mg to about 75 mg, about 3 mg to about 50 mg, about 4 mg to about 40 mg, about 5 mg to about 25 mg in the composition, e.g., a single dosage form. In some embodiments, the dapagliflozin citric acid co-crystal is present in an amount of about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 12 mg, about 15 mg, about 20 mg, or about 25 mg in the composition. In some embodiments, the dapagliflozin citric acid co-crystal is in an effective amount in the pharmaceutical composition. The term an "effective amount" of an agent, as used herein, is that amount sufficient to effect beneficial or desired results, such as clinical results, and, as such, an "effective amount" depends upon the context in which it is being applied.

In some embodiments, the pharmaceutically acceptable excipients are selected from one or more of a diluent, a binder, a disintegrant, a lubricant, and mixtures thereof. In some embodiments, the pharmaceutical composition is free of binder.

In some embodiments, the disclosure of the present inventions provides compositions with increase stability over time, increased stability at various temperatures and/or increased stability at various humidity levels. For example, in some embodiments, the present disclosure provides compositions stable for 3 months, 6 months, 9 months, 12 months, 15 months, 18 months or 24 months when stored at 30°C at 65% relative humidity ("RH"). In some embodiments, the present disclosure provides compositions stable for 3 months, 6 months, 9 months, 12 months, 15 months, 18 months or 24 months when stored at 40°C at 75% RH.

In some embodiments, the compositions are stable for three months when stored at 30°C and 65% relative humidity ("RH"). In some embodiments, the compositions stable for three months when stored at 40°C and 75% RH. In some embodiments, the compositions are stable for three months when stored at 40°C and 75% RH. In some embodiments, the compositions are stable for three months when stored at 40°C and 75% RH and when stored at 40°C and 75% RH.

In some embodiments, the compositions are stable for six months when stored at 30°C and 65% relative humidity ("RH"). In some embodiments, the compositions are stable for six months when stored at 40°C and 75% RH. In some embodiments, the compositions are stable for six months when stored at 40°C and 75% RH. In some

embodiments, the compositions are stable for six months when stored at 40°C and 75% RH and when stored at 40°C and 75% RH.

In some embodiments, the compositions are stable for nine months when stored at 30°C and 65% relative humidity (“RH”). In some embodiments, the compositions are stable for nine months when stored at 40°C and 75% RH. In some embodiments, the compositions are stable for nine months when stored at 40°C and 75% RH. In some embodiments, the compositions are stable for nine months when stored at 40°C and 75% RH and when stored at 40°C and 75% RH.

In some embodiments, the compositions are stable for twelve months when stored at 30°C and 65% relative humidity (“RH”). In some embodiments, the compositions are stable for twelve months when stored at 40°C and 75% RH. In some embodiments, the compositions are stable for twelve months when stored at 40°C and 75% RH. In some embodiments, the compositions are stable for twelve months when stored at 40°C and 75% RH and when stored at 40°C and 75% RH.

In some embodiments, the term “stable” refers to a pharmaceutical composition, e.g., dosage form, in which at least 85%, at least 90%, at least 95% or at least 96% of the active agent, e.g., dapagliflozin, remains active at the designated time period compared to the original amount of active agent. In some embodiments, the term “stable” refers to a pharmaceutical composition comprising impurities less than 0.8%, less than 0.7%, less than 0.6%, less than 0.5%, less than 0.4%, less than 0.3%, or less than 0.2% wt/wt as determined by HPLC at the termination of the designated time period compared to the original amount of active agent as determined by HPLC.

In some embodiments, the disclosure provides for a pharmaceutical composition having a rapidly dissolving *in vitro* dissolution profile. In some embodiments as described herein, dissolution is determined in 1000 mL pH 4.5 acetate buffer using USP apparatus Type-I at 60 RPM, at 37°C ±0.5°C. In some embodiments, the composition exhibits a rapidly dissolving *in vitro* dissolution profile, such that after 10 minutes, not less than 80%, 85%, 90%, or 92% of drug is released. In some embodiments, the composition exhibits a rapidly dissolving *in vitro* dissolution profile, such that after 10 minutes, not less than 85% of drug is released. In some embodiments, the composition exhibits a rapidly dissolving *in vitro* dissolution profile, such that after 10 minutes, not less than 90% of drug is released.

In some embodiments, the composition exhibits a rapidly dissolving *in vitro* dissolution profile, such that after 15 minutes, not less than 80%, 85%, 90%, 92% or 94% of drug is released. In some embodiments, the composition exhibits a rapidly dissolving *in vitro* dissolution profile, such that after 15 minutes, not less than 85% of drug is released.

- 5 In some embodiments, the composition exhibits a rapidly dissolving *in vitro* dissolution profile, such that after 15 minutes, not less than 92% of drug is released.

In some embodiments, the composition exhibits a rapidly dissolving *in vitro* dissolution profile, such that after 30 minutes, not less than 90%, 92%, 94%, 96% or 98% of drug is released. In some embodiments, the composition exhibits a rapidly dissolving *in vitro* dissolution profile, such that after 30 minutes, not less than 95% of drug is released.

10 In some embodiments, the composition exhibits a rapidly dissolving *in vitro* dissolution profile, such that after 30 minutes, not less than 98% of drug is released.

In some embodiments, the disclosure provides for a rapidly dissolving, stable pharmaceutical composition, e.g., dosage form, comprising:

- 15 (i) from about 1% to about 25% dapagliflozin citric acid co-crystal;
(ii) from about 40% to about 90% diluent;
(iii) from about 2% to about 20% disintegrant;
(iv) from about 0.5% to about 5% glidant; and
(v) about 0.1% to about 3% lubricant,

20 wherein the total composition does not exceed 100%.

In some embodiments, the disclosure provides for a rapidly dissolving, stable pharmaceutical composition, e.g., dosage form, comprising:

- (i) from about 1% to about 25% dapagliflozin citric acid co-crystal;
(ii) from about 40% to about 90% microcrystalline cellulose, lactose, or
25 combinations thereof;
(iii) from about 2% to about 20% crospovidone;
(iv) from about 0.5% to about 5% silicon dioxide; and
(v) about 0.1% to about 3% magnesium stearate, sodium stearyl fumarate, or combinations thereof,

30 wherein the total composition does not exceed 100%.

In some embodiments, the disclosure provides for a rapidly dissolving, stable pharmaceutical composition comprising an intragranular part, and an extragranular part, the intragranular part comprising:

- (i) from about 1% to about 25% dapagliflozin citric acid co-crystal;
- 5 (ii) from about 40% to about 90% diluent;
- (iii) from about 2% to about 20% disintegrant;
- (iv) from about 0.5% to about 5% glidant; and
- (v) from about 0.1% to about 3% lubricant,

wherein the intragranular part does not exceed 100%; and the extragranular part
10 comprising:

- (i) from about 60% to about 95% diluent;
- (ii) from about 5% to about 30% disintegrant;
- (iii) from about 1% to about 10% glidant; and
- (iv) from about 0.1% to about 3% lubricant,

15 wherein the extragranular part does not exceed 100%; and wherein the composition comprises about 60% to about 95% intragranular part, and about 5% to about 40% extragranular part. In some embodiments, the composition comprises about 75% to about 90% intragranular part, and about 10% to about 25% extragranular part, or about 80% to intragranular part, and about 20% extragranular part. The term “intragranular” refers to
20 granules comprising the active agent, and the term “extragranular” refers to granules not comprising the active agent.

In some embodiments, present disclosure provides a process for making an oral pharmaceutical composition comprising:

- (a) mixing dapagliflozin citric acid co-crystal with one or more pharmaceutically
25 acceptable excipients to form a blend; and
- (b) directly compressing the blend of (a) into a solid dosage form.

In some embodiments, the present disclosure provides a process for making an oral pharmaceutical composition comprising:

- (a) mixing dapagliflozin citric acid co-crystal with one or more pharmaceutically
30 acceptable excipients to form a blend;
- (b) compacting the blend of (a) into a slug or a compact;

- (c) milling the slug or compact of (b) into granules;
- (d) optionally mixing the granules of (c) with further pharmaceutically acceptable excipients to form a final blend; and
- (e) optionally compressing the final blend of (d) into a solid dosage form.

5 In some embodiments, the present disclosure provides a process for making an oral pharmaceutical composition comprising:

- (a) mixing dapagliflozin citric acid co-crystal with one or more pharmaceutically acceptable excipients to form a blend;
- (b) granulating the blend of (a) with a granulating liquid to obtain granules;
- 10 (c) drying the granules of (b) to obtain dried granules;
- (d) optionally milling the dried granules of (c);
- (e) adding at least one lubricant to the granules of (c) or the milled material of (d), and optionally mixing with further pharmaceutically acceptable excipients to form a final blend; and
- 15 (f) optionally compressing the final blend of (d) into a solid dosage form.

 In some embodiments, the present disclosure provides a method of treating diabetes by administering an oral pharmaceutical composition as described herein comprising dapagliflozin citric acid co-crystal and one or more pharmaceutically acceptable excipients.

20 According to one embodiment, the method of treatment further comprises administration of an additional anti-diabetic agent.

 The term “pharmaceutical composition,” as used herein, includes solid dosage forms such as powder, pellets, mini-tablets, granules, tablets, capsules, and the like. In some embodiments, the composition is in the form of powder, granules, tablets, caplet,
25 gelcap, or capsules.

 The term “dapagliflozin citric acid co-crystal,” as used herein, refers to a stoichiometric multi component system comprising dapagliflozin base and citric acid in a stoichiometric ratio of 1:1 and connected by non-covalent interactions. In some embodiments, the term “dapagliflozin citric acid co-crystal” is as described in
30 WO 2015/198227, incorporated herein in its entirety. In some embodiments, the

dapagliflozin citric acid co-crystal is present in the composition in an amount of from about 0.5% to about 25% by weight based on the total weight of the composition. One of skill in the art will appreciate that not 100% of the dapagliflozin citric acid necessarily will be in crystalline form. Thus, as used herein, in some embodiments the term “dapagliflozin
5 citric acid co-crystal” includes a composition wherein at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least 98% or at least 99% of the dapagliflozin citric acid in the composition is in crystalline form.

The term “anti-diabetic agents,” as used herein, includes, but is not limited to metformin, pioglitazone, rosiglitazone, sitagliptin, linagliptin, saxagliptin, alogliptin,
10 pramlintide, repaglinide, nateglinide, acarbose, miglitol, glimepiride, glyburide, glipizide, and voglibose.

The term “about,” as used herein, refers to any value which lies within the range defined by a variation of up to $\pm 10\%$ of the value.

The term “active moiety,” as used herein, refers to the dapagliflozin base. For
15 example, 14.7 mg of dapagliflozin citric acid co-crystal corresponds to 10 mg of dapagliflozin base.

The term “pharmaceutically acceptable excipients,” as used herein, includes diluents, binders, disintegrants, lubricants, glidants, and mixtures thereof.

Various diluents can be used. In some embodiments, suitable diluents are selected
20 from the group consisting of lactose, *e.g.*, lactose anhydrous and lactose monohydrate; cellulose, *e.g.*, microcrystalline cellulose, co-processed microcrystalline cellulose, and powdered cellulose; starch, *e.g.*, pregelatinized starch, maize starch, rice starch, potato starch, and wheat starch; sugar alcohols, *e.g.*, mannitol, sorbitol, xylitol, and erythritol; inorganic salts, *e.g.*, calcium carbonate, calcium phosphate, calcium sulfate, dibasic
25 calcium phosphate, dibasic calcium phosphate anhydrate, dibasic calcium phosphate dihydrate, and tribasic calcium phosphate; and mixtures thereof. The diluents can be present in an amount of from about 20% to about 98% by weight of the composition, preferably from about 30% to about 95% by weight of the composition. In some
embodiments, the diluents are about 60% to about 90% by weight of the composition,
30 about 70% to about 90% by weight of the composition, or about 80% to about 90% by weight of the composition.

Various binders can be used according to the present disclosure. In some embodiments, suitable binders are selected from the group consisting of povidone, copovidone, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, ethyl cellulose, carboxymethyl cellulose sodium, xanthan gum, gum acacia, gum arabic, tragacanth, corn starch, modified corn starch, maize starch, pregelatinized starch, methacrylates, carboxyvinyl polymers, waxes, and mixtures thereof. The binder can be present in an amount of from about 0% to about 30% by weight of the composition, preferably from about 0% to about 20% by weight of the composition. In some embodiments, the binders are about 0% to about 10% by weight of the composition, about 0% to about 5% by weight of the composition, or about 0% to about 1% by weight of the composition. In some embodiments, no binder is present in the compositions, i.e., the composition comprises 0% binder.

Various disintegrants can be used according to the present disclosure. In some embodiments, suitable disintegrants are selected from the group consisting of croscarmellose sodium, hydroxypropyl cellulose, crospovidone, low substituted hydroxypropyl cellulose, microcrystalline cellulose, carboxymethyl cellulose sodium, carboxymethyl cellulose calcium, starch, corn starch, pregelatinized starch, modified starch, sodium starch glycolate, carboxymethyl starch, polyacrylates, and mixtures thereof. The disintegrant can be present in an amount of from about 0% to about 30% by weight of the composition, preferably from about 0% to about 20% by weight of the composition. In some embodiments, the disintegrants are about 1% to about 10% by weight of the composition, about 1% to about 5% by weight of the composition, or about 5% to about 7% by weight of the composition.

Various lubricants can be used according to the present disclosure. In some embodiments, suitable lubricants are selected from the group consisting of stearic acid, magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, polyethylene glycol, talc, hydrogenated vegetable oils, fatty acids, waxes, and mixtures thereof. The lubricant can be present in an amount of from about 0.1% to about 10% by weight of the composition, preferably from about 0.1% to about 5% by weight of the composition. In some embodiments, the lubricant is about 0.01% to about 5% by weight of the composition, about 0.1% to about 2% by weight of the composition, or about 1% to about 2% by weight of the composition.

Various glidants can be used according to the present disclosure. In some embodiments, suitable glidants or anti-sticking agents are selected from the group consisting of talc, silicon dioxide, colloidal silicon dioxide (colloidal anhydrous silica), calcium silicate, magnesium silicate, hydrated silica, and mixtures thereof. The glidant
5 can be present in an amount of from about 0.1% to about 10% by weight of the composition, preferably from about 0.1% to about 5% by weight of the composition. In some embodiments, the lubricant is about 0% to about 5% by weight of the composition, about 0.1% to about 5% by weight of the composition, or about 1% to about 2% by weight of the composition.

10 The oral pharmaceutical composition may be prepared by a wet granulation process or by a dry process such as direct compression and dry granulation. Preferably, the pharmaceutical composition is prepared by a dry process. The composition can have a coating, or optionally can be uncoated. In some embodiments, the oral pharmaceutical composition is further film-coated using techniques well known in the art, such as spray
15 coating in a conventional coating pan or dip coating. The film coat comprises film-forming polymers and one or more coating additives. The target weight gain after the coating can vary between 1% and 10% by weight of the uncoated composition, between 1.5% and 6% by weight of the uncoated composition, or between 2% and 4% by weight of the uncoated composition.

20 Suitable film-forming polymers are selected from the group comprising cellulose derivatives, *e.g.*, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxymethylethyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, and ethyl cellulose; vinyl polymers, *e.g.*, polyvinylpyrrolidones; acrylic polymers; and mixtures thereof. Alternatively,
25 commercially available coating compositions comprising film-forming polymers marketed under various trade names, *e.g.*, Opadry®, may be used for coating.

In some embodiments, the film-coating provides for immediate release, extended release, sustained release, delayed release, enteric release, or intestinal release of the active agent, *e.g.*, dapagliflozin citric acid co-crystal, to the subject in which the dosage form
30 was administered. In some embodiments, the film-coating provides for immediate release of the active agent.

As used herein, the term "delayed release" refers to a pharmaceutical preparation, e.g., an orally administered formulation, which passes through the stomach substantially intact and dissolves in the small and/or large intestine (e.g., the colon). In some embodiments, delayed release of the active agent (e.g., dapagliflozin citric acid co-crystal as described herein) results from the use of an enteric coating of an oral medication (e.g., an oral dosage form). The terms "extended release" or "sustained release" interchangeably refer to a drug formulation that provides for gradual release of a drug over an extended period of time, e.g., 6-12 hours or more, compared to an immediate release formulation of the same drug. In some embodiments, although not necessarily, extended release results in substantially constant blood levels of a drug over an extended time period that are within therapeutic levels. As used herein, the terms "enteric release" refer to pharmaceutical compositions, e.g., oral dosage forms, for oral administration able to provide protection from dissolution in the high acid (low pH) environment of the stomach. Enteric formulations can be obtained by, for example, incorporating into the pharmaceutical composition a polymer resistant to dissolution in gastric juices. In some embodiments, the polymers have an optimum pH for dissolution in the range of approximately 5.0 to 7.0 ("pH sensitive polymers").

The film coating, "film" or "coating additives comprise one or more of plasticizers, glidants or flow regulators, lubricants, coloring agents, and opacifiers. Suitable plasticizers are selected from the group comprising castor oil, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, glycerin, polyethylene glycols, propylene glycols, triacetin, triethyl citrate, and mixtures thereof. An opacifier, like titanium dioxide, may also be present in the coating.

Examples of solvents used for preparing the coating solution are selected from purified water, methyl alcohol, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, acetone, acetonitrile, chloroform, methylene chloride, and mixtures thereof.

The oral pharmaceutical composition will be bioequivalent to the marketed formulation of dapagliflozin (as propanediol monohydrate) available under the brand name Farxiga® (AstraZeneca, United Kingdom).

The oral pharmaceutical composition is used for treating diabetes, particularly Type II diabetes. The pharmaceutical composition may be administered in combination with other anti-diabetic agents. Various regimens are known to those in the art. In some

embodiments, the oral pharmaceutical composition is administered once daily. In some embodiments, the oral pharmaceutical composition is administered twice daily. In some embodiments, the oral pharmaceutical composition is administered every other day. One of skill in the art can also appreciate that in some embodiments, the pharmaceutical composition can be divided (e.g., split in half), with one or more of the divided parts taken at the same time or at different times.

The present invention is illustrated below by reference to the following examples. However, one skilled in the art will appreciate that the specific methods and results discussed are merely illustrative of the invention, and not to be construed as limiting the invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

EXAMPLES

Example 1:

Ingredients	Percent (%) w/w
Dapagliflozin citric acid co-crystal	5.88
Microcrystalline cellulose (Avicel® PH 101)	6.00
Microcrystalline cellulose (Avicel® PH 112)	61.62
Lactose anhydrous/monohydrate	20.00
Crospovidone	4.00
Silicon dioxide	1.50
Magnesium stearate	1.00
Total	100.00
Opadry® coating (PVA based)	q.s. to 2% to 4%

Procedure:

1. Dapagliflozin citric acid co-crystal, microcrystalline cellulose, lactose, crospovidone, and silicon dioxide were mixed in a blender.
2. Magnesium stearate was added to the above blend in the blender and mixed.
3. The blend of step 2 was compressed into tablets.
4. An Opadry® dispersion was prepared, and the tablets of step 3 were coated to a weight build-up of 2% to 4% w/w.

Dissolution Study

The tablets of Example 1 were subjected to an *in-vitro* dissolution study in 1000 mL of pH 4.5 acetate buffer at 37°C ±0.5° C for 30 minutes, using USP apparatus Type-I at 60 RPM. The results are given in Table 1 below:

5 **Table 1. Dissolution profile of tablets of Example 1**

Time (minutes)	Cumulative Release (%)
10	92
15	94
30	98

Example 2:

Ingredients	Percent (%) w/w
Dapagliflozin citric acid co-crystal	5.88
Microcrystalline cellulose (Avicel® PH 112)	67.62
Lactose anhydrous/monohydrate	20.00
Crospovidone	4.00
Silicon dioxide	1.50
Magnesium stearate	1.00
Total	100.00
Opadry® coating (PVA based)	q.s. to 2% to 4%

Procedure:

1. Dapagliflozin citric acid co-crystal, microcrystalline cellulose, lactose, crospovidone and silicon dioxide were mixed in a blender.
- 10 2. Magnesium stearate was added to the above blend in the blender and mixed.
3. The blend of step 2 was compressed into tablets.
4. An Opadry® dispersion was prepared, and the tablets of step 3 were coated to a weight build-up of 2% to 4% w/w.

Stability Data:

- 15 Tablets prepared according to Example 2 were stored at 30°C and 65% RH and at 40°C and 75% RH for six months, and were then tested by HPLC to determine the amount of total impurities. The stability data is given in Table 2.

Table 2. Stability data of the tablets of Example 2.

	30°C and 65% RH			40°C and 75% RH		
	Initial	3 Months	6 Months	Initial	3 Months	6 Months
Assay (%)	99.4	98.3	97.1	99.4	97.9	96.2
Total impurities (% w/w)	0.14	0.18	0.32	0.14	0.5	0.64

Examples 3-4:

Ingredients	Percent (%) w/w	
	Example 3	Example 4
Dapagliflozin citric acid co-crystal	5.88	5.88
Microcrystalline cellulose	63.62	63.62
Lactose anhydrous/monohydrate	20.00	20.00
Povidone	4.00	4.00
Crospovidone	4.00	4.00
Silicon dioxide	1.50	1.50
Magnesium stearate	1.00	-
Sodium stearyl fumarate	-	1.00
Total	100.00	100.00
Opadry® coating (PVA based)	q.s. to 2% to 4%	q.s. to 2% to 4%

Procedure:

- Blend Dapagliflozin citric acid co-crystal, microcrystalline cellulose, lactose, povidone, crospovidone, and silicon dioxide in a blender.
- Add Magnesium stearate or sodium stearyl fumarate to the above blend in the blender and mixed.
- Compress the blend of step 2 into tablets.
- Prepare Opadry® dispersion and coat the tablets of step 3 to a weight build-up of 2% to 4% w/w.

Example 5:

Ingredients	Percent (%) w/w
Intragranular	
Dapagliflozin citric acid co-crystal	5.88
Microcrystalline cellulose	60.62
Lactose anhydrous	20.00
Crospovidone	2.00
Silicon dioxide	1.00
Magnesium stearate	1.00
Extra granular	
Microcrystalline cellulose	6.00
Crospovidone	2.00
Silicon dioxide	0.50
Magnesium stearate	1.00
Total	100.00
Opadry® coating (PVA based)	q.s. to 2% to 4%

Procedure:

1. Blend Dapagliflozin citric acid co-crystal, microcrystalline cellulose, lactose anhydrous, crospovidone, and silicon dioxide in a blender.
2. Compact the blend of step 1 followed by milling to obtain granules.
3. Blend the extra granular excipients with the granules obtained in step 2.
4. Compress the blend of step 3 into tablets.
5. Prepare Opadry® dispersion, and coat the tablets of step 4 with the Opadry® dispersion to a weight build-up of 2% to 4% w/w.

Examples 6-8:

Ingredients	Percent (%) w/w		
	Example 6	Example 7	Example 8
Intragranular			
Dapagliflozin citric acid co-crystal	5.88	5.88	5.88
Hydroxypropyl methylcellulose	4.00	-	-
Hydroxypropyl cellulose (HPC-L)	-	4.00	-
Povidone	-	-	4.00
Isopropyl alcohol	q.s.	-	-
Methylene chloride	q.s.	-	-
Purified water	-	q.s.	q.s.
Lactose anhydrous/monohydrate	21.00	21.00	21.00
Microcrystalline cellulose	50.62	50.62	50.62
Extragranular			
Microcrystalline cellulose	12.00	12.00	12.00
Crospovidone	4.00	4.00	4.00
Colloidal anhydrous silica	1.50	1.50	1.50
Magnesium stearate	1.00	1.00	1.00
Total	100.00	100.00	100.00
Opadry® coating (PVA based)	q.s. to 2% to 4%	q.s. to 2% to 4%	q.s. to 2% to 4%

Procedure:

1. Blend lactose anhydrous/monohydrate, microcrystalline cellulose, and dapagliflozin citric acid co-crystal in a blender.
- 5 2. Dissolve Hydroxypropyl cellulose or hydroxypropylmethyl cellulose or povidone in a solvent mixture or purified water to obtain a binder solution.
3. Granulate the material of step 1 with the binder solution of step 2.
4. Dry and mill the granules obtained in step 3.
5. Add extragranular microcrystalline cellulose and crospovidone to the granules of step 4, and mixed.
- 10 6. Add colloidal anhydrous silica and magnesium stearate to the material of step 5, and mixed.
7. Compress the blend of step 6 into tablets.
8. Prepare Opadry® dispersion and coat the tablets of step 7 with the Opadry® dispersion to a weight build-up of 2% to 4% w/w.
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We Claim:

- 1 1. An oral pharmaceutical composition comprising dapagliflozin citric acid co-crystal
2 and one or more pharmaceutically acceptable excipients, wherein the dapagliflozin
3 citric acid co-crystal is from about 0.5% to about 25% by weight of the total weight of
4 the composition.
- 1 2. The oral pharmaceutical composition according to claim 1, wherein the dapagliflozin
2 citric acid co-crystal in the pharmaceutical composition is from about 1 mg to about
3 100 mg.
- 1 3. The oral pharmaceutical composition according to any one of claims 1 to 2, wherein
2 the pharmaceutically acceptable excipients are selected from one or more of diluents,
3 binders, disintegrants, lubricants, and mixtures thereof.
- 1 4. The oral pharmaceutical composition according to any one of claims 1 to 3, wherein
2 the composition is free of binder.
- 1 5. The oral pharmaceutical composition according to any one of claims 1 to 4, wherein
2 the composition is in the form of powder, pellets, mini-tablets, granules, tablets, or
3 capsules.
- 1 6. The oral pharmaceutical composition according to any one of claims 1 to 5, wherein
2 the composition further comprises a film-coating.
- 1 7. The oral pharmaceutical composition according to any one of claims 1 to 6, wherein
2 the composition is stable for six months when stored at 30°C and 65% RH or 40°C and
3 75% RH.
- 1 8. The oral pharmaceutical composition according to any one of claims 1 to 7, wherein
2 the composition exhibits a rapidly dissolving *in-vitro* release profile.
- 1 9. The oral pharmaceutical composition according to claim 8, wherein the composition
2 releases not less than 85% of the drug in 15 minutes, when tested in 1000 mL pH 4.5
3 acetate buffer using USP apparatus Type-I at 60 RPM, at 37°C ±0.5°C.
- 1 10. The oral pharmaceutical composition according to any one of claims 1 to 9, wherein
2 the composition is bioequivalent to the marketed Farxiga® tablet.
- 1 11. The oral pharmaceutical composition according to any one of claims 1 to 10, wherein
2 the composition is prepared by a wet granulation process.

- 1 12. The oral pharmaceutical composition according to any one of claims 1 to 10, wherein
2 the composition is prepared by a dry process selected from direct compression and dry
3 granulation.
- 1 13. A process of preparing an oral pharmaceutical composition comprising dapagliflozin
2 citric acid co-crystal and one or more pharmaceutically acceptable excipients, wherein
3 the process comprises:
- 4 (a) mixing dapagliflozin citric acid co-crystal with one or more pharmaceutically
5 acceptable excipients to form a blend; and
- 6 (b) directly compressing the blend of (a) into a solid dosage form.
- 1 14. A process of preparing an oral pharmaceutical composition comprising dapagliflozin
2 citric acid co-crystal and one or more pharmaceutically acceptable excipients, wherein
3 the process comprises:
- 4 (a) mixing dapagliflozin citric acid co-crystal with one or more pharmaceutically
5 acceptable excipients to form a blend;
- 6 (b) granulating the blend of (a) with a granulating liquid to obtain granules;
- 7 (c) drying the granules of (b) to obtain dried granules;
- 8 (d) adding at least one lubricant to the dried granules of step (c) to form a final
9 blend.
- 1 15. The process of claim 14, further comprising milling the dried granules of (c).
- 1 16. The process of any one of claims 14 or 15, comprising further mixing additional
2 pharmaceutical excipients with the lubricant of (d) to form the final blend.
- 1 17. The process of any one of claims 14 to 16, further comprising compressing the final
2 blend of (d) into a solid dosage form.
- 1 18. A method of the treatment of type 2 diabetes mellitus, said method comprising
2 administering an oral pharmaceutical composition according to any one of claims 1 to
3 17 to a subject in need thereof.
- 1 19. The method according to claim 18, wherein method of treatment further comprises
2 administration of an additional anti-diabetic agent.

- 1 20. The method according to claim 19, wherein the additional anti-diabetic agent is
- 2 selected from the group consisting of metformin, pioglitazone, rosiglitazone,
- 3 sitagliptin, linagliptin, saxagliptin, alogliptin, pramlintide, repaglinide, nateglinide,
- 4 acarbose, miglitol, glimepiride, glyburide, glipizide, and voglibose.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 17/53155

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A61K 31/70, A61K 9/14, A61K 31/7024 (2017.01)
 CPC - C07D 309/10, C07H 3/04, A61K 9/145, A61K 31/7024

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)

See Search History Document

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

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015/198227 A1 (SUN PHARMACEUTICAL INDUSTRIES LIMITED) 30 December 2015 (30.12.2015); pg 5 ln 16-18	1-3, 13-16
Y	US 2012/0041069 A1 (SESHA) 16 February 2012 (16.02.2012); para [0072], [0084], [0093], [0096], [0104], [0111]-[0112], [0144], [0150]	1-3, 13-16
A	US 2014/0343010 A1 (MAPI PHARMA LTD.) 20 November 2014 (20.11.2014); see entire document	1-3, 13-16
A	US 2014/0249098 A1 (PUSKAS et al.) 04 September 2014 (04.09.2014); see entire document	1-3, 13-16

☐ 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

06 September 2017 (06.09.2017)

Date of mailing of the international search report

26 SEP 2017

Name and mailing address of the ISA/US

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 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 17/53155

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.: 4-12, 17-20
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:

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

Remark on Protest

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