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(54) **Title:** PHARMACEUTICAL COMPOSITION COMPRISING SGLT2 INHIBITOR

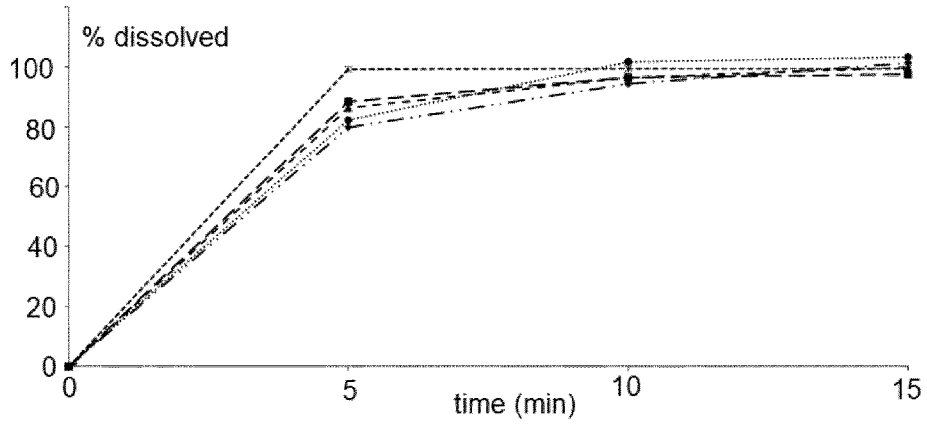


**Fig. 4**

(57) **Abstract:** Pharmaceutical compositions are provided which contain at least one SGLT2 inhibitor. Specifically, the present invention provides pharmaceutical compositions containing one or more SGLT2 inhibitor such as dapagliflozin, optionally in a combination with one or more other active substances.

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# Pharmaceutical composition comprising SGLT2 inhibitor

## 1. Technical field of the invention

The present invention pertains to new pharmaceutical compositions containing at least one sodium-glucose co-transporter-2 (SGLT2) inhibitor. In particular, the present invention provides pharmaceutical compositions containing one or more SGLT2 inhibitors such as dapagliflozin, optionally in a combination with one or more other active substances. The pharmaceutical compositions according to the present invention are physically and chemically stable and are easy to manufacture. The pharmaceutical compositions according to the present invention are in a solid form suitable for oral administration. The present invention further provides methods for making the same.

## 2. Background of the invention

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a group of oral medicines used for treating diabetes that have been approved since 2013. SGLT2 inhibitors prevent the kidneys from re-absorbing glucose back into the blood by passing into the bladder. Glucose is re-absorbed back into the blood via the renal proximal tubules. SGLT2 is a protein predominantly expressed in the renal proximal tubules and is likely to be major transporter responsible for this uptake. Glucose-lowering effect of SGLT2 inhibitors occurs via an insulin-independent mechanism mostly through glucosuria by increasing the urinary excretion of glucose.

It has been shown that the treatment with SGLT2 inhibitors in patients with type II diabetes lowers HbA1c, reduces body weight, lowers systemic blood pressure (BP) and induces a small increase in LDL-C and HDL-C levels.

SGLT2 inhibitors inhibit the reabsorption of sodium and glucose from the tubule and hence, more sodium is delivered in the macula densa causing arteriole dilation, reduced intraglomerular

pressure and decreased hyperfiltration. SGLT2 inhibitors cause natriuresis and volume depletion, and an increase in circulating levels of renin, angiotensin and aldosterone. They also reduce albuminuria and slow GFR loss through mechanisms that appear independent of glycemia.

Dapagliflozin is a highly potent and reversible SGLT2 inhibitor, which increases the amount of glucose excreted in the urine and improves both fasting and post-prandial plasma glucose levels in patients with type 2 diabetes. Dapagliflozin has also been shown to tend to reduce liver fat content in some studies in a diabetic population.

Dapagliflozin is available on the market in the form of dapagliflozin propanediol monohydrate and is sold under trade name Forxiga or Farxiga in the form of film-coated tablets. Further it is available on the market as a combination product with metformin hydrochloride which is sold under trade name Xigduo IR or Xigduo XR in the form of film-coated tablets. In addition, it is available on the market as a combination product with saxagliptin hydrochloride which is sold under trade name Qtern in the form of film-coated tablets. Moreover, it is available on the market as a combination product with saxagliptin hydrochloride and metformin hydrochloride which is sold under trade name Qternmet XR in the form of film-coated tablets.

Dapagliflozin as a monotherapy and in a combination with other active substances has demonstrated its efficacy in improving glycaemic control and reducing body weight and blood pressure in a broad spectrum of patients with type II diabetes, including those with high baseline HbA1c and the elderly. A sustained reduction in serum uric acid concentration was also observed. Dapagliflozin provides significant improvement in HbA1c, reduction in insulin dose and reduction in body weight in patients with type1 diabetes as adjunct therapy to adjustable insulin.

Prior art documents already provided some compositions of SGLT2 inhibitor dapagliflozin.

WO2008116179 discloses immediate release formulation in the form of a stock granulation or in the form of a capsule or a tablet which comprises dapagliflozin propylene glycol hydrate, one or more bulking agent, one or more binder and one or more disintegrant.

WO2011060256 describes the bilayer tablet comprising dapagliflozin having sustained release profile in one layer and metformin in another layer while WO2011060290 describes immediate release formulation of dapagliflozin and metformin.

WO2012163546 discloses the pharmaceutical composition comprising cyclodextrin and dapagliflozin.

Co-crystals of dapagliflozin with lactose are described in WO2014178040.

Solid dispersion compositions comprising amorphous dapagliflozin and at least one polymer are disclosed in WO2015011113 and in WO2015128853.

CN103721261 discloses the combination of SGLT2 inhibitor with vitamins such as vitamin B.

Pharmaceutical composition preparation comprising dapagliflozin L-prolin and metformin and/or DPP-IV inhibitor is disclosed in WO2018124497.

EP2252289A1 provides a combination of SGLT inhibitor with DPP4 inhibitor showing synergistic effect in increasing plasma active GLP-1 level in a patient over that provided by administration of the SGLT inhibitor or the DPP4 inhibitor alone.

EP2395983A1 relates to a pharmaceutical composition comprising a SGLT2 inhibitor, a DPP4 inhibitor and a third antidiabetic agent which is suitable in the treatment or prevention of one or more conditions selected from type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance and hyperglycemia.

However, for various reasons, there remains a need for alternative pharmaceutical compositions exhibiting a desired physical and chemical stability. The present invention has been completed based on these findings.

Pharmaceutical composition of the present invention exhibits excellent chemical and physical stability, it is stable under normal storage conditions and at the same time it provides improved content uniformity. The pharmaceutical composition according to the present invention exhibits high stability on storage which is not limited by physical or chemical instability of active substance(s) or other substances present in the composition. The pharmaceutical composition according to the present invention is well tolerated physiologically. The pharmaceutical composition according to the present invention provides composition with at least one SGLT2

inhibitor, particularly dapagliflozin and optionally one or more other active substances of purity level and uniformity and bioavailability required for regulatory approval. The composition is prepared by an economical process suitable for use on an industrial scale production. It has been surprisingly found that the pharmaceutical composition according to the present invention can be prepared by simple technological process using fluid bed granulation, or high shear granulation or roller compaction or direct compression which results in excellent physical and chemical stability.

## 3. Summary of the invention

In accordance with the present invention, pharmaceutical compositions for oral administration are provided designed for immediate or sustained release of at least one active ingredient which is sodium-glucose co-transporter-2 (SGLT2) inhibitor which is preferably dapagliflozin and pharmaceutically acceptable excipients.

In one embodiment the pharmaceutical composition of the present invention comprises dapagliflozin in a combination with one or more other active substances and pharmaceutically acceptable excipients.

In one embodiment the pharmaceutical composition of the present invention comprises dapagliflozin in predominately amorphous form.

In one embodiment dapagliflozin used in the pharmaceutical composition of the present invention is in the form of dapagliflozin propylene glycol hydrate.

In one embodiment the pharmaceutical composition according to the present invention is prepared by means of any processes known from the state of the art, such as direct compression, fluid bed granulation, wet granulation, dry granulation, high-shear granulation, roller compaction, dry and/or melt and/or dispersion coating of suitable cores such as granules, pellets and/or tablets or any other pharmaceutically acceptable process.

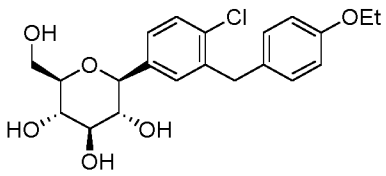
In one embodiment the pharmaceutical composition of the present invention comprises dapagliflozin in predominantly amorphous form prepared by dry granulation.

In one embodiment the pharmaceutical composition of the present invention comprises dapagliflozin in form of amorphous solid dispersion prepared by fluid bed granulation.

In one embodiment the pharmaceutical composition of the present invention comprises dapagliflozin in combination with metformin, wherein both active ingredients are included in the same granulate or in a separate granulates or wherein dapagliflozin is present in extragranular phase.

In one embodiment the pharmaceutical composition of the present invention comprises dapagliflozin in combination with sitagliptin and at least one pharmaceutically acceptable ingredient. Preferably, the composition is substantially free of lactose and calcium hydrogen phosphate; especially, the composition can be free of lactose and calcium hydrogen phosphate. In a preferred embodiment the composition comprises microcrystalline cellulose, optionally a further diluent, optionally a binder, a disintegrant, a glidant and a lubricant selected from magnesium stearate.

In particular, the following items are provided herein: 1. A pharmaceutical compositions for oral administration comprising at least one active ingredient which is dapagliflozin of formula 1



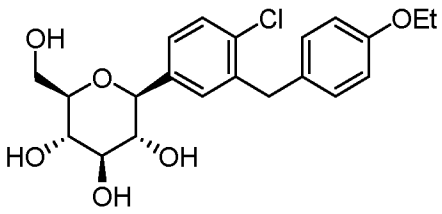

formula 1

in any crystalline or amorphous forms or co-crystal complex or a hydrate or a solvate thereof or any polymorph forms or any mixtures thereof and at least one pharmaceutically acceptable excipient selected from the group comprising at least one binder, at least one diluent, at least one disintegrant, at least one glidant and at least one lubricant. 2. The pharmaceutical composition according to item 1 further comprising metformin or any pharmaceutically acceptable salts thereof. 3. The pharmaceutical composition according to item 1 further comprising sitagliptin or any pharmaceutically acceptable salts thereof. 4. The pharmaceutical composition according to item 1 further comprising metformin or any pharmaceutically acceptable salts thereof and sitagliptin or any pharmaceutically acceptable salts thereof. 5. The pharmaceutical composition according to any one of the preceding items wherein dapagliflozin is in amorphous form. 6. The pharmaceutical composition according to any one of the preceding items wherein dapagliflozin is dapagliflozin propylene glycol hydrate.

## 4. Detailed description of the invention

The pharmaceutical composition of the present invention comprises at least one SGLT2 inhibitor optionally in a combination with one or more other active substances and one or more pharmaceutically acceptable excipients.

In one embodiment the pharmaceutical composition of the present invention comprises SGLT2 inhibitor which is preferably dapagliflozin as shown in formula (1)




Formula 1

or a stereoisomer thereof.

In addition to dapagliflozin as defined above, the pharmaceutical composition of the present invention may comprise dapagliflozin in any crystalline or amorphous forms or co-crystal complex or a hydrate or a solvate thereof or any polymorph forms or any mixtures thereof.

The pharmaceutically acceptable co-crystal may be selected from the group consisting of amino acid or carboxylic acid, preferably from the group consisting of L-proline, L-tryptophan and L-phenyalanine or citric acid, oxalic acid, succinic acid, fumaric acid.

The term 'hydrate' as used herein designates crystalline compound in which one or more water molecules are incorporated into the crystal lattice.

The pharmaceutically acceptable solvate may be selected from the group consisting of alcohol, preferably from the group consisting of 1,2-propylene glycol, 2,3-butandiol, methanol, 1,4-butyne-diol.

Dapagliflozin used in the pharmaceutical composition according to the present invention may be in any known form or any polymorph forms known from the state of the art such as disclosed in WO2008002824, WO2010022313, WO2013064909, WO2013079501, WO2014139447, CN104045614, WO2015104658, US20150307540, WO2015132803, WO2016018024, CN105524033, WO2016147197, WO2016155578, CN106146446, WO2016178148,

CN106543124, US9845303, CN105486767, WO2017118945, CN105503802, WO2017191539, WO2017202264, WO2018014866, CN10851696.

In one embodiment dapagliflozin used in the pharmaceutical composition of the present invention is in an amorphous form.

In another embodiment the pharmaceutical composition of the present invention comprises dapagliflozin in predominately amorphous form, wherein dapagliflozin in the composition is at least 70% amorphous, preferably at least 85% amorphous and most preferably at least 95% amorphous.

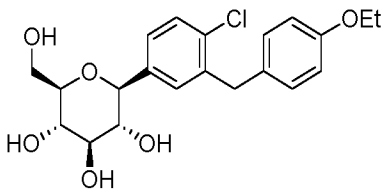
In one embodiment dapagliflozin used in the pharmaceutical composition of the present invention is in the form of dapagliflozin propylene glycol hydrate.

In one embodiment dapagliflozin used in the pharmaceutical composition of the present invention is in the form of dapagliflozin (S) propylene glycol hydrate (1:1:1) or dapagliflozin (R) propylene glycol hydrate (1:1:1), preferably dapagliflozin (S) propylene glycol hydrate (1:1:1).

Dapagliflozin used in the pharmaceutical composition according to the present invention may be prepared according to any manufacturing process known from the state of the art such as for example WO0127128, WO03099836, WO2004063209, WO2006034489, WO2010022313, WO2012019496, WO2013064909, WO2013068850, WO2013079501, WO2014094544, WO2014159151, WO2014206299, WO2015040571, WO2015044849, WO2015063726, WO2015132803, WO2015155739, WO2016098016, WO2016128995, WO2016178148, WO2017042683, WO2017063617, WO2018029611, WO2018029264, WO2018142422.

The term ‘dapagliflozin’ as used in the present application refers to dapagliflozin in all forms as stated above.

The term ‘dapagliflozin’ as used in the present application in particular comprises dapagliflozin of formula 1




formula 1

in crystalline or amorphous form, a co-crystal complex thereof (which can be in crystalline or amorphous form or which can be a mixture comprising crystalline and amorphous form), a hydrate thereof (which can be in crystalline or amorphous form or which can be a mixture comprising crystalline and amorphous form), or a solvate thereof (which can be in crystalline or amorphous form or which can be a mixture comprising crystalline and amorphous form), and any mixtures thereof.

Dapagliflozin in accordance with the present invention can be characterised by particle size distribution (PSD) as determined by the laser diffraction method such as Malvern Master Sizer.

In one embodiment dapagliflozin (S) propylene glycol hydrate (1:1:1) used in the pharmaceutical composition according to the present invention has a d(0.9) value less than 150µm, preferably between 1 µm and 100 µm and more preferably between 1µm and 50µm.

In one embodiment dapagliflozin (S) propylene glycol hydrate (1:1:1) used in the pharmaceutical composition according to the present invention has a d(0.5) value less than 100 µm, preferably between 1 µm and 50 µm and more preferably between 1 µm and 30 µm.

In one embodiment dapagliflozin (S) propylene glycol hydrate (1:1:1) used in the pharmaceutical composition according to the present invention has a d(0.1) value less than 50 µm, preferably between 1 µm and 30 µm and more preferably between 1 µm and 10 µm.

In one embodiment dapagliflozin used in the pharmaceutical composition according to the present invention has a d(0.9) value less than 200 µm, preferably between 1 µm and 150 µm and more preferably between 1 µm and 100 µm.

In one embodiment dapagliflozin used in the pharmaceutical composition according to the present invention has a d(0.5) value less than 150 µm, preferably between 1 µm and 100 µm and more preferably between 1 µm and 50 µm.

In one embodiment dapagliflozin used in the pharmaceutical composition according to the present invention has a d(0.1) value less than 100 µm, preferably between 1 µm and 50 µm and more preferably between 1 µm and 25 µm.

According to the present invention and unless specified, all amount indications are provided on a weight basis or weight/weight basis, as appropriate. If the active pharmaceutical ingredient is used in the form of a pharmaceutically acceptable salt, the weight of the entire salt is to be considered, including the weight component of the counter ion. If the active pharmaceutical ingredient is used in the form of a solvate or hydrate, the additional weight associated with solvent or water components in the substance is to be disregarded. That is, a theoretical weight of the anhydrous pure substance (or its pharmaceutically acceptable salt and/or hydrate or solvate, if appropriate) is to be calculated and considered in connection with the present invention.

The pharmaceutical composition according to the present invention comprises dapagliflozin and one or more pharmaceutically acceptable excipients. The term "excipient" as used herein refers to any pharmaceutically acceptable substance that has no therapeutic activity as such. Pharmaceutically acceptable excipients may for example be selected from diluents, lubricants, glidants, disintegrants and binders. In one embodiment the pharmaceutical composition according to the present invention may further comprise any other pharmaceutical acceptable excipients that can be selected among any known state of the art for solid dosage forms, as described e.g. in Remington: The Science and Practice of Pharmacy, Edited by Loyd V. Allen, Jr, Pharmaceutical Press, 22 Edition, 2012. Individual excipients may have polyfunctional properties in the pharmaceutical composition according to the invention, e.g. may exert both disintegrating and binding properties or both lubricating and gliding properties or my exert filling, binding and disintegrating properties.

The pharmaceutical composition according to the invention may comprise one or more diluents (fillers). Diluents are selected from, but not limited to, lactose (e.g. anhydrous or hydrate or amorphous (partially or completely)), polysaccharides (e.g. starches or celluloses), monosaccharides, disaccharides, oligosaccharides, sugar alcohols, inorganic salts of phosphoric acid, inorganic salts and any mixture thereof. Starch may be selected from partially or wholly pregelatinized starch, corn starch, wheat starch, rice starch, tapioca starch, potato starch and any mixture thereof. Cellulose may be selected from powdered cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, co-processed microcrystalline cellulose with other excipients

such as lactose, starch, silicon dioxide, mannitol, etc. and any mixture thereof. Monosaccharides, disaccharides, oligosaccharides and sugar alcohols may be selected from glucose, fructose, sucrose, lactose monohydrate, anhydrous lactose, α-lactose, β-lactose, raffinose, isomaltose, trehalose, dextrates, mannitol, erythritol, sorbitol, maltitol, xylitol, lactitol, compressible sugars, and mixtures thereof. Inorganic salts may be selected from calcium carbonate, calcium sulfate, calcium phosphate salts in anhydrous or hydrated forms such as dibasic calcium phospate anhydrate, dibasic calcium phospate dihydrate, tribasic calcium phosphate and any mixture thereof.

The pharmaceutical composition according to the invention may comprise one or more disintegrants. Disintegrants are selected from, but not limited to, crospovidone, starch, maize starch, pregelatinized starch, sodium starch glycollate, modified starch, hydroxypropyl starch, carboxymethyl starch, microcrystalline cellulose, sodium and/or calcium salts of carboxymethyl cellulose, cross-linked carboxymethylcellulose (e.g. croscarmellose sodium and/or croscarmellose calcium), polacrilin potassium, low substituted hydroxypropylcellulose (L-HPC), alginic acid or alginates, sodium and/or calcium alginate, polyacrylates, docusate sodium, methylcellulose, agar, guar gum, chitosan, gums and mixtures thereof.

The pharmaceutical composition according to the invention may comprise one or more binders. Binders are selected from, but not limited to, to povidone (polyvinylpyrrolidone), copovidone (vinylpyrrolidone-vinyl acetate copolymer), powdered cellulose, crystalline cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose derivatives such as cellulose esters or cellulose ethers (e.g. hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, low substituted hydroxypropylcellulose and hydroxypropylmethylcellulose), polyvinyl alcohol, starch (e.g. corn starch, potato starch, or rice starch), α-starch, pregelatinized starch, dextrin, gum arabic, pullulan, poly(meth)acrylates and any mixture thereof.

The pharmaceutical composition according to the invention may comprise one or more lubricants. Lubricants are selected from, but not limited to, fatty acids (i.e. carboxylic acids with 12 to 20 carbon atoms); fatty acid esters including glyceride esters such as glyceryl monostearate, glyceryl tribehenate, or glyceryl dibehenate (e.g. Compritol® 888); metal salts of fatty acids, including magnesium, calcium, aluminum or zinc salts of fatty acids (e.g. magnesium, calcium, aluminum or zinc stearate, magnesium palmitate, or magnesium oleate); hydrogenated vegetable oil,

hydrogenated castor oil; waxes (e.g. Sterotex® NF, Lubriwax® [hydrogenated vegetable oil type], meads wax or spermaceti); boric acid; sodium stearyl fumarate; polymers (e.g., PEG, macrogols); sugar esters such as sorbitan monostearate and sucrose monopalmitate and any mixtures thereof.

The pharmaceutical composition according to the invention may comprise one or more glidants. Glidants are selected from, but not limited to, colloidal silicon dioxide (colloidal silica), talc, magnesium trisilicate, and mixtures thereof. Preferred glidants are colloidal silica, talc and any mixtures thereof.

The pharmaceutical composition according to the present invention may further comprise one or more other pharmaceutically acceptable excipients such as for example surfactants and emulsifiers, plasticizers, carriers, flow controlling agents, crystallization retarders, solubilizers, prolonged release polymers, functional polymers for prolonged release of active pharmaceutical ingredients, coloring agents and similar.

The pharmaceutical composition according to the present invention is a solid dosage form. Preferred solid pharmaceutical dosage forms according to the invention include, but are not limited to, capsules, powders, tablets, minitablets, microtablets, coated or uncoated tablets, coated or uncoated minitablets, coated or uncoated microtablets, coated or uncoated multilayer tablets, coated or uncoated bilayer tablets, coated pellets, pills, lozenges, and the like. Preferably, the pharmaceutical dosage form according to the invention is uncoated or coated tablet. Preferably, the pharmaceutical dosage form according to the invention is uncoated or coated bilayer tablet. The term tablet as used herein encompasses tablets of all shapes and sizes.

In one embodiment the tablet is a coated tablet. In case the coating is applied onto the solid pharmaceutical formulation it is composed of at least one film forming polymer for coating and at least one further pharmaceutically acceptable excipient, which can be selected from, but not limited to, plasticizers, anti-tacking agents, pigments and coloring agents, pore formers and any mixture thereof. Film forming polymers for coating are selected from, but not limited to, cellulose ethers such as low molecular weight hydroxypropylmethyl cellulose and low molecular weight hydroxypropyl cellulose, polyvinyl alcohol, copolymers of vinyl alcohol and ethylene glycol such as Kollicoat® IR and/or Kollicoat® Protect manufactured by BASF. In one embodiment, ready to use products for film coating such as Opadry® can be used. In one embodiment, the film coating can comprise polyvinyl alcohol, and polyethyleneglycol.

The thickness of the coating can be in the range from 1 to 80 μm, preferably 4-50 μm and most preferably 5-40 μm.

In one embodiment the pharmaceutical composition of the present invention comprises dapagliflozin in predominantly amorphous form and is prepared by dry granulation. It was surprisingly shown that pharmaceutical composition comprising amorphous form of dapagliflozin was chemically and physically stable. The prior art attempts to provide chemically and physically stable forms of dapagliflozin were in preparing solvates or co-crystal forms of active ingredients or preparing solid dispersions with polymers. These approaches are disadvantageous, as beside of active ingredient in therapeutic amounts the patient is burdened with an amount of organic compounds such as organic solvents and other organic compounds, which may be toxic to the patients. The inventors have surprisingly found out that amorphous form incorporated in the pharmaceutical composition provides an advantageous storage stability of the product which can be at least on the same level as stability of the product comprising solvate form of dapagliflozin as it is shown in the Experimental section.
It has been surprisingly shown that the use of particular diluents i.e. the mixture of microcrystalline cellulose and lactose makes dry granulation process advantageously applicable for the manufacture of dapagliflozin tablets showing desired chemical stability, dose uniformity, tablet hardness and flow properties.

In one embodiment the pharmaceutical composition of the present invention comprises dapagliflozin in the form of amorphous solid dispersion prepared by fluid bed granulation.

It was found out by the present inventors that the optimal processability in the process of dry granulation and fluid bed granulation is achieved by using a specific ratio of lactose and microcrystalline cellulose.
The amount of microcrystalline cellulose in the pharmaceutical composition is typically in the range of about 20-90 % by weight of the pharmaceutical composition. Preferably, the amount of microcrystalline cellulose is 30% by weight to 80 % by weight, especially 40-70 % by weight, based on the total weight of the pharmaceutical composition. Preferably, a partial amount of microcrystalline cellulose is incorporated intragranularly, and the remaining amount of microcrystalline cellulose is incorporated extragranularly.

Microcrystalline cellulose (MCC) may be selected from microcrystalline cellulose with average particle size from 10 μm to 200 μm, preferably from 20 to 150 μm and optionally moisture content ≤ 5%. Particularly, microcrystalline cellulose may be selected from microcrystalline cellulose with average particle size 20μm and a moisture content≤ 5%, such as Avicel PH-105, microcrystalline cellulose with average particle size 50μm and a moisture content ≤ 5%, such as Avicel PH-101 or Vivapur 101 or Ceolus KG-802, microcrystalline cellulose with average particle size 50μm and a moisture content≤ 2%, such as Avicel PH-1 13, microcrystalline cellulose with average particle size 90 to 120 μm and a moisture content ≤ 5%, such as Avicel PH-102 or Vivapur 102, microcrystalline cellulose with average particle size 90 to 120 μm and a moisture content≤ 1 .5%, such as Avicel PH-1 12, microcrystalline cellulose with average particle size 200 μm and a moisture content≤ 1 .5%, such as Avicel PH-200 .

The amount of lactose in the pharmaceutical composition can be typically in the range of 10 - 60 wt. %, preferably 15-50% wt. %, based on the total weight of the pharmaceutical composition. The amount of microcrystalline cellulose (MCC) in the pharmaceutical composition can be from 20-90 wt. %, preferably 30-80 wt. %, more preferably 40-70 wt. %, based on the total weight of the pharmaceutical composition.

The typical weight ratio of microcrystalline cellulose to lactose in a pharmaceutical composition of the present invention can be from 100:1 to 0.5:1, preferably 20:1 to 0.5:1, more preferably from 5:1 to 1:1. Granule(s) comprising dapagliflozin, which are prepared by wet granulation (especially fluid bed granulation), can comprise MCC and lactose in a weight ratio MCC:lactose from 1:2 to 2:1, preferably 1:1.5 to 1:1, based on the total weight of the granule(s) comprising dapagliflozin. A pharmaceutical composition comprising granule(s) comprising dapagliflozin, which are prepared by wet granulation, can comprise MCC and lactose in a weight ratio MCC:lactose from 4:1 to 1:2, preferably 3:1 to 1:1, in particular about 1:1. Granule(s) comprising dapagliflozin, which are prepared by wet granulation, preferably comprise a weight amount of lactose which is higher than the weight amount of MCC, as this can provide a particularly advantageous bulk density providing good processibility of tabletting.

Pharmaceutical compositions prepared by a process which is or comprises dry granulation preferably comprise both MCC and lactose, especially can comprise MCC and lactose in a weight ratio MCC:lactose from 5:1 to 1:1, preferably 4:1 to 1:1. Presence of lactose, as well as presence of both lactose and MCC provides an advantageous compactability.

Granule(s) comprising dapagliflozin, which are prepared by dry granulation (especially dry granulation which is or comprises roller compaction), preferably comprise both MCC and lactose, especially can comprise MCC and lactose in a weight ratio MCC:lactose from 10:1 to 1:1, preferably 5:1 to 1:1.

Pharmaceutical compositions of the present invention can comprise dapagliflozin and MCC in a weight ratio 1:10 to 1:30, preferably 1:10 to 1:20. Granule(s) comprising dapagliflozin can comprise dapagliflozin and MCC in a weight ratio 1:10 to 1:30, preferably 1:10 to 1:20.

For the production of tablets of the present invention it is preferred that the particle size of all excipients is of the same particle size range in order to minimize the segregation of the component of the mixture. The average particle size (especially weight average size) of the excipients used are preferably in the range of 20 to 200 μm, more preferably in the range of 50 to 150 μm The main advantages of the use of the exipients with a particle size of the same degree are a high content uniformity due to a low segregation tendency, an excellent compactability, leading to constant tablet hardness, a good flowability providing a high weight consistency at various tableting speeds.

As may be seen from the experimental section, the compositions absent of lactose result in higher hardness variability and also lower dissolution profiles.

In one embodiment the pharmaceutical composition according to the present invention may in addition to dapagliflozin further comprises one or more any other active ingredients suitable for the treatment of diabetes and any other one or more active ingredients that show beneficial effect on diabetic patient in respect of blood glucose concentrations and/or other pathological manifestations of diabetes.

In one embodiment the pharmaceutical composition according to the present invention may in addition to dapagliflozin further comprise any one or more other active ingredients suitable to be incorporated into the same composition such as for example:

- SGLT2 inhibitor which is not dapagliflozin,
- active ingredients for the treatment of diabetes such as for example biguanides, GLP-1 agonists, DPP-4 inhibitors or any other antidiabetic drugs,
- active ingredients for the treatment of cardiovascular diseases such as for example active ingredients for the treatment of hypertension, antiplatelet agents;

- active ingredients for the treatment of chronic kidney disease,
- active ingredients for lipid-lowering therapy such as for example statins,
- active ingredients for the treatment of obesity or promoting weight loss,
- active ingredients for the treatment of NASH/NAFLD,
- active ingredients for the treatment of hyperuricemia or increased serum uric acid levels.

In another embodiment the pharmaceutical composition according to the present invention may in addition to dapagliflozin further comprise at least one additional active pharmaceutical ingredient selected from, but not limited to, active ingredients having antidiabetic activity in humans such as derivatives of sulfonylurea, thiazolidinedione, α-glucosidaze inhibitors, meglitinide, glucagon-like peptide 1 (GLP-1) agonists, insulin, fructose 1,6-bis phosphatase inhibitors, insulin secretogogues selected from sulfonylureas (such as glyburide, glipizide and glimepiride) and/or glinides (such as nateglinide and/or repaglined), insulin sensitizers, glucokinaze activators, glucocorticoid antagonists, AMP kinase activators, modulators of the incretin pathway, bile acid receptor agonists such as TGR5 agonist, dopamine receptor agonists, aldose reductase inhibitors, PPAKγagonists, PPARα agonists, PPARδafonists or antagonists, PPAR α/γ dual agonists, 11-β-HSD-1 inhibitors, dipeptidyl peptidase IV (DPP4) inhibitors , SGLT2 inhibtors other than dapagliflozin.

Preferably, the additional active pharmaceutical ingredient is selected from

- dipeptidyl peptidase-4 (DPP-4) inhibitors; preferably selected from the group consisting of sitagliptin, vildagliptin, saxagliptin, linagliptin, anagliptin, teneligliptin, alogliptin, trelagliptin, gemigliptin, dutogliptin, and the physiologically acceptable salts thereof; preferably sitagliptin and the physiologically acceptable salts thereof;
- biguanides; preferably metformin and the physiologically acceptable salts thereof;
- sulfonylureas; preferably selected from the group consisting of glyburide, glipizide, gliclazide, glibenclamide, glimepiride, tolazamide, tolbutamide, and the physiologically acceptable salts thereof; and
- alpha-glucosidase inhibitors; preferably selected from the group consisting of acarbose, voglibose, miglitol, and the physiologically acceptable salts thereof

and any combinations thereof.

In another embodiment the pharmaceutical composition according to the present invention comprises dapagliflozin and as an additional pharmaceutical active ingredient at least one biguanide.

In another embodiment the pharmaceutical composition according to the present invention comprises dapagliflozin and as an additional pharmaceutical active ingredient metformin or a physiologically acceptable salt thereof, preferably hydrochloride. The pharmaceutical composition of the present invention comprises dapagliflozin in combination with metformin, wherein both active ingredients are included in the same granulate or in a separate granulates or wherein dapagliflozin is present in extragranular phase.

In another embodiment the pharmaceutical composition according to the present invention comprises dapagliflozin and as an additional pharmaceutical active ingredient at least one DPP-4 inhibitor.

In another embodiment the pharmaceutical composition according to the present invention comprises dapagliflozin and as additional pharmaceutical active ingredient sitagliptin or a physiologically acceptable salt thereof, preferably phosphate, more preferably phosphate monohydrate.The pharmaceutical composition of the present invention comprises dapagliflozin in combination with sitagliptin or a physiologically acceptable salt thereof and at least one pharmaceutically acceptable ingredient. Preferably the composition is substantially free of lactose and calcium hydrogen phosphate. In a preferred embodiment the composition comprises microcrystalline cellulose, optionally a further diluent, optionally a binder, a disintegrant, a glidant and a lubricant, which lubricant is or comprises magnesium stearate.

In another embodiment the pharmaceutical composition according to the present invention comprises dapagliflozin and as an additional pharmaceutical active ingredient at least one biguanide and at least one DPP-4 inhibitor.

In another embodiment the pharmaceutical composition according to the present invention comprises dapagliflozin and as an additional pharmaceutical active ingredient metformin or a pharmaceutically acceptable salt thereof and sitagliptin or a pharmaceutically acceptable salt thereof.

In yet another embodiment the pharmaceutical composition according to the present invention comprises dapagliflozin, preferably amorphous dapagliflozin or dapagliflozin propanediol monohydrate in combination with metformin hydrochloride and sitagliptin base or sitagliptin phosphate or sitagliptine phosphate monohydrate.

The above-mentioned components of the pharmaceutical composition according to the present invention may be present in relative amounts as shown in the following tables. Amount indications in the following tables may be understood as indications in parts by weight.

Table 1

| | **Amount according to one embodiment (wt%)** | **Amount according to one embodiment (wt%)** | **Amount according to one embodiment (wt%)** |
|---|---|---|---|
| dapagliflozin | 0.5-70 | 1-50 | 1.5-30 |
| binder | 0.1-20 | 0.5-15 | 1-10 |
| diluent/filler | 1-95 | 20-95 | 40-95 |
| disintegrant | 0.1-50 | 0.5-30 | 1-15 |
| glidant | 0.025-20 | 0.05-15 | 0.1-10 |
| lubricant | 0.025-5 | 0.05-5 | 0.1-5 |
| coating | 0.1-20 | 0.5-15 | 0.5-10 |

Table 2

| | **Amount according to one embodiment (wt%)** | **Amount according to one embodiment (wt%)** | **Amount according to one embodiment (wt%)** |
|---|---|---|---|
| dapagliflozin | 0.05 - 50 | 0.05-20 | 0.05 - 10 |
| compound A | 1-95 | 5-90 | 10-85 |
| binder | 0.1 - 20 | 0.5-15 | 1 - 15 |
| diluent/filler | 1-95 | 1-88 | 1-70 |
| disintegrant | 0.1-50 | 0.1-30 | 0.5-20 |
| glidant | 0.025-20 | 0.05-15 | 0.1-10 |
| surfactant | 0-20 | 0-15 | 0-10 |
| lubricant | 0.025-10 | 0.05-10 | 0.05-5 |
| coating | 0.1-20 | 0.5-15 | 0.5-10 |

The term ‘compound A’ as used above designates active ingredient other than dapagliflozin and as defined above. The term ‘compound A’ may encompass more than one active ingredients i.e. a combination of two or more active ingredients as defined above.

The pharmaceutical composition according to the invention is preferably suitable and intended for oral administration, preferably for peroral administration.

In one embodiment the amount of dapagliflozin used in the pharmaceutical composition of the present invention is between 0.05 % and 70 %, preferably between 0.05 % and 50 % and more preferably between 0.05 % and 30 %.

In one embodiment the amount of active ingredient other than dapagliflozin used in the pharmaceutical composition of the present invention is between 1% and 95%, preferably between 5% and 90% and more preferably between 10% and 85%.

In one embodiment the amount of metformin or any pharmaceutically acceptable salt thereof used in the pharmaceutical composition of the present invention is between 1% and 95%, preferably between 20% and 90% and more preferably between 50% and 85%.

In one embodiment the amount of sitagliptin or any pharmaceutically acceptable salt thereof used in the pharmaceutical composition of the present invention is between 1% and 90%, preferably between 5% and 70% and more preferably between 10% and 50%.

The pharmaceutical composition according to the present invention provides immediate release and/or sustained release of the active ingredient(s) present in the composition.

As discussed supra, a pharmaceutical composition comprising dapagliflozin in amorphous form is highly advantageous.

In particular, there is provided a pharmaceutical composition for oral administration (preferably tablet) comprising at least one active ingredient, which at least one active ingredient is or comprises dapagliflozin in amorphous form, and at least one pharmaceutically acceptable excipient selected from the group comprising at least one binder, at least one diluent, at least one disintegrant, at least one glidant and at least one lubricant,
preferably the pharmaceutical composition being prepared by a process for the preparation of a pharmaceutical composition, which is or comprises dry granulation or by a process which is or comprises wet granulation, especially fluid bed granulation. Optionally, the at least one pharmaceutically acceptable excipient comprises microcrystalline cellulose and optionally one or more further diluents, optionally at least one disintegrant, optionally at least one glidant, and optionally at least one lubricant. In an embodiment, where said pharmaceutical composition is prepared by a process which is or comprises fluid bed granulation, the pharmaceutical composition comprises dapagliflozin in the form of amorphous solid dispersion prepared by fluid bed granulation. Said

pharmaceutical composition for oral administration can be prepared by the skilled person based on the general knowledge in the art or can be prepared according to any of the processes disclosed herein. Especially, the pharmaceutical composition for oral administration (preferably tablet) can be prepared by "preparation process (A)" or "preparation process (B)" or "preparation process (C)" or "preparation process (D)" or "preparation process (E)" disclosed herein.

A pharmaceutical composition for oral administration (preferably tablet) comprising at least one active ingredient, which is or comprises dapagliflozin in amorphous form, preferably dapagliflozin of formula I in amorphous form, and at least one pharmaceutically acceptable excipient selected from the group comprising

- at least one binder,
- at least one diluent, preferably the at least one diluent is or comprises microcrystalline cellulose and at least one further diluent, more preferably the at least one diluent is or comprises microcrystalline cellulose and lactose (especially lactose which is or comprises lactose anhydrous),
- at least one disintegrant,
- at least one glidant and
- at least one lubricant,

can be or can comprise dapagliflozin containing granules prepared by dry granulation (which preferably is or comprises roller compaction), preferably can be or can comprise a compressed mixture (especially tablet) comprising granules prepared by dry granulation. Said pharmaceutical composition can also comprise dapagliflozin in a form different from amorphous form (in particular in crystalline form). Preferably, the pharmaceutical composition comprises dapagliflozin which is predominantly in amorphous form, especially dapagliflozin wherein at least 70 %, optionally at least 85 %, further optionally at least 95 % of the dapagliflozin in the pharmaceutical composition is amorphous dapagliflozin.

A pharmaceutical composition of the present invention can be or can comprise a compressed mixture, especially tablet, which compressed mixture comprises an extragranular phase comprising microcrystalline cellulose and dapagliflozin containing granules, said dapagliflozin containing granules comprise dapagliflozin and microcrystalline cellulose.

A pharmaceutical composition for oral administration which comprises granules prepared by dry granulation can be prepared by the skilled person based on the general knowledge in the art or can

be prepared according to any of the processes disclosed herein, especially by "preparation process (A)", as defined herein.

A process (said process being also referred to herein as "preparation process (A)") for the preparation of a pharmaceutical composition (especially according to the present invention) comprising at least one active ingredient which is or comprises dapagliflozin, comprising dry granulation, can be a process comprising the following steps:

a) dapagliflozin, especially dapagliflozin which is or comprises dapagliflozin in amorphous form, preferably dapagliflozin of formula I in amorphous form or dapagliflozin propanediol monohydrate, is mixed with diluent, preferably the diluent is or comprises microcrystalline cellulose and optionally lactose, optional disintegrant, preferably the optional disintegrant is or comprises a disintegrant selected from crospovidone and croscarmellose sodium, and optional glidant, preferably the optional glidant is or comprises colloidal silicon dioxide, and optionally one or more further active ingredients which can be selected from sitagliptin, pharmaceutically acceptable salts of sitagliptin, metformin, and pharmaceutically acceptable salts of metformin, and optionally other pharmaceutically acceptable excipient(s),

b) the obtained powder blend is compacted, preferably by roller compaction, to obtain a compacted powder blend,

c) optionally the size of the compacted powder blend (also referred to herein as granulate) is reduced, preferably by sieving or milling,

d) the obtained granules are blended with diluent, preferably the diluent comprising microcrystalline cellulose, optionally disintegrant, preferably the optional disintegrant being or comprising a disintegrant selected from crospovidone and croscarmellose sodium, and optionally glidant, preferably the optional glidant being or comprising colloidal silicon dioxide, optionally one or more further active ingredients, which can be selected from sitagliptin, pharmaceutically acceptable salts of sitagliptin, metformin, and pharmaceutically acceptable salts of metformin, dapagliflozin (preferably dapagliflozin in amorphous form), and optionally one or more other pharmaceutically acceptable excipient(s),

e) the obtained mixture is lubricated with lubricant, preferably magnesium stearate,

f) the obtained compression mixture is compressed into tablets, and

g) optionally the obtained tablets are coated.

The term "mixture is lubricated with lubricant" can be used in the present application interchangeably with the term "mixture is mixed with lubricant".

A pharmaceutical composition for oral administration (preferably tablet) comprising at least one active ingredient, which at least one active ingredient is or comprises dapagliflozin (preferably in an amorphous form), e.g. dapagliflozin of formula 1 or dapagliflozin propanediol monohydrate, and at least one pharmaceutically acceptable excipient selected from the group comprising

- at least one binder, optionally the at least one binder can be or comprise binder selected from the group consisting of povidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, copovidone, and mixtures thereof,
- at least one diluent, preferably the at least one diluent is or comprises microcrystalline cellulose and at least one further diluent, more preferably the at least one diluent is or comprises microcrystalline cellulose and lactose (especially lactose which is or comprises lactose anhydrous),
- at least one disintegrant,
- at least one glidant and
- at least one lubricant,

can be or can comprise dapagliflozin containing granules prepared by wet granulation (preferably fluid bed granulation), using solvent being or comprising ethanol (as granulation fluid), preferably can be or comprise a compressed mixture (especially tablet) comprising the dapagliflozin containing granules prepared by wet granulation (preferably fluid bed granulation). The granules prepared by fluid bed granulation can comprise dapagliflozin in the form of amorphous solid dispersion. In particular, the weight ratio of microcrystalline cellulose to lactose in the pharmaceutical composition (especially tablet) prepared by a process comprising wet granulation, especially fluid bed granulation, is from 4 : 1 to 1:2, preferably 3:1 to 1:1. Especially, the weight ratio of microcrystalline cellulose to lactose in the dapagliflozin containing granules prepared by wet granulation, especially fluid bed granulation, can be from 1:2 to 2:1, preferably 1:1.5 to 1:1. The pharmaceutical composition can be or can comprise a compressed mixture, especially tablet, which compressed mixture comprises an extragranular phase comprising microcrystalline cellulose and dapagliflozin containing granules, said dapagliflozin containing granules comprise dapagliflozin and microcrystalline cellulose.

Especially, a pharmaceutical composition for oral administration of the present invention can be a pharmaceutical composition wherein the at least one active ingredient is or comprises

dapagliflozin and a pharmaceutically active ingredient selected from sitagliptin and a pharmaceutically acceptable salt thereof, and metformin and a pharmaceutically acceptable salt thereof. Optionally, a pharmaceutical composition of the present invention can be free of sitagliptin or a salt thereof or can be free of metformin or a pharmaceutically acceptable salt thereof.

A pharmaceutical composition for oral administration which comprises granules prepared by wet granulation (preferably fluid bed granulation) can be prepared by the skilled person based on the general knowledge in the art or can be prepared according to any of the processes disclosed herein, especially by "preparation process (B)", as defined herein.

A process for the preparation of a pharmaceutical composition comprising at least one active ingredient which is or comprises dapagliflozin (said process being also referred to herein as "preparation process (B)"), especially of a pharmaceutical composition of the present invention, can be a process comprising the following steps:

a) binder is added to solvent which is or comprises ethanol, optionally the binder being selected from the group consisting of povidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose (in particular hydroxypropyl cellulose SSL or EF, preferably HPC EF), copovidone, and mixtures thereof, to obtain a binder solution,

b) optionally dapagliflozin is dissolved in the obtained binder solution,

c) the dapagliflozin-binder solution obtained in step b) or the binder solution obtained in step a) is contacted with (preferably sprayed onto) a mixture comprising diluent and optionally disintegrant and optionally an active ingredient selected from sitagliptin, pharmaceutically acceptable salts of sitagliptin, metformin, and pharmaceutically acceptable salts of metformin, dapagliflozin (preferably dapagliflozin in amorphous form),

d) the obtained granules are optionally blended with at least one or all of disintegrant, glidant and diluent, and optional other excipient(s), and optional active ingredient(s), preferably selected from sitagliptin, pharmaceutically acceptable salts of sitagliptin, metformin, and pharmaceutically acceptable salts of metformin, dapagliflozin, preferably dapagliflozin in amorphous form,

e) the obtained mixture is lubricated with lubricant,

f) the obtained compression mixture is compressed into tablets,

g) optionally the obtained tablets are coated; said step c) can be carried out using a fluid bed granulator, especially said step c) can be or comprise that the dapagliflozin-binder

solution obtained in step b) or the binder solution obtained in step a) is sprayed onto the mixture in a fluidised bed, thereby performing a fluid bed granulation to obtain granules.

Furthermore, a pharmaceutical composition is highly advantageous wherein the at least one active ingredient is or comprises dapagliflozin (as first active ingredient) and metformin or a pharmaceutically acceptable salt thereof (as second active ingredient), and optionally sitagliptin or a pharmaceutically acceptable salt thereof and optionally one or more further active ingredients.

In particular, there is provided a pharmaceutical composition for oral administration (preferably tablet) comprising at least one active ingredient, which at least one active ingredient is or comprises dapagliflozin,
and metformin or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient selected from the group comprising

- at least one binder, optionally selected from the group consisting of povidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose (in particular hydroxypropyl cellulose SSL or EF, preferably HPC EF), copovidone, and mixtures thereof,
- at least one diluent, preferably the at least one diluent is or comprises microcrystalline cellulose
- at least one disintegrant,
- at least one glidant and
- at least one lubricant,

which pharmaceutical composition is or comprises a compressed mixture (especially tablet) comprising granules prepared by granulation,

(i) wherein the pharmaceutical composition comprises granules each containing in combination dapagliflozin and metformin or a pharmaceutically acceptable salt thereof, which are prepared by wet granulation (preferably fluid bed granulation) using preferably solvent which is or comprises ethanol (as granulation fluid), and optionally further comprises dapagliflozin in the extragranular phase of the compression mixture, or

(ii) wherein the pharmaceutical composition comprises granules comprising dapagliflozin, preferably prepared by wet granulation (preferably fluid bed granulation) using solvent which is or comprises ethanol (as granulation fluid), and granules comprising metformin or a pharmaceutically acceptable salt thereof, preferably prepared by wet granulation (preferably fluid bed granulation) using solvent which is or comprises ethanol (as granulation fluid), or

(iii) wherein the pharmaceutical composition comprises granules comprising metformin or a pharmaceutically acceptable salt thereof, preferably prepared by wet granulation (preferably fluid bed granulation) using solvent which is or comprises ethanol (as granulation fluid), and comprises dapagliflozin in the extragranular phase of the compression mixture.

The solvent which is or comprises ethanol (used in the granulation processes disclosed herein) can be a solvent which comprises at least 96 % by weight of ethanol, preferably at least 98 % by weight of ethanol, more preferably at least 99 % by weight of ethanol or 100% by weight of ethanol. Furthermore, said solvent can comprise less than 4 % by weight of water, preferably less than 1% by weight of water, especially is free of water.

Preferably, the pharmaceutical composition for oral administration (preferably tablet) comprising at least one active ingredient, which is or comprises dapagliflozin (and optionally metformin or a pharmaceutically acceptable salt thereof), comprises at least one binder selected from the group consisting of povidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose (in particular hydroxypropyl cellulose SSL or EF, preferably HPC EF), copovidone, and mixtures thereof; optionally, the pharmaceutical composition further comprises dapagliflozin in the extragranular phase of the compression mixture.
Hydroxypropyl cellulose (HPC) can be for example HPC SSL, HPC EF, HPC SL, HPC L, HPC EXF, HPC ELF. Preferably, HPC can be one of HPC SSL and HPC EF, preferably HPC EF.

Preferred HPC for use as a binder in the present invention can have a molar mass distribution falling in the range of between 1000 and 400,000 g/mole, preferably between 1000 and 300,000 g/mole and more preferably between 1000 and 200,000 g/mole, and optionally can further have a weight average molar mass of less than 90,000 g/mole, more preferably of less than 70,000 g/mole and even more preferably of less than 40,000 g/mole. Furthermore, an advantageous HPC for use as a binder in the present invention, can have a number average molar mass of less than 50,000 g/mole, more preferably of less than 45,000 g/mole and even more preferably of less than 25,000 g/mole. Furthermore, an advantageous HPC for use as a binder in the present invention, can have a number average molar mass of less than 100,000 g/mole, more preferably of less than 90,000 g/mole and even more preferably about 80,000 g/mole.

The weight average molar mass, $M_w$, is defined as

$$M_w = \frac{\sum_i N_i M_i^2}{\sum_i N_i M_i}$$ , where $N_i$ is the number of molecules of molar mass $M_i$.

The number average molar mass, $M_n$, is defined as

$$M_n = \frac{\sum_i N_i M_i}{\sum_i N_i}$$ , where $N_i$ is the number of molecules of molar mass $M_i$.

A pharmaceutical composition for oral administration (preferably tablet) comprising at least one active ingredient, which is or comprises dapagliflozin, and metformin or a pharmaceutically acceptable salt thereof, can be prepared by the skilled person based on the general knowledge or can be prepared applying one of the processes disclosed herein. Especially, a pharmaceutical composition for oral administration (especially a composition as disclosed herein) comprising at least one active ingredient, which is or comprises dapagliflozin and metformin or a pharmaceutically acceptable salt thereof, can be prepared by a process (which is also referred to herein as "preparation process (C)"). A process for the preparation of a pharmaceutical composition comprising at least one active ingredient which is or comprises dapagliflozin (said process being also referred to herein as "preparation process (C)"), especially of a pharmaceutical composition of the present invention, can be a process comprising the following steps:

a)

a-1) binder is added to solvent which is or comprises ethanol, optionally the binder being selected from the group consisting of povidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose (in particular hydroxypropyl cellulose SSL or EF), copovidone, and mixtures thereof, to obtain a binder solution, and dapagliflozin is dissolved in the obtained binder solution,

or

a-2) preparing a solution comprising a solvent which is or comprises ethanol, and dapagliflozin,

b) the dapagliflozin-binder solution obtained in step a-1) or the dapagliflozin solution obtained in step a-2) is contacted with (preferably sprayed) onto metformin or a pharmaceutically acceptable salt thereof and optional pharmaceutically acceptable excipient(s), e.g. pharmaceutically acceptable excipient(s) comprising at least one or both of diluent and disintegrant,

c) the obtained granules are optionally blended with at least one of disintegrant, glidant and diluent,

e) the obtained mixture is lubricated with lubricant,

f) the obtained compression mixture is compressed into tablets,

g) optionally the obtained tablets are coated; preferably said step b) can be carried out using a fluid bed granulator, especially said step b) can be or comprise that the dapagliflozin-binder solution obtained in step a-1) or the dapagliflozin solution obtained in step a-2) is sprayed onto metformin and optional pharmaceutically acceptable excipient(s) in a fluidised bed, thereby performing a fluid bed granulation to obtain granules.

Furthermore, pharmaceutical compositions are highly advantageous wherein the at least one active ingredient is or comprises dapagliflozin (as first active ingredient) and sitagliptin or a pharmaceutically acceptable salt thereof (as second active ingredient), and optionally metformin or a pharmaceutically acceptable salt thereof and optionally one or more further active ingredients.

In particular, there is provided a pharmaceutical composition for oral administration (preferably tablet) comprising at least one active ingredient, which is or comprises dapagliflozin (e.g. dapagliflozin of formula 1 or dapagliflozin propanediol monohydrate), preferably in amorphous form,

and sitagliptin or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient selected from the group comprising

- at least one binder,
- at least one diluent, preferably said at least one diluent is or comprises microcrystalline cellulose,
- at least one disintegrant,
- at least one glidant and
- at least one lubricant,

which pharmaceutical composition is free of lactose and free of calcium hydrogen phosphate.

Furthermore, a pharmaceutical composition for oral administration (preferably tablet) comprising at least one active ingredient, which at least one active ingredient is or comprises dapagliflozin, preferably in amorphous form, and sitagliptin or a pharmaceutically acceptable salt thereof, can be pharmaceutical composition which comprises at least one diluent, optionally at least one binder, optionally at least one disintegrant, optionally at least one glidant, and optionally at least one lubricant (which preferably is or comprises magnesium stearate), which pharmaceutical

composition is preferably free of lactose and calcium hydrogen phosphate. Advantageously, said at least one diluent is or comprises microcrystalline cellulose and optionally one or more further diluents.

In pharmaceutical compositions comprising both dapagliflozin and sitagliptin or a pharmaceutically acceptable salt thereof, preferably microcrystalline cellulose is the main excipient. The term main excipient can be the excipient which is present in the highest weight amount of all excipients in the pharmaceutical composition. In a pharmaceutical composition of the present invention comprising sitagliptin or a salt thereof, microcrystalline cellulose can be e.g. present in an amount of at least 50 wt.-%, preferably of at least 80 wt.-%, based on the total weight of the excipient(s) of the composition. A pharmaceutical composition of the present invention comprising sitagliptin or a salt thereof can comprise microcrystalline cellulose e.g. in an amount of 40 to 90 wt.-%, preferably e.g. in an amount of 45 to 85 wt.-%, based on the total weight of the composition.

A pharmaceutical composition for oral administration (preferably tablet) comprising at least one active ingredient, which is or comprises dapagliflozin, preferably in amorphous form, and sitagliptin or a pharmaceutically acceptable salt thereof, can be prepared by the skilled person based on the general knowledge or can be prepared applying one of the processes disclosed herein, especially "preparation process (D)"or "preparation process (E)".

A process for preparing a pharmaceutical composition for oral administration (preferably tablet) (especially of a composition as disclosed herein) comprising at least one active ingredient, which is or comprises dapagliflozin, and sitagliptin or a pharmaceutically acceptable salt thereof, can be a process (also referred to herein as "preparation process (D)") comprising the following steps:

a) dapagliflozin (especially in amorphous form) is mixed with diluent, preferably the diluent is or comprises microcrystalline cellulose, optionally disintegrant, preferably the optional disintegrant is or comprises a disintegrant selected from crospovidone and croscarmellose sodium, and optionally glidant, preferably the optional glidant is or comprises colloidal silicon dioxide, and sitagliptin or a pharmaceutically acceptable salt of sitagliptin, and optionally other pharmaceutically acceptable excipient(s) and optionally other active ingredient(s),

b) the obtained powder blend is compacted, preferably by roller compaction, to obtain a compacted powder blend (also referred to herein as granules),

c) the size of the compacted powder blend is reduced, preferably by sieving or milling, to obtain granules,

d) the obtained granules are blended with diluent, preferably the diluent is or comprises microcrystalline cellulose, optionally disintegrant, preferably the optional disintegrant is or comprises a disintegrant selected from crospovidone and croscarmellose sodium, and optionally glidant, preferably the optional glidant is or comprises colloidal silicon dioxide, optionally one or more further active ingredients, which can be selected from sitagliptin, pharmaceutically acceptable salts of sitagliptin, metformin, and pharmaceutically acceptable salts of metformin, dapagliflozin (preferably dapagliflozin in amorphous form),

e) the obtained mixture is lubricated with lubricant, preferably magnesium stearate,

f) the obtained compression mixture is compressed into tablets, and

g) optionally the obtained tablets are coated.

A process for the preparation of a pharmaceutical composition comprising at least one active ingredient which is or comprises dapagliflozin and sitagliptin or a salt thereof (said process being also referred to herein as "preparation process (E)"), especially of a pharmaceutical composition of the present invention, can be a process comprising the following steps:

a) binder is added to solvent which is or comprises ethanol, optionally the binder being selected from the group consisting of povidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose (in particular HPC SSL or EF), copovidone, and mixtures thereof, to obtain a binder solution,

b) optionally dapagliflozin is dissolved in the obtained binder solution,

c) the dapagliflozin-binder solution obtained in step b) or the binder solution obtained in step a) is contacted with (preferably sprayed onto) a mixture comprising optional diluent (optionally diluent can be or comprise microcrystalline cellulose) and at least one active ingredient selected from sitagliptin, pharmaceutically acceptable salts of sitagliptin, dapagliflozin (preferably dapagliflozin in amorphous form), and optionally metformin or a pharmaceutically acceptable salt thereof, and optionally disintegrant,

d) the obtained granules are optionally blended with at least one or two or all of disintegrant, glidant and diluent, optionally sitagliptin or a pharmaceutically acceptable salt thereof, optionally dapagliflozin and optional other excipient(s),

e) the obtained mixture is lubricated with lubricant,

f) the obtained compression mixture is compressed into tablets,

g) optionally the obtained tablets are coated; said step c) can be carried out using a fluid bed granulator, especially said step c) can be or comprise that the dapagliflozin-binder solution obtained in step b) or the binder solution obtained in step a) is sprayed onto the mixture in a fluidised bed, thereby performing a fluid bed granulation to obtain granules.

The pharmaceutical compositions of the present invention comprising dapagliflozin can be compositions providing an immediate release of dapagliflozin, i.e. release more than 75% of dapagliflozin in less than 1 hour, especially release more than 75% of dapagliflozin in less than 15 minutes, preferably release more than 85% of the dapagliflozin in less than 15 minutes, more preferably more than 95% in 15 minutes (preferably applying the dissolution test described herein). The pharmaceutical compositions of the present invention comprising both dapagliflozin and a further active ingredient selected from metformin, a pharmaceutically acceptable salt thereof, sitagliptin and a pharmaceutically acceptable salt thereof, can be compositions providing an immediate release of dapagliflozin and optionally of said further active ingredient, i.e. release more than 75% of dapagliflozin in less than 1 hour, preferably release more than 85% of the dapagliflozin in less than 15 minutes and optionally release more than 75% of said further active ingredient in less than 1 hour, preferably release more than 85% of said further active ingredient in less than 15 minutes (preferably applying the dissolution test described herein).

In one embodiment the pharmaceutical composition according to the present invention is used in:

- preventing, slowing the progression, delaying or treating diabetes, particularly type I diabetes mellitus, type II diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, metabolic syndrome, insulin resistance;
- preventing, slowing, delaying or reversing progression from IGT, IFG, insulin resistance and metabolic syndrome to type II diabetes mellitus;
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance;
- treating conditions caused by increased blood glucose level - hyperglycemia;
- preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion;
- preventing, slowing, delaying or treating a disorder/disease condition belonging to the group of diabetes mellitus complications, including micro- and macrovascular diseases (such as nephropathy, retinopathy, neuropathy, tissue ischemia, diabetic foot, arteriosclerosis, myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke,

peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis);

- improvement of glycemic control and /or reduction of HbA1c, FPG and PPG in patients diagnosed with IGT, IFG, insulin resistance, metabolic syndrome, type 1 or type 1 diabetes or pre-diabetes;

- preventing, slowing, delaying or treating diseases associated with abnormal accumulation of liver fat such as non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), diabetic fatty liver, alcohol-induced fatty liver and general fatty liver;

- reducing body weight and/or body fat or preventing an increase in body weight and/or body fat or facilitating a reduction in body weight and/or body fat; treating obesity;

- preventing or treating chronic heart failure, reduction of risk of cardiovascular death, reduction of risk for hospitalization for heart failure, for reducing all-cause mortality, for reducing the risk of a new onset of atrial fibrillation, for improving health-related quality of life in a patient with chronic heart failure; for improving renal function or protecting renal function in a patient with chronic heart failure;

- preventing, treating, reducing the risk of, delaying the occurrence or delaying the progression of chronic kidney disease or improving renal outcomes associated with this condition, for treating and preventing kidney stones;

- for the reduction of serum uric acid levels, treating hyperuricemia and hyperuricemia associated conditions;

- for the treatment of hyponatremia.

The pharmaceutical compositions of the present invention may be manufactured by means of any processes known from the state of the art, for example direct compression, fluid bed granulation, wet granulation, dry granulation, high-shear granulation, roller compaction, dry and/or melt and/or dispersion coating of suitable cores such as granules, pellets and/or tablets or any other pharmaceutically acceptable process.

In particular, the process for the preparation of the pharmaceutical composition of the present invention comprises the following steps:

a) binder is added to solvent,

b) dapagliflozin is dissolved in the obtained binder solution,

c) the obtained dapagliflozin-binder solution is sprayed onto the mixture of diluent and disintegrant and optional other excipients,

d) the obtained granules are optionally blended with glidant and diluent,
e) the obtained mixture is lubricated with lubricant,
f) the obtained compression mixture is compressed into tablets,
g) the obtained tablets are coated.

High-shear or Fluid bed granulators can be used in step c).

In addition, the process of the present invention can be a process comprising the following steps:

a) dapagliflozin is mixed with diluent, disintegrant and glidant and optionally other pharmaceutically acceptable excipients,
b) the obtained powder blend is compacted,
c) the size of granules is reduced,
d) the obtained granules are blended with diluent, disintegrant and glidant,
e) the obtained mixture is lubricated with lubricant,
f) the obtained compression mixture is compressed into tablets,
g) the obtained tablets are coated.

In addition, the process of the present invention can be a process comprising the following steps:

a) dapagliflozin is added to solvent,
b) diluent and disintegrant are pre-mixed in a high-shear granulator together with binder,
c) dapagliflozin solution of step a) is sprayed onto the mixture prepared in step b),
d) the obtained granulate is optionally dried in a fluid bed processor,
e) the obtained granules are lubricated with lubricant,
f) the obtained compression mixture is compressed into tablets,
g) the obtained tablets are coated.

High-shear or Fluid bed granulators can be used in steps b and c).

In addition, the process of the present invention can be a process comprising the following steps:

a) dapagliflozin is mixed with diluent, disintegrant and glidant,
b) the obtained powder blend is granulated by melted/softened binder,
c) the obtained granulate is cooled to the room temperature and optionally sieved,
d) the obtained granules are blended with at least one excipient selected from diluent, disintegrant and glidant,
e) the obtained mixture is lubricated with lubricant,
f) the obtained compression mixture is compressed into tablets,

g) the obtained tablets are coated.

Step b) is performed either by "in situ" melted binder or by spraying melted binder onto the powder mixture obtained in step a).

High-shear or Fluid bed granulators can be used in step b).

In addition, the process of the present invention can be a process comprising the following steps:

a) dapagliflozin is mixed with binder having melting or softening point (glass transition poit) below 165°C, preferably below 150 °C, diluent and optional other excipients,
b) the homogenous mixture is transferred to extrusion device and melt extruded;
c) obtained extrudates are optionally cut and cooled down to room temperature,
d) the obtained granules can be optionally shaped on spheronizer,
e) the granules are homogenized with extragranular excipients selected from diluents/fillers, disintegrants and/or glidants
f) the obtained mixture is lubricated with lubricant,
g) the obtained compression mixture is compressed into tablets,
h) the obtained tablets are film coated.

When the pharmaceutical composition according to the present invention comprises more than one active ingredient, the composition can be in the form of monolytic film coated or uncoated tablets, bilayer film coated or uncoated tablets, coated or uncoated multilayer tablets, coated tablets, capsules or sachets.

In one embodiment of the present invention, preparation of pharmaceutical composition with dapagliflozin and at least one additional active pharmaceutical ingredient selected from active pharmaceutical ingredients with anti-diabetic activity the solid pharmaceutical composition is prepared by direct compression. Optionally sieved dapagliflozin and at least one DPP-4 inhibitor except saxagliptin and optional additional active pharmaceutical ingredient with anti-diabetic activity are homogenized together with optionally sieved/de-agglomerated excipients selected from but not limited to diluents/fillers, dry binders such as low substituted hydroxypropyl cellulose and/or povidone, disintegrants, glidants and lubricants in state of the art mixer such as high shear mixer, container blenders of various shapes or the like. Ordered mixing know in the state of the art such as Aulton's Pharmaceutics, 4$^{th}$ Edition, Elsivere Ltd. 2013, can be used to assure acceptable mixture homogeneity and quality of the final product. The obtained homogenous mixture is compressed into tablets and optionally film coated.

In another embodiment of the present invention preparation of pharmaceutical composition with dapagliflozin and at least one additional active pharmaceutical ingredient comprise preparation of dapagliflozin granulate by state of the art dry granulation methods such as dry compaction or slugging.

Dapagliflozin and at least one additional active pharmaceutical ingredient together with at least one pharmaceutically acceptable excipient can be compacted together or separately meaning that two or more separate dry granulates with individual active pharmaceutical ingredients are prepared. To the obtained dry granulate comprising at least one active pharmaceutical ingredient with anti-diabetic activity, the additional active pharmaceutical ingredients can be admixed together with extragranular excipients selected from but not limited to diluents/fillers, disintegrants, glidants and/or lubricants by using state of the art mixers and processes to obtain a homogenous mixture which is compressed into tablets and optionally further film coated.

In another embodiment of the present invention preparation of pharmaceutical composition with dapagliflozin comprise preparation of dapagliflozin granulate. The granulation step in preparation of dapagliflozin granulate includes dissolving or dispersing of dapagliflozin in the granulation liquid or mixing with at least one solid pharmaceutically acceptable excipient and granulating with granulation liquid. Granulation liquid according to present invention comprise at least one solvent, at least one binder dissolved in the solvent and optional other excipients dispersed in it.

In one embodiment dapagliflozin and at least one additional active pharmaceutical ingredient such as metformin or its salt can be formulated into single granulate which is than mixed with extragranular pharmaceutically acceptable excipients and optional third active pharmaceutical ingredient such as sitagliptin and compressed into tablets which can be optionally film coated.

In another embodiment of the present invention metformin or its salt optionally admixed with second active pharmaceutical ingredient selected from, but not limited to DPP-4 inhibitors except saxagliptin is granulated with granulation liquid comprising dissolved dapagliflozin, and optional second active pharmaceutical ingredient selected from DPP-4 inhibitors and a binder and optionally additional excipients by using state of the art granulation equipment and processes such as granulation in high shear mixers/granulators or fluid bed granulators. The obtained granulate can be optionally dried and sieved. The obtained dry granulate is mixed with extragranular

excipients selected from diluents/fillers, disintegrants, glidants and/or lubricants and compressed into tablets. The obtained tablets can be optionally film coated.

In yet another embodiment of the present invention dapagliflozin is formulated together with at least one pharmaceutically acceptable excipient selected from, but not limited to, binders, diluents/fillers, disintegrants, stabilizers, glidants and surfactants separately in the first granulate by the above mentioned processes and at least one another active ingredient together with at least one pharmaceutically acceptable excipient, which can be the same or different as for dapagliflozin granulate, in the second granulate which are then mixed together with extragranular pharmaceutically acceptable excipients and compressed into tablets which can be optionally film coated.

In yet another embodiment of the present invention active ingredient that is not dapagliflozin such as e.g. metformin or pharmaceutically acceptable salt thereof, and sitagliptin or pharmaceutically acceptable salt thereof, is formulated into granulate together with at least one pharmaceutically acceptable excipient selected from, but not limited to, binders, diluents/fillers and disintegrants by the state of the art processes. Dapagliflozin and optional other active pharmaceutical ingredient are then admixed to the obtained granulate together with at least one pharmaceutically acceptable excipient selected from, but not limited to, diluents, binders, disintegrants, glidants, lubricants and compressed into tablets which can optionally be further film coated.

In yet another embodiment of the present invention active ingredient that is not dapagliflozin such as e.g. metformin or pharmaceutically acceptable salt thereof, and sitagliptin or pharmaceutically acceptable salt thereof, is formulated into granulate together with at least one pharmaceutically acceptable excipient selected from, but not limited to, binders, diluents/fillers and disintegrants. Dapagliflozin and optional other active ingredient are dispersed in a coating dispersion comprising pharmaceutically acceptable solvent, at least one binder and optional other pharmaceutically acceptable excipients selected from, but not limited to, diluents, plasticizers, wetting agents/surfactants, stabilizers and then the obtained coating dispersion is coated onto the obtained granulate using state of the art coating equipment and process parameters where fluid bed coating is being preferred. The coated granulate is then mixed with additional pharmaceutically acceptable excipients and compressed into tablets which can be optionally film coated or filled into capsules.

In yet another embodiment of the present invention dapagliflozin and at least one active ingredient that is not dapagliflozin are formulated into multilayer tablets, preferably bilayer tablets, in which dapagliflozin and optional another active ingredient selected from, but not limited to DPP-4 inhibitors are formulated together with appropriate pharmaceutically acceptable excipients selected from, but not limited to diluents/fillers, binders, disintegrants, glidants, lubricants, etc. into one layer and the another active pharmaceutical ingredient preferably metformin or its salt is formulated together with pharmaceutically acceptable excipients selected from, but not limited to, diluents/fillers, binders, disintegrants, glidants, lubricants and optionally functional polymers which prolong the release of the another active ingredient, preferably metformin or its salt into the second layer. Functional polymers can be selected from, but not limited to, hydrophilic high molecular weight polymers such as cellulose ethers, preferably hydroxypropylmethyl cellulose having molecular weight of more than 100 kDa and/or hydroxypropyl cellulose having molecular weight of more than 70 kDa, polyethylene oxides having molecular weight of more than 100,000, preferably of more than 1,000,000, carragenans, locus been gums, xantanes or the like and/or unsoluble polymers such as ethylcellulose, polymethacrylates such as Eudragit® RL, Eudragit® RS, Eudragit® NE and/or lipophilic excipients such as fatty alcohols having at least 8 carbon atoms, glycerol esters, waxes.

In one embodiment dapagliflozin and optional additional active pharmaceutical ingredient with anti-diabetic activity with at least one pharmaceutically acceptable excipient can be coated onto the cores of such as tablets or pellets containing second active pharmaceutical ingredient, preferably metformin or its salts and optionally at least one DPP-4 inhibitor excluding saxagliptin, where release kinetic of second active pharmaceutical ingredient formulated into the cores can be either immediate release, i.e. more than 75% of the second active pharmaceutical ingredient dose is released in less than 1 hour or prolonged release, i.e. where the incorporated second active pharmaceutical ingredient dose is released over at least 6 hours, preferably at least 10 hours and even more preferably over at least 12 hours. Dapagliflozin and optional another drug are released in immediate or prolonged manner, where immediate release being prefer, meaning that more than 75% of dapagliflozin dose formulated into the coating is released in less than 1 hour, preferably in less than 45 minutes and most preferably in less than 30 minutes.

Granulation steps in the above disclosed procedures of preparing pharmaceutical composition according to the present invention can be performed by any state of the art equipment and granulation processes which may include dry granulation, wet granulation by aqueous or organic

granulation liquids and/or melt or thermoplastic granulations. Melt granulation can be performed in high shear or fluid bed granulators or by melt extrusion. Dry granulation can be performed using slugging and/or roller compactor equipment. Wet granulation can be performed in high shear and/or fluid bed granulators and /or extrudors using aqueous or organic solvent based granulation liquids.

Preferred specific embodiments of the present invention are described in the following examples. It is, however, to be understood that the present invention is not limited to these examples.

**Examples**

**Methods**

**Related substances/Impurities of dapagliflozin and sitagliptin by HPLC**

The analytical method used for determining impurities of dapagliflozin was gradient HPLC method, using YMC Hydrosphere column with stationary phase C18, with UV detection at wavelength 223 nm (for dapagliflozin impurities) and at wavelength 266 nm (for sitagliptin impurities). The mobile phase was a combination of water, acetonitrile and potassium dihydrogen phosphate.

**Dissolution profile**

Dissolution profiles (especially for determining immediate release) can be determined by a dissolution test performed on the compositions (tablets) to be tested according to Chapter 711 (Dissolution) of US Pharmacopeia (e.g. as in force on the priority date of the present application), especially using Apparatus 1:

Dissolution method for DAPAGLIFLOZIN and DAPAGLIFLOZIN/SITAGLIPTIN: Apparatus 1 as described in Chapter 711 (Dissolution) of the US Pharmacopeia under the following conditions: Stirring speed: 100 rpm, Temperature: 37 °C, Dissolution medium: 0.1 M Hydrochloric acid, Medium volume: 900 mL, dissolution time: 15 min, sampling interval: 5 min.

Dissolution method for DAPAGLIFLOZIN/METFORMIN: Apparatus 1 as described in Chapter 711 (Dissolution) of the US Pharmacopeia under the following conditions: Stirring speed: 100 rpm, 20 mesh-size baskets, Temperature: 37 °C, Dissolution medium: 0.1 M Hydrochloric acid, Medium volume: 900 mL, dissolution time: 30 min, sampling interval: 5 min (e.g. 5min, 10min, 15min, 20min and 30 min) .

The dissolution profiles shown in Figures 1 to 5 were determined as indicated supra, at a temperature: 37 °C (± 0.5 °C). To establish the dissolution profile aliquots were taken at regular intervals of 5 or10 minutes from the dissolution vessels and the concentration of the drug therein was determined by HPLC.

**Hardness of a tablet core** (Ph. Eur. 2.9.8.RESISTANCE TO CRUSHING OF TABLETS), **flow time** (Ph, Eur. 2.9.16.Flowability), are determined in accordance with standard procedures as disclosed in Ph Eur.

**The content uniformity** of the tablets is characterized by the relative standard deviation (RSD) and Acceptance Value (AV), which are determined according to standard procedures as described in European Pharmacopoeia (2.9.40. Uniformity of Dosage Units).The test for content uniformity of preparations presented in dosage units is based on the assay of the individual contents of active substance of a number of dosage units.

In the following examples, the term "Dapagliflozin amorphous" designates dapagliflozin of formula 1 in amorphous form. Microcrystalline cellulose can be abbreviated as MCC, hydroxypropyl cellulose can be abbreviated as HPC.

**Examples1 - 4: Dapagliflozin film coated tablets prepared by roller compaction**

**Table 3**

| | | **Ex. 1** | **Ex. 2** | **Ex. 3** | **Ex. 4** | **Ex. 4A** | **Ex. 4B** |
|---|---|---|---|---|---|---|---|
| Name of constituents | Function | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] |
| Intragranular phase: | | | | | | | |
| Dapagliflozin amorphous | API | 10.00 | 5.00 | 10.00 | - | 10.00 | 10.00 |
| Dapagliflozin propanediol monohydrate | API | - | - | - | 12.30 | - | - |
| MCC 101 | diluent | 175.00 | 87.50 | 195.00 | 171.45 | 100.00 | 175.00 |
| MCC 102 | diluent | - | - | - | - | 75.00 | - |
| Mannitol | diluent | 50.00 | - | - | - | - | - |
| Corn starch | diluent | - | 25.00 | - | - | - | - |
| Lactose anhydrous | diluent | - | - | - | 50.00 | 40.00 | 40.00 |
| Crospovidone | disintegrant | 4.75 | 2.375 | 4.75 | 5.00 | - | - |
| Croscarmellose Sodium | disintegrant | - | - | - | - | 3.75 | 3.75 |
| Colloidal silicon dioxide | glidant | 1.55 | 0.775 | 1.55 | 1.87 | 1.87 | 1.87 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Extragranular phase: | | | | | | | |
| MCC 102 | diluent | - | - | 30.00 | - | - | - |
| Lactose anhydrous | diluent | - | - | - | - | 10.00 | 10.00 |
| Crospovidone | disintegrant | 4.75 | 2.375 | 4.75 | 5.00 | - | - |
| Croscarmellose Sodium | disintegrant | - | - | - | - | 5.00 | 5.00 |
| Colloidal silicon dioxide | glidant | 1.55 | 0.775 | 1.55 | 1.88 | 1.88 | 1.88 |
| Sodium stearyl fumarate | lubricant | 2.40 | - | 2.40 | - | 2.50 | 2.50 |
| Magnesium stearate | lubricant | - | 1.20 | - | 2.50 | - | - |
| Film Coating phase: | | | | | | | |
| Opadry® | | 9.85 | 4.927 | 9.85 | 9.85 | 9.85 | 9.85 |
| Iron Oxide. Yellow | | 0.15 | 0.073 | 0.15 | 0.15 | 0.15 | 0.15 |
| Water. Purified | | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. |
| Σ | | 260.00 | 130.00 | 260.00 | 260.00 | 260.00 | 260.00 |

Dapagliflozin was screened/deaggregated* using suitable screen and mixed together with microcrystalline cellulose type PH 101 and lactose anhydrous (ex.4) or mannitol (ex. 1) or corn starch (ex. 2), crospovidone and colloidal silicon dioxide (except ex. 4). Prepared powder blend was compacted and reduced to obtain uniform granules using suitable screen.

The granules were blended with MCC (ex. 3), crospovidone and colloidal silicon dioxide (except ex. 4) to obtain a mixture which was further lubricated with sodium stearyl fumarate (ex. 1, ex. 3) or magnesium stearate (ex. 2, ex. 4) to obtain compression mixture which was compressed into tablets.

The tablets were coated with Opadry® and yellow iron oxide by conventional coating process.

***Ex. 4A: Preparation of triturate (dapagliflozin and MCC101) and co-milling of triturate: dapagliflozin was mixed with MCC101 (ratio 1:10) and co-milled using suitable screen size.**

**Table 3A**

| **Example** | **Ex. 4** | **Ex. 4B** | **Ex. 4A** | **Ex. 3** |
|---|---|---|---|---|
| **Compaction force [kN]** | **23** | **18,0** | **18,0** | **10** |
| **Flow time [s]** | **39,1** | **54,2** | **28,2** | **50,6** |
| **Main compression force [kN]** | **11,5** | **8,6** | **8,3** | **5,3** |
| **Hardness [N]** | **94** | **99** | **89** | **84** |
| **Friability [%]** | **0** | **0** | **0** | **0,05** |
| **Content of dapagliflozin [%]** | **100,0** | **100,4** | **97,7** | **93,1** |
| **AV / RSD** | **5,3 / 2,2** | **3,2 / 1,3** | **3,8 / 1,3** | **7,9 / 1,1** |

**Table 3B**

| Sample | Stress condition/RRt | Impurities of dapagliflozin [%] | | |
|---|---|---|---|---|
| | | RRt 0.64 | RRt 0.74 | Total |
| **Ex. 4 (OPA/Al/PVC)** | **t0** | / | / | **b.r.l. (≤ 0.10)** |
| | **40 °C/75 % RH/6m** | / | / | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | / | 0.06 = b.r.l. | **b.r.l. (≤ 0.10)** |
| **Ex. 4B (OPA/Al/PVC)** | **t0** | 0.03 = b.r.l. | / | **b.r.l. (≤ 0.10)** |
| | **40 °C/75 % RH/6m** | 0.04 = b.r.l. | / | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.03 = b.r.l. | 0.05 = b.r.l. | **b.r.l. (≤ 0.10)** |
| **Ex. 4A (OPA/Al/PVC)** | **t0** | / | / | **b.r.l. (≤ 0.10)** |
| | **40 °C/75 % RH/6m** | 0.09 = b.r.l. | 0.06 = b.r.l. | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.05 = b.r.l. | 0.07 = b.r.l. | **b.r.l. (≤ 0.10)** |

**Note:** b.r.l. = below reporting limit (≤ 0.10 %); / : < 0,03 % ; Total = sum of impurities above reporting limit (> 0.10 %)

**Examples 5 – 11: Dapagliflozin film coated tablets prepared by wet granulation**

**Table 4:**

| Name of constituents | Function | Ex. 5 per unit [mg] | Ex. 6 per unit [mg] | Ex. 7 per unit [mg] | Ex. 8 per unit [mg] | Ex. 9 per unit [mg] |
|---|---|---|---|---|---|---|
| **Spray Solution:** | | | | | | |
| Dapagliflozin amorphous | API | - | 10.00 | - | - | 10.00 |
| Dapagliflozin propanediol monohydrate | API | 12.30 | - | 12,30 | 12.30 | - |
| HPC SSL | binder | 7.70 | - | 7.70 | 6.25 | 6.25 |
| HPC EF | binder | - | - | - | - | - |
| Povidone K30 | binder | - | 6.25 | - | - | - |
| Ethanol anhydrous | solvent | q.s. | q.s. | q.s. | q.s. | q.s. |
| **Intragranular phase:** | | | | | | |
| HPC SSL | binder | - | - | - | - | - |
| MCC 101 | diluent | 172.50 | 175.23 | 192.5 | 172.93 | 175.23 |
| Lactose monohydrate | diluent | 50.00 | 50.00 | - | - | - |
| Mannitol | diluent | - | - | - | - | 50.00 |
| Corn starch | diluent | - | - | - | 50.00 | - |
| Crospovidone | disintegrant | 2.50 | 6.02 | 2.50 | 6.02 | 6.02 |
| Colloidal silicon dioxide | glidant | - | - | - | - | - |
| **Extragranular phase:** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| MCC 102 | diluent | - | - | 30.00 | - | - |
| Colloidal silicon dioxide | glidant | - | - | - | - | - |
| Crospovidone | disintegrant | 2.50 | - | 2.50 | - | - |
| Sodium stearyl fumarate | lubricant | 2.50 | 2.50 | 2.50 | 2.50 | 2.50 |
| Magnesium stearate | lubricant | - | - | - | - | - |
| **Film Coating phase**: | | | | | | |
| Opadry® | | 9.85 | 9.85 | 9.85 | 9.85 | 9.85 |
| Iron Oxide. Yellow | | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 |
| Water. Purified | | q.s. | q.s. | q.s. | q.s. | q.s. |
| Σ | | 260.00 | 260.00 | 260.00 | 260.00 | 260.00 |

**Table 4 (continuation):**

| | | **Ex. 10** | **Ex. 11** | **Ex. 10A** | **Ex. 10B** |
|---|---|---|---|---|---|
| Name of constituents | Function | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] |
| **Spray Solution**: | | | | | |
| Dapagliflozin amorphous | API | - | 10.00 | 10.00 | 10.00 |
| Dapagliflozin propanediol monohydrate | API | 12.30 | - | - | - |
| HPC SSL | binder | 12.50 | - | 7.00 | - |
| HPC EF | binder | - | - | - | 70.. |
| Povidone K30 | binder | - | - | - | - |
| Ethanol anhydrous | solvent | q.s. | q.s. | q.s. | q.s. |
| **Intragranular phase:** | | | | | |
| HPC SSL | binder | - | 6.25 | - | - |
| MCC 101 | diluent | 152.70 | 175.23 | 102.50 | 102.50 |
| Lactose monohydrate | diluent | 50.00 | 50.00 | 102.50 | 102.50 |
| Mannitol | diluent | - | - | - | - |
| Corn starch | diluent | - | - | - | - |
| Crospovidone | disintegrant | 16.25 | 6.02 | 2.50 | 2.50 |
| Colloidal silicon dioxide | glidant | 1.88 | - | - | - |
| **Extragranular phase:** | | | | | |
| MCC 102 | diluent | - | - | 20.00 | 23.00 |
| Colloidal silicon dioxide | glidant | 1.87 | - | - | - |
| Crospovidone | disintegrant | - | - | 3.00 | - |
| Sodium stearyl fumarate | lubricant | - | - | 2.50 | 2.50 |
| Magnesium stearate | lubricant | 2.50 | 2.50 | - | - |
| **Film Coating phase:** | | | | | |
| Opadry® | | 9.85 | 9.85 | 9.85 | 9.85 |
| Iron Oxide. Yellow | | 0.15 | 0.15 | 0.15 | 0.15 |
| Water. Purified | | q.s. | q.s. | q.s. | q.s. |
| Σ | | 260.00 | 260.00 | 260.00 | 260.00 |

**Ex 5-10:**

Hydroxypropylcellulose SSL (ex. 5, ex. 7-10) or Povidone K30 (ex. 6) was added to ethanol anhydrous and mixed until a solution was obtained. Dapagliflozin was added to obtained solution and mixed until completely dissolved.

The API-binder (HPC or Povidone) solution was sprayed onto the mixture of microcrystalline cellulose type PH 101 and crospovidone or onto the mixture of microcrystalline cellulose type PH 101 and crospovidone and lactose monohydrate (ex. 5-6, ex. 10) or mannitol (ex. 9) or corn starch (ex. 8) or colloidal silicon dioxide (ex. 10) by top spraying process to obtain dry granulate, which was sieved through sieve with mesh 800 to obtain uniform granules.

The granules were blended with MCC (ex. 7), colloidal silicon dioxide (ex. 10) to obtain a mixture which was further lubricated with sodium stearyl fumarate (ex. 5, ex. 7-9) or magnesium stearate (ex. 6, ex. 10) to obtain compression mixture which was compressed into tablets.

The tablets were coated with Opadry® and yellow iron oxide by conventional coating process.

**Ex 11:**

Dapagliflozin was added to ethanol anhydrous and mixed until a solution was obtained. Microcrystalline cellulose 101, lactose monohydrate and crospovidone were pre-mixed in a high shear granulator together with hydroxypropylcellulose SSL. Dapagliflozin solution was sprayed onto prepared powder mixture during mixing and wet massed to obtain wet granulate.

The granulate was dried in a fluid bed processor and sieved through sieve with mesh 800 to obtain uniform granules. The granules were lubricated with magnesium stearate to obtain compression mixture which was compressed into tablets.

The tablets were coated with Opadry® and yellow iron oxide by conventional coating process.

**Table 4A**

| Example | Ex 7 | Ex 5 | Ex 10A | Ex 10B | Ex 6 |
|---|---|---|---|---|---|
| | Only MCC | MCC : laktose = 4,5 : 1 | MCC : laktose = 1 : 1 | MCC : laktose = 1 : 1 | Povidon K30 |
| Bulk volume [ml/g] | **3,85** | **3,57** | **3,23** | **3,80** | **3,01** |
| Flow time [s] | **86,4** | **82,1** | **39,9** | **42,0** | **83,2** |
| Mass RSD [%] | **2,31** | **1,21** | **0,45** | **0,88** | **0,75** |
| Main compressi | **6,5** | **6,5** | **6,7** | **5,8** | **6,0** |

| | | | | | |
|---|---|---|---|---|---|
| on force [kN] | | | | | |
| Hardness [N] | **90** | **95** | **103** | **94** | **88** |
| Hardness RSD [%] | **12,78** | **7,75** | **4,47** | **5,22** | **5,96** |
| Friability [%] | **0** | **0** | **0** | **0** | **0,28** |
| Content of dapagliflozin [%] | **102,8** | **101,0** | **98,8** | **99,9** | **99,6** |
| AV / RSD | 5,3 / 1,6 | 4,4 / 1,8 | 1,7 / 0,7 | 2,1 / 0,9 | 1,9 / 0,8 |

**Table 4B**

| **Sample** | **Stress condition/RRt** | **Impurities of dapagliflozin [%]** | | |
|---|---|---|---|---|
| | | **RRt 0.64** | **RRt 0.74** | **Total** |
| **Ex. 6 (OPA/Al/PVC)** | **t0** | n.a. | n.a. | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | n.a. | n.a. | **b.r.l. (≤ 0.10)** |
| **Ex. 5 (OPA/Al/PVC)** | **t0** | / | / | **b.r.l. (≤ 0.10)** |
| | **40 °C/75 % RH/6m** | 0.03 = b.r.l. | 0.04 = b.r.l. | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.03 = b.r.l. | 0.05 = b.r.l. | **b.r.l. (≤ 0.10)** |
| **Ex. 7 (OPA/Al/PVC)** | **t0** | n.a. | n.a. | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | n.a. | n.a. | **b.r.l. (≤ 0.10)** |
| **Ex. 5A (OPA/Al/PVC)** | **t0** | / | / | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.03 = b.r.l. | 0.04 = b.r.l. | **b.r.l. (≤ 0.10)** |
| **Ex. 10B (OPA/Al/PVC)** | **t0** | / | / | **b.r.l. (≤ 0.10)** |
| | **40 °C/75 % RH/6m** | 0.03 = b.r.l. | 0.06 = b.r.l. | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.03 = b.r.l. | 0.06 = b.r.l. | **b.r.l. (≤ 0.10)** |
| **Ex. 10A (OPA/Al/PVC)** | **t0** | / | / | **b.r.l. (≤ 0.10)** |
| | **40 °C/75 % RH/6m** | 0.03 = b.r.l. | 0.04 = b.r.l. | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.03 = b.r.l. | 0.04 = b.r.l. | **b.r.l. (≤ 0.10)** |

Note: **b.r.l. = below reporting limit (≤ 0.10 %); / : < 0,03 %; Total = sum of impurities above reporting limit (> 0.10 %)**

**Examples 12 -16: Dapagliflozin/Sitagliptin film coated tablets prepared by roller compaction**

**Table 5**

| | | **Ex. 12** | **Ex. 13** | **Ex. 14** | **Ex. 15** | **Ex. 16** | **Ex. 16A** | **Ex. 16B** |
|---|---|---|---|---|---|---|---|---|
| Name of constituents | Function | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] |
| **Intragranular phase:** | | | | | | | | |
| Dapagliflozin amorphous | API | - | | 10.00 | 10.00 | | 10.00 | 10.00 |
| Dapagliflozin propanediol monohydrate | | | 12.30 | | | 12.30 | - | - |
| Sitagliptin phosphate monohydrate | API | 128.48 | - | - | 128.48 | 128.48 | 128.48 | 128.48 |
| Sitagliptin base | API | - | 100.00 | - | - | - | - | - |
| MCC 101 | diluent | 183.22 | 164.95 | 187.25 | 185.52 | 123.46 | - | - |
| MCC 802 | diluent | - | - | - | - | - | 162.06 | 226.81 |
| Mannitol | diluent | 50.00 | - | - | - | - | - | - |
| Corn starch | diluent | - | 50.00 | - | - | - | - | - |
| Lactose anhydrous | diluent | - | - | - | 40.00 | - | - | - |
| Calcium Hydrogen Phosphate | diluent | - | - | - | - | 123.76 | - | - |
| Crospovidone (Kollidon CL-F) | disintegrant | 8.00 | 7.00 | 7.00 | 8.00 | - | 8.00 | 10.00 |
| Croscarmellose sodium | disintegrant | | | | - | 8.00 | - | - |
| Colloidal silicon dioxide | glidant | 3.00 | 2.63 | 2.63 | 3.00 | - | 3.00 | 3.75 |
| Magnesium stearate | lubricant | - | - | - | 1.33 | 1.33 | 2.67 | 3.33 |
| **Extragranular phase:** | | | | | | | | |
| Dapagliflozin propanediol monohydrate | API | 12.30 | - | - | - | - | - | - |
| Sitagliptin base | API | - | - | 100.00 | - | - | - | - |
| MCC 102 | diluent | - | - | 30.00 | - | - | - | - |
| MCC 200 | diluent | - | - | - | - | - | 69.46 | 92.21 |
| Lactose anhydrous | diluent | - | - | - | 10.00 | - | - | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Calcium Hydrogen Phosphate | diluent | - | - | - | - | - | - | - |
| Crospovidone (Kollidon CL-F) | disintegrant | 8.00 | 7.00 | 7.00 | 8.00 | - | - | - |
| Crospovidone (Kollidon CL) | disintegrant | - | - | - | - | - | 8.00 | 10.00 |
| Croscarmellose sodium | disintegrant | - | - | - | - | - | - | - |
| Colloidal silicon dioxide | glidant | 3.00 | 2.62 | 2.62 | 3.00 | - | 3.00 | 3.75 |
| Magnesium stearate | lubricant | 4.00 | 3.50 | 3.50 | 2.67 | 2.67 | 5.33 | 6.67 |
| **Film Coating phase:** | | | | | | | | |
| Opadry® | | 16.00 | 14.00 | 14.00 | 16.00 | 16.00 | 16.00 | 20 |
| Water. Purified | | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. | q.s. |
| Σ (dry) | | 416.00 | 364.00 | 364.00 | 416.00 | 416.00 | 416.00 | 520.00 |

Dapagliflozin (except ex. 12) and/or sitagliptin (except ex. 14) were sieved using suitable sieve and mixed with MCC type PH 101 or mannitol (ex. 12) or lactose anhydrous (ex. 15) or corn starch (ex. 13) or calcium hydrogen phosphate (ex. 16) or MCC type PH 802 (ex. 16A, 16B), crospovidone (except ex. 16) or croscarmellose sodium (ex. 16), colloidal silicon dioxide (ex. 12–15, 16A, 16B) and lubricated with magnesium stearate (ex. 15-16B).

Prepared powder blend was compacted and sieved to obtain uniform granules using suitable sieve. The granules were blended with a dapagliflozin (ex. 12) or sitagliptin (ex. 14), crospovidone (ex. 12–15, 16A, 16B), colloidal silicon dioxide (ex. 12–15, 16A, 16B), lactose anhydrous (ex. 15), MCC PH 102 (ex.14) and MCC PH 200 (ex. 16A, 16B) to obtain a mixture which was further lubricated with magnesium stearate to obtain compression mixture which was compressed into tablets.

The tablets were coated with Opadry® by conventional coating process.

Example 16A and 16B present the superior formulations in comparison with other stated examples for the reasons stated below:

- As shown in table 5C (stability) the lactose and calcium hydrogen phosphate are less suitable diluents in a composition due to the increase in impurities, thus preferably MCC can be used as diluent and also enables appropriate processing properties of the tableting mixture
- Furthermore the type of MCC chosen in roll-compaction process (MCC KG-802) and in an outer phase of the tableting mixture (MCC PH 200) advantageously contribute to the

processing of these formulations without other diluents. MCC Ceolus KG-802 can be superior in a roll-compaction process to other types of MCC, due to its excellent balance between compactibility and disintegration properties, arising from the particle shape (rode-like shaped) enabling the roll compaction process with advantageous formation of granules. Whereas MCC PH 200 was chosen as a diluent in the tableting mixture due to the larger particle size range, which is comparable to the size range of the made granulate and thus enables appropriate flow properties without the segregation that could be related with better flow properties of mixtures differing in size.

- With the same reason as MCC PH 200, also Kollidon CL (instead of Kollidon CL-F) can be chosen as a disintegrant in the outer phase due to is larger and thus more appropriate particle size.
- Magnesium stearate is chosen as a preferable lubricant, due to its high lubricating ability as well as compatibility with APIs.
- Preferable concentration of magnesium stearate is between 1.5 to 2.5%, enabling appropriate flow properties without affecting the release profiles of the formulation.
- The differences between the Example 16A and 16B are the final mass of the tablet (tablet core: 400mg vs. 500 mg), and the % of excipients; the higher mass of the tablet core can result in a higher content of excipients and a lower content of APIs, which is showing superior flow properties and better tabletability, shown also in lower AV (acceptance value) values of produced tablets.

Table 5A: The compositions of Ex. 16A and Ex 16B given with their %.

| | | **Ex. 16A** | **%** | **Ex. 16B** | **%** |
|---|---|---|---|---|---|
| Name of constituents | Function | per unit [mg] | | per unit [mg] | |
| **Intragranular phase:** | | | | | |
| Dapagliflozin amorphous | API | 10.00 | 2,50 | 10.00 | 2,00 |
| Sitagliptin phosphate monohydrate | API | 128.48 | 32,12 | 128.48 | 25,70 |
| MCC 802 | diluent | 162.06 | **40,52** | 226.81 | **45,36** |
| Crospovidone (Kollidon CL-F) | disintegrant | 8.00 | 2,00 | 10.00 | 2,00 |
| Colloidal silicon dioxide | glidant | 3.00 | 0,75 | 3.75 | 0,75 |

| | | | | | |
|---|---|---|---|---|---|
| Magnesium stearate | lubricant | 2.67 | 0,67 | 3.33 | 0,67 |
| **Extragranular phase:** | | | 0,00 | | 0,00 |
| MCC 200 | diluent | 69,46 | **17,37** | 92.21 | **18,44** |
| Crospovidone (Kollidon CL) | disintegrant | 8.00 | 2,00 | 10.00 | 2,00 |
| Colloidal silicon dioxide | glidant | 3.00 | 0,75 | 3.75 | 0,75 |
| Magnesium stearate | lubricant | 5.33 | 1,33 | 6.67 | 1,33 |
| **Film Coating phase:** | | | | | |
| Opadry® | | 16.00 | | 20 | |
| Water. Purified | | q.s. | | q.s. | |
| Σ (dry) | | 416.00 | | 520.00 | |

Experimental results in the table below, show that desired hardness of tablets was reached with acceptable main compression force with appropriate ejection force, where again Ex.16B showed superior properties (with regard to the higher tablet mass the compression force and ejection force are comparatively low).

Table 5B

| **Example** | **Ex. 15** | **Ex. 16** | **Ex. 16A** | **Ex. 16B** |
|---|---|---|---|---|
| Main compression force | 11.5 | 13 | 9,2 | 11 |
| Ejection force | 270 | 240 | 250 | 190 |
| Hardness (of tablet cores) | 107 | 126 | 121 | 131 |
| **Content (%) SITAGLIPTINE** | 97.1 | 96.6 | 99.3 | 98.7 |
| **AV** | 1.9 | 3.0 | 2.2 | 1.0 |
| **Content (%) DAPAGLIFLOZIN** | 102.7 | 98.6 | 99.8 | 101.5 |
| **AV** | 5.0 | 4.8 | 3.7 | 3.0 |

Next page - Table 5C: Table with the identified impurities in the Ex.15 (lactose); Ex.16 (Ca-hydrogen phosphate), Ex.16A (only MCC as diluent).

Note: b.r.l. = below reporting limit (≤ 0.10 %); / : < 0,03 % ; Total = sum of impurities above reporting limit (> 0.10 %); closed vial ≈ OPA/Al/PVC

| Sample | Stress condition/RRt | Impurities of dapagliflozin [%] | | | | | Impurities of sitagliptin [%] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **RRt 0.84** | **RRt 0.91** | **RRt 0.99** | **RRt 1.12** | **Total** | **RRt 0.71** | **RRt 0.97** | **RRt 1.72** | **RRt 1.74** | **RRt 1.78** | **Total** |
| Example 15 (closed vial) | t0 | / | / | / | / | **b.r.l. (≤ 0.10)** | / | / | / | / | / | **b.r.l. (≤ 0.10)** |
| | 50 °C/75 % RH/1m | 0.06 = b.r.l. | / | / | / | **b.r.l. (≤ 0.10)** | 0.03 = b.r.l. | 0.07 = b.r.l. | / | 0.04 = b.r.l. | 0.06 = b.r.l. | **b.r.l. (≤ 0.10)** |
| Example 15 (PVC/PVDC) | t0 | / | / | / | / | **b.r.l. (≤ 0.10)** | / | / | / | / | / | **b.r.l. (≤ 0.10)** |
| | 50 °C/75 % RH/1m | 0.18 | 0.13 | / | / | **0.31** | 0.18 | 0.33 | 0.38 | 0.15 | 0.24 | **1.28** |
| Example 15 (OPA/Al/PVC) | t0 | / | / | / | / | **b.r.l. (≤ 0.10)** | / | / | / | / | / | **b.r.l. (≤ 0.10)** |
| | 50 °C/75 % RH/1m | 0.07 = p.m.n. | / | / | / | **b.r.l. (≤ 0.10)** | 0.03 = b.r.l. | 0.06 = b.r.l. | / | 0.04 = b.r.l. | 0.03 = b.r.l. | **b.r.l. (≤ 0.10)** |
| Example 16 (closed vial) | t0 | / | / | / | / | **b.r.l. (≤ 0.10)** | / | / | / | / | / | **b.r.l. (≤ 0.10)** |
| | 50 °C/75 % RH/1m | 0.08 = b.r.l. | / | 0.48 | 0.91 | **1.39** | 0.03 = b.r.l. | / | / | / | 0.04 = b.r.l. | **b.r.l. (≤ 0.10)** |
| Example 16A (PVC/PVDC) | t0 | / | / | / | / | **b.r.l. (≤ 0.10)** | / | / | / | / | / | **b.r.l. (≤ 0.10)** |
| | 50 °C/75 % RH/1m | 0.17 | 0.10 = b.r.l. | / | / | **0.17** | 0.22 | / | / | 0.07 = b.r.l. | 0.14 | **0.36** |
| Example 16A (OPA/Al/PVC) | t0 | / | / | / | / | **b.r.l. (≤ 0.10)** | / | / | / | / | / | **b.r.l. (≤ 0.10)** |
| | 50 °C/75 % RH/1m | 0.09 = b.r.l. | 0.05 = b.r.l. | / | / | **b.r.l. (≤ 0.10)** | 0.05 = b.r.l. | / | / | 0.04 = b.r.l. | 0.07 = b.r.l. | **b.r.l. (≤ 0.10)** |

As shown in Figure 1, comparable dissolution profiles of both drugs, dapagliflozin and sitagliptin, from the commercially available originator product and from the newly developed dapagliflozin/sitagliptin product (Ex. 16A) are achieved, reaching more than 85% of drug dissolved in less than 15 minutes.

Figure 1 shows the release profile of Ex.16A in comparison with the originator mono products in 0.1 M hydrochloric acid.

**Example 17 – Dapagliflozin/Sitagliptin film coated tablets prepared by direct compression**

**Table 6**

| | | **Ex. 17** |
|---|---|---|
| Name of constituents | Function | per unit [mg] |
| Dapagliflozin propanediol monohydrate | API | 12.30 |
| Sitagliptin phosphate monohydrate | API | 128.48 |
| MCC 102 | diluent | 123.46 |
| Calcium Hydrogen Phosphate | diluent | 123.76 |
| Croscarmellose sodium | disintegrant | 8.00 |
| Magnesium stearate | lubricant | 4.00 |
| **Film Coating:** | | |
| Opadry® | | 16.00 |
| Water. Purified | | q.s. |
| Σ (dry) | | 416.00 |

Dapagliflozin and sitagliptin were sieved using suitable sieve and mixed together with MCC type PH 102. Prepared triturate was mixed with calcium hydrogen phosphate and croscarmellose sodium to obtain a mixture, which was further lubricated with magnesium stearate to obtain compression mixture, which was compressed into tablets.

The tablets were coated with Opadry® by conventional coating process.

**Examples 18 – 22: Dapagliflozin/Sitagliptin film coated tablets prepared by wet granulation**

**Table 7**

| | | **Ex. 18** | **Ex. 19** | **Ex. 20** | **Ex. 21** | **Ex. 22** |
|---|---|---|---|---|---|---|
| Name of constituents | Function | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] |
| **Spray Solution:** | | | | | | |
| Dapagliflozin amorphous | API | - | 10.00 | - | - | 10.00 |
| Dapagliflozin propanediol monohydrate | API | 12.30 | - | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| HPC SSL | binder | 20.00 | - | 20.00 | 20.00 | 20.00 |
| Povidone K30 | binder | - | 20.00 | - | - | - |
| HPC EF | binder | | | | | |
| Ethanol. Anhydrous | solvent | q.s. | q.s. | q.s. | q.s. | q.s. |
| **Intragranular phase:** | | | | | | |
| Dapagliflozin propanediol monohydrate | API | - | - | 12.30 | - | - |
| Sitagliptin phosphate monohydrate | API | 128.48 | - | 128.48 | - | - |
| Sitagliptin base | API | - | - | - | 100.00 | 100.00 |
| MCC 101 | diluent | 163.22 | 171.52 | 189.22 | 191.70 | 194.00 |
| Lactose monohydrate | diluent | 50.00 | 50.00 | - | - | - |
| Mannitol | diluent | - | - | - | - | 50.00 |
| Corn starch | diluent | - | - | - | 50.00 | - |
| Crospovidone (Collidon CL-F) | disintegrant | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 |
| Colloidal silicon dioxide | glidant | 3.00 | - | - | 3.00 | 3.00 |
| **Extragranular phase:** | | | | | | |
| Dapagliflozin propanediol monohydrate | API | - | - | - | 12.30 | - |
| Sitagliptin phosphate monohydrate | API | - | 128.48 | - | - | - |
| MCC 102 | diluent | - | - | 30.00 | - | - |
| MCC 112 | diluent | - | - | - | - | - |
| Crospovidone (Collidon CL) | disintegrant | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 |
| Croscarmellose sodium | disintegrant | - | - | - | - | - |
| Colloidal silicon dioxide | glidant | 3.00 | - | - | 3.00 | 3.00 |
| Magnesium stearate | lubricant | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 |
| **Film Coating:** | | | | | | |
| Opadry® | | 16.00 | 16.00 | 16.00 | 16.00 | 16.00 |
| Water. Purified | | q.s. | q.s. | q.s. | q.s. | q.s. |
| Σ (dry) | | 416.00 | 416.00 | 416.00 | 416.00 | 416.00 |

**Table 7 (continuation)**

| | | **Ex.22A** | **Ex.22B** | **Ex.22C** | **Ex. 22D** | **Ex.22E** |
|---|---|---|---|---|---|---|
| Name of constituents | Func-tion | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] |
| **Spray Solution:** | | | | | | |
| Dapagliflozin amorphous | API | - | - | - | - | - |
| Dapagliflozin propanediol monohydrate | API | 12.30 | 12.30 | 12.30 | 12.30 | 12.30 |
| HPC SSL | binder | - | - | - | - | - |
| Povidone K30 | binder | - | - | - | - | - |
| HPC EF | binder | 20.00 | 20.00 | 20.00 | 20.00 | 20.00 |
| Ethanol. Anhydrous | solvent | q.s. | q.s. | q.s. | q.s. | q.s. |
| **Intragranular phase:** | | | | | | |
| Dapagliflozin propanediol monohydrate | API | - | - | - | - | - |
| Sitagliptin phosphate monohydrate | API | 128.48 | 128.48 | 128.48 | 128.48 | 128.48 |
| Sitagliptin base | API | - | - | - | - | - |
| MCC 101 | diluent | 111.45 | 143.65 | 140.85 | 140.85 | 140.85 |
| Lactose monohydrate | diluent | 50.00 | - | - | - | - |
| Mannitol | diluent | - | - | - | - | - |
| Corn starch | diluent | - | - | - | - | - |
| Crospovidone (Collidon CL-F) | disinteg rant | 8.00 | 8.00 | 12.00 | 12.00 | 12.00 |
| Colloidal silicon dioxide | glidant | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 |
| **Extragranular phase:** | | | | | | |
| Dapagliflozin propanediol monohydrate | API | - | - | - | - | - |
| Sitagliptin phosphate monohydrate | API | - | - | - | - | - |
| MCC 102 | diluent | 47.77 | 61.57 | 60.37 | 60.37 | - |
| MCC 112 | diluent | - | - | - | - | 60.37 |
| Crospovidone (Collidon CL) | disinteg rant | 8.00 | 12.00 | 12.00 | - | 12.00 |
| Croscarmellose sodium | disinteg rant | - | - | - | 12.00 | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| Colloidal silicon dioxide | glidant | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 |
| Magnesium stearate | lubricant | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 |
| **Film Coating:** | | | | | | |
| Opadry® | | 16.00 | 16.00 | 16.00 | 16.00 | 16.00 |
| Water. Purified | | q.s. | q.s. | q.s. | q.s. | q.s. |
| Σ (dry) | | 416.00 | 416.00 | 416.00 | 416.00 | 416.00 |

HPC SSL (ex. 18, ex. 20-22) or Povidone K30 (ex. 19) or HPC EF (ex. 22A – 22E) was added to ethanol and mixed until a clear solution was obtained. Dapagliflozin (ex. 18, ex. 19 and ex. 22, 22A – 22D) was added to obtained binder solution and mixed until completely dissolved.

The dapagliflozin-binder solution or binder solution was sprayed onto the mixture of dapagliflozin (ex. 20) and/or sitagliptin (ex. 18, ex. 20-22, 22A-22E), microcrystalline cellulose type PH 101, lactose monohydrate (ex. 18-19, 22A) or corn starch (ex. 21) or mannitol (ex. 22), colloidal silicon dioxide (ex. 18, ex. 21-22, 22A-22D) and crospovidone by top spraying process to obtain dry granulate, which was sieved through sieve with mesh 800 to obtain uniform granules.

The granules were blended with dapagliflozin (ex. 21) or sitagliptin (ex. 19), MCC PH 102 (ex. 20, 22A-22D), MCC PH 112 (Ex. 22E), crospovidone (except Ex. 22D), croscarmellose sodium (Ex. 22D) and colloidal silicon dioxide (ex. 18, ex. 21- 22, 22A-22E) to obtain a mixture which was further lubricated with magnesium stearate to obtain compression mixture which was compressed into tablets.

The tablets were coated with Opadry® by conventional coating process.

Stability results (Table 7B) show that HPC binders can be chosen preferably. Here HPC SSL was firstly used (Ex 18). Further granulations were made with HPC EF, as a more viscous polymer, with higher molecular weight, that provided even better granulate properties with even better flow properties (table below, the longest flow time is shown for granulate with HPC SSL, whereas HPC EF results in shorter flow times). Superiority of HPC EF as a binder is shown also in AV (acceptance value) values (table below) which are the lowest for formulations with HPC EF as a binder.Again similarly to roll compaction formulations, in several embodiments lactose as a filler was removed from the formulation, and in particular MCC of different grades provides highly advantageous tableting properties. MCC PH 101 used in wet granulation as a MCC of choice for wet granulation and MCC PH 102 and PH 112 as an outer phase diluents, which both have similar size and provide appropriate size distribution for the made granulate that enables appropriate flow properties without the segregation that could be related with better flow properties of mixtures differing in size.

**Table 7A**

| **Example** | **Ex. 18** | **Ex. 19 )** | **Ex.22A** | **Ex.22B** | **Ex.22C** | **EX. 22D** | **Ex.22E** |
|---|---|---|---|---|---|---|---|
| Differentiation | *HPC SSL as a binder (low viscous)* | *Povidon K30 as a binder* | *HPC EF as a binder, more Mg-stearate)* | *Without lactose as a diluent, increased amount of disintegrant* | *Increased amount of disintegrant* | *Croscarmellose sodium as disintegrant* | *MCC 112 as diluent* |
| **Flow time (s)** | 72.9 | 45.2 | 37.3 | 45 | 41.3 | 42 | 36 |
| Main compression force (kN) | 7.0 | 7,7 | 10,3 | 10.0 | 9,5 | 9,5 | 9,5 |
| Ejection force (N) | / | 190 | 190 | 110 | 115 | 100 | 115 |
| Hardness (N) (of tablet cores) | 124 | 116 | 126 | 121 | 119 | 121 | 117 |
| **Content (%) SITAGLIPTINE** | 99.5 | 101.7 | 101.1 | 99.8 | 99.3 | 98.9 | 101.6 |
| **AV** | 3.5 | 1.8 | **2.1** | **1.9** | **0.9** | **1.5** | **1.0** |
| **Content (%) DAPAGLIFLOZIN** | 99.3 | 97.5 | 100.2 | 98.7 | 99.8 | 100.9 | 99.9 |
| **AV** | 3.8 | 2.8 | **1.6** | **1.4** | **1.4** | **1.6** | **2.0** |

Again all the examples (with results shown in the table above) show advantageous tableting properties, enabling us to achieve advantageous tablet hardness with acceptable compression force and ejection force. MCC PH 112 and MCC PH 102 are used interchangeably with no effect on the processibility.

**Table 7B:** *Table with the identified impurities in the Ex.19 (PVP K30), Ex.22A (lactose), Ex 22B (only MCC as diluent).*

| Sample | Stress condition/RRt | Impurities of dapagliflozin [%] | | | Impurities of sitagliptin [%] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | RRt 0.84 | RRt 0.91 | Total | RRt 0.71 | RRt 0.97 | RRt 1.72 | RRt 1.74 | RRt 1.78 | Total |
| **Ex.19 (PVC/PVDC)** | **t0** | / | / | **b.r.l. (≤ 0.10)** | / | / | / | / | / | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.20 | 0.10 = b.r.l. | **0.20** | 0.12 | 0.69 | 0.46 | 0.17 | 0.36 | **1.80** |
| **Ex.19 (OPA/Al/PVC)** | **t0** | / | / | **b.r.l. (≤ 0.10)** | / | / | / | / | / | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.04 = b.r.l. | 0.03 = b.r.l. | **b.r.l. (≤ 0.10)** | 0.03 = b.r.l. | 0.04 = b.r.l. | / | 0.04 = b.r.l. | / | **b.r.l. (≤ 0.10)** |
| **Ex. 22A (PVC/PVDC)** | **t0** | / | / | **b.r.l. (≤ 0.10)** | / | / | / | / | / | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.12 | 0.04 = b.r.l. | **0.12** | 0.14 | 0.33 | 0.31 | 0.16 | 0.26 | **1.20** |
| **Ex. 22A (OPA/Al/PVC)** | **t0** | / | / | **b.r.l. (≤ 0.10)** | / | / | / | / | / | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.05 = b.r.l. | / | **b.r.l. (≤ 0.10)** | / | 0.06 = b.r.l. | / | 0.04 = b.r.l. | / | **b.r.l. (≤ 0.10)** |
| **Ex.22B (PVC/PVDC)** | **t0** | / | / | **b.r.l. (≤ 0.10)** | / | / | / | / | / | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.12 | 0.06 = b.r.l. | **0.12** | 0.15 | / | / | 0.13 | 0.17 | **0.45** |
| **Ex.22B (OPA/Al/PVC)** | **t0** | / | / | **b.r.l. (≤ 0.10)** | / | / | / | / | / | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.05 = b.r.l. | / | **b.r.l. (≤ 0.10)** | / | / | / | 0.05 = b.r.l. | / | **b.r.l. (≤ 0.10)** |

**Note:** b.r.l. = below reporting limit (≤ 0.10 %); / : < 0,03 % ; Total = sum of impurities above reporting limit (> 0.10 %)

As shown in figure 2, comparable dissolution profiles of both drugs, dapagliflozin and sitagliptin, from the commercially available originator product and from the newly developed dapagliflozin/sitagliptin product (Ex. 22E) are achieved, reaching more than 85% of drug dissolved in less than 15 minutes.

Figure 2 shows the release profile of Ex.22E in comparison with the originator mono products in 0.1 M hydrochloric acid.

**Examples 23 – 27: Dapagliflozin/Sitagliptin film coated tablets prepared by wet granulation**

**Table 8**

| | | **Ex. 23** | **Ex. 24** | **Ex. 25** | **Ex. 26** | **Ex. 27** |
|---|---|---|---|---|---|---|
| Name of constituents | Function | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] |
| **Spray Solution:** | | | | | | |
| Dapagliflozin amorphous | API | - | - | - | - | 10.00 |
| Dapagliflozin propanediol monohydrate | API | - | - | - | 12.30 | - |
| HPC SSL | binder | 20.00 | - | 20.00 | - | - |
| Povidone K30 | binder | - | 20.00 | - | - | - |
| Ethanol. Anhydrous | solvent | q.s. | q.s. | q.s. | q.s. | q.s. |
| **Intragranular phase:** | | | | | | |
| Dapagliflozin amorphous | API | - | 10.00 | - | - | - |
| Dapagliflozin propanediol monohydrate | API | 12.30 | - | - | - | - |
| Sitagliptin phosphate monohydrate | API | 128.48 | - | 128.48 | - | - |
| Sitagliptin base | API | - | - | - | 100.00 | - |
| MCC 101 | diluent | 163.22 | 171.52 | 189.22 | 191.70 | 194.00 |
| Lactose monohydrate | diluent | 50.00 | 50.00 | - | - | - |
| HPC SSL | binder | - | - | - | 20.00 | - |
| Povidone K30 | binder | - | - | - | - | 20.00 |
| Mannitol | diluent | - | - | - | - | 50.00 |
| Corn starch | diluent | - | - | - | 50.00 | - |
| Crospovidone | disintegrant | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 |
| Colloidal silicon dioxide | glidant | 3.00 | - | - | 3.00 | 3.00 |
| **Extragranular phase:** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Sitagliptin phosphate monohydrate | API | - | 128.48 | - | - | - |
| Sitagliptin base | API | - | - | - | - | 100.00 |
| Dapagliflozin propanediol monohydrate | API | - | - | 12.30 | - | - |
| MCC 102 | diluent | - | - | 30.00 | - | - |
| Crospovidone | disintegrant | 8.00 | 8.00 | 8.00 | 8.00 | 8.00 |
| Colloidal silicon dioxide | glidant | 3.00 | - | - | 3.00 | 3.00 |
| Magnesium stearate | lubricant | 4.00 | 4.00 | 4.00 | 4.00 | 4.00 |
| **Film Coating phase:** | | | | | | |
| Opadry® | | 16.00 | 16.00 | 16.00 | 16.00 | 16.00 |
| Water. Purified | | q.s. | q.s. | q.s. | q.s. | q.s. |
| Σ (dry) | | 416.00 | 416.00 | 416.00 | 416.00 | 416.00 |

HPC SSL (ex. 23, ex. 25) or povidone K30 (ex. 24) was added to ethanol and mixed until a clear solution was obtained or dapagliflozin (ex. 26-27) was added to ethanol anhydrous and mixed until a clear solution was obtained.

Dapagliflozin (ex. 23- 24) and/or sitagliptin (ex. 23, ex. 25-26) were pre-mixed in a high shear granulator together with hydroxypropylcellulose SSL (ex. 26) or povidone K30 (ex. 27), MCC PH 101, lactose monohydrate (ex. 23-24) or mannitol (ex. 27) or corn starch (ex. 26), crospovidone and colloidal silicon dioxide (ex. 23, ex. 26-27). Dapagliflozin solution or binder solution was sprayed onto prepared powder mixture during mixing and wet massed to obtain wet granulate. Granulate was dried in a fluid bed processor and sieved through sieve with mesh 800 to obtain uniform granules.

The granules were blended with sitagliptin (ex. 24 and ex. 27), dapagliflozin (ex. 25) and MCC (ex. 25), crospovidone and colloidal silicon dioxide (ex. 23, ex. 26-27) to obtain a mixture which was further lubricated with magnesium stearate to obtain compression mixture which was compressed into tablets. The tablets were coated with Opadry® by conventional coating process.

**Examples 28 – 32 and 36 - 38: Dapagliflozin/Metformin film coated tablets prepared by wet granulation**

**Table 9**

| | | **Ex. 28** | **Ex. 29** | **Ex. 30** | **Ex. 31** |
|---|---|---|---|---|---|
| Name of constituents | Function | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] |
| **Spray Solution**: | | | | | |
| Dapagliflozin amorphous | API | - | 5.00 | - | - |
| Dapagliflozin propanediol monohydrate | API | 6.15 | - | 6.15 | 6.15 |
| Povidone K30 | binder | 170.40 | | | |
| HPC SSL | binder | - | 96.60 | 114.00 | - |
| Copovidone | binder | - | - | - | - |
| HPMC | binder | - | - | - | |
| Ethanol. Anhydrous | solvent | - | q.s. | q.s. | q.s. |
| Water. Purified | solvent | q.s. | - | - | - |
| **Intragranular phase:** | | | | | |
| HPC SSL | binder | - | - | - | 114.00 |
| Povidone K90 | binder | - | - | - | - |
| Metformin HCl | API | 1000.00 | 850.00 | 1000.00 | 1000.00 |
| Sodium Starch Glycolate | disintegrant | 114.00 | - | - | - |
| **Extragranular phase:** | | | | | |
| Mannitol | diluent | - | - | - | 164.70 |
| MCC 102 | diluent | 105.31 | 150.90 | 164.70 | - |
| Sodium Starch Glycolate | disintegrant | - | - | - | 114.00 |
| Crospovidone | disintegrant | - | 96.60 | - | - |
| Croscarmellose sodium | disintegrant | - | - | 114.00 | - |
| Magnesium stearate | lubricant | 24.14 | - | - | 21.30 |
| Sodium stearyl fumarate | lubricant | - | 7.30 | 21.30 | - |
| **Film Coating phase:** | | | | | |
| Opadry® | | 48.85 | 42.60 | 48.85 | 48.85 |
| Iron Oxide. Yellow | | 1.00 | 1.00 | 1.00 | 1.00 |
| Water. Purified | | q.s. | q.s. | q.s. | q.s. |
| Σ (dry) | | 1470.00 | 1250.00 | 1470.00 | 1470.00 |

**Table 9 (continuation)**

| | | **Ex. 32** | **Ex. 30A** | **Ex. 30B** | **Ex. 30C** |
|---|---|---|---|---|---|
| Name of constituents | Function | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] |
| **Spray Solution:** | | | | | |
| Dapagliflozin amorphous | API | - | - | - | - |
| Dapagliflozin propanediol monohydrate | API | 6.15 | 6.15 | 6.15 | 6.15 |
| Povidone K30 | binder | | 170.40 | - | - |
| HPC SSL | binder | - | - | - | - |

| | | | | | |
|---|---|---|---|---|---|
| Copovidone | binder | - | - | - | 170.40 |
| HPMC | binder | - | - | 114.00 | - |
| Ethanol. Anhydrous | solvent | q.s. | q.s. | q.s. | q.s. |
| Water. Purified | solvent | - | - | q. s. | - |
| **Intragranular phase:** | | | | | |
| HPC SSL | binder | - | - | - | - |
| Povidone K90 | binder | 114.00 | - | - | - |
| Metformin HCl | API | 1000.00 | 1000.00 | 1000.00 | 1000.00 |
| Sodium Starch Glycolate | disintegrant | - | 114.00 | 114.00 | 114.00 |
| **Extragranular phase:** | | | | | |
| Mannitol | diluent | - | - | - | - |
| MCC 102 | diluent | 164.70 | 105.31 | 161.71 | 105.31 |
| Sodium Starch Glycolate | disintegrant | - | - | - | - |
| Crospovidone | disintegrant | 114.00 | - | - | - |
| Croscarmellose sodium | disintegrant | - | - | - | - |
| Magnesium stearate | lubricant | - | 24.14 | 24.14 | 24.14 |
| Sodium stearyl fumarate | lubricant | 21.30 | - | - | - |
| **Film Coating phase:** | | | | | |
| Opadry® | | 48.85 | 49.00 | 49.00 | 49.00 |
| Iron Oxide. Yellow | | 1.00 | 1.00 | 1.00 | 1.00 |
| Water. Purified | | q.s. | q.s. | q.s. | q.s. |
| Σ (dry) | | 1470.00 | 1470.00 | 1470.00 | 1470.00 |

**Ex 28-30:**

HPC SSL (ex. 29-30) or povidone K90 (ex. 28) was added to ethanol anhydrous and mixed until a clear solution was obtained. Dapagliflozin was added to the obtained solution and mixed until completely dissolved.

The dapagliflozin-binder solution was sprayed onto the metformin by top spraying process to obtain dry granulate, which was sieved through sieve with mesh 800 to obtain uniform granules. The granules were blended with mannitol (ex. 28) or microcrystalline cellulose type PH 102 (ex. 29-30) and sodium starch glycolate (ex. 28) or crospovidone (ex. 29) or croscarmellose sodium (ex. 30) to obtain a mixture which was further lubricated with magnesium stearate (ex, 28) or sodium stearyl fumarate (ex. 29-30) to obtain compression mixture which was compressed into tablets.

The tablets were coated with Opadry® and yellow iron oxide by conventional coating process.

**Ex 31-32:**

Dapagliflozin was added to ethanol anhydrous and mixed until a solution was obtained.

**Table 9A**

| Example | Ex. 30A | Ex. 30B | Ex. 30C | Ex. 28 |
|---|---|---|---|---|
| | Povidon K30 | HPMC | Copovidone | Povidon K30 Water |
| Bulk volume [ml/g] | **2,36** | **2,30** | **2,3** | **2,57** |
| Flow time [s] | **23,5** | **24,8** | **24,9** | **35,7** |
| Mass RSD [%] | **0,25** | **0,40** | **0,6** | **0,51** |
| Main compression force [kN] | **26,4** | **27,3** | **29,6** | **25,8** |
| Hardness [N] | **197** | **244** | **239** | **191** |
| Hardness RSD [%] | **2,2** | **2,32** | **3,31** | **4,12** |
| Friability [%] | **0,17** | **0,16** | **0,11** | **0,05** |
| Content of dapagliflozin [%] | **95,4** | **98,6** | **99,1** | **73,5** |
| AV / RSD | **4,2 / 0,5** | **1,1 / 0,5** | **1,3 / 0,5** | **27,7 / 1,5** |
| Content of metformin [%] | **100,2** | **99,7** | **99,3** | **95,8** |

Metformin was pre-mixed in a high shear granulator together with hydroxypropylcellulose SSL (ex. 31) or povidone K90 (ex. 32). Dapagliflozin solution was sprayed onto prepared powder mixture during mixing and wet massed to obtain wet granulate.

Granulate was dried in a fluid bed processor and sieved through sieve with mesh 800 to obtain uniform granules. The granules were blended with mannitol (ex. 31) or microcrystalline cellulose type PH 102 (ex. 32) and sodium starch glycolate (ex. 31) or crospovidone (ex. 32) to obtain a mixture which was further lubricated with magnesium stearate (ex. 31) or sodium stearyl fumarate (ex. 32) to obtain compression mixture which was compressed into tablets.

The tablets were coated with Opadry® and yellow iron oxide by conventional coating process.

**Table 9B**

| Sample | Stress condition/RRt | Impurities of dapagliflozin [%] | | |
|---|---|---|---|---|
| | | **RRt 0.69** | **RRt 0.90** | **Total** |
| **Ex. 30A (PVC/PVDC/PVC)** | **t0** | 0.03 = b.r.l. | / | **b.r.l. (≤ 0.10)** |
| | **40 °C/75 % RH/3m** | 0.04 = b.r.l. | 0.03 = b.r.l. | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.04 = b.r.l. | 0.05 = b.r.l. | **b.r.l. (≤ 0.10)** |
| **Ex. 30B (PVC/PVDC/PVC)** | **t0** | / | / | **b.r.l. (≤ 0.10)** |
| | **40 °C/75 % RH/3m** | / | / | **b.r.l. (≤ 0.10)** |

| | | | | |
|---|---|---|---|---|
| | **50 °C/75 % RH/1m** | 0.03 = b.r.l. | / | **b.r.l. (≤ 0.10)** |
| **Ex. 30C (PVC/PVDC/PVC)** | **t0** | 0.03 = b.r.l. | / | **b.r.l. (≤ 0.10)** |
| | **40 °C/75 % RH/3m** | 0.04 = b.r.l. | 0.03 = b.r.l. | **b.r.l. (≤ 0.10)** |
| | **50 °C/75 % RH/1m** | 0.04 = b.r.l. | 0.04 = b.r.l. | **b.r.l. (≤ 0.10)** |

Note: b.r.l. = below reporting limit (≤ 0.10 %); / : < 0,03 % ; Total = sum of impurities above reporting limit (> 0.10 %)

**Table 9C**

| | | **Ex. 36** | **Ex. 37** | **Ex. 38** | **Ex. 39** |
|---|---|---|---|---|---|
| Name of constituents | Function | per unit [mg] | per unit [mg] | per unit [mg] | per unit [mg] |
| **Spray Solution:** | | | | | |
| Povidone K30 | binder | 170.40 | - | - | - |
| Copovidone | binder | - | - | 170.40 | 170.40 |
| HPMC | binder | - | 114.00 | - | - |
| Ethanol. Anhydrous | solvent | q.s. | q.s. | q.s. | q.s. |
| **Intragranular phase:** | | | | | |
| Metformin HCl | API | 1000.00 | 1000.00 | 1000.00 | 1000.00 |
| Dapagliflozin propanediol monohydrate | API | - | 6.15 | 6.15 | 6.15 |
| MCC 101 | diluent | - | - | 61.5 | 52.6 |
| Sodium Starch Glycolate | disintegrant | 114.00 | - | - | - |
| Crospovidone | disintegrant | - | 114.00 | - | - |
| Croscarmellose sodium | disintegrant | - | - | 114.00 | 114.00 |
| **Extragranular phase:** | | | | | |
| Dapagliflozin propanediol monohydrate | API | 6.15 | - | - | - |
| MCC 102 | diluent | 105.31 | 161.71 | 43.81 | 52.71 |
| Magnesium stearate | lubricant | 24.14 | - | 24.14 | - |
| Sodium stearyl fumarate | lubricant | - | 24.14 | - | 24.14 |
| **Film Coating phase:** | | | | | |
| Opadry® | | 49.00 | 49.00 | 49.00 | 49.00 |
| Iron Oxide. Yellow | | 1.00 | 1.00 | 1.00 | 1.00 |
| Water. Purified | | q.s. | q.s. | q.s. | q.s. |
| Σ (dry) | | 1470.00 | 1470.00 | 1470.00 | 1470.00 |

**Ex 36-39:**

Povidone K30 (ex. 36) or HPMC (ex. 37) or Copovidone (ex. 38, ex. 39) was added to ethanol anhydrous and mixed until a clear solution was obtained. Binder solution was sprayed onto metformin (ex. 36) or prepared triturate of metformin and dapagliflozin (ex. 37) or metformin, prepared triturate of microcrystalline cellulose type PH 101 and dapagliflozin (ex. 38) or prepared

triturate of metformin, dapagliflozin and microcrystalline cellulose type PH 101 (ex. 39) and disintegrant (ex. 36-39) by top spraying process to obtain dry granulate, which was sieved through sieve with mesh 800 to obtain uniform granules.

The granules were blended with dapagliflozin (ex. 36) and microcrystalline cellulose type PH 102 to obtain a mixture which was further lubricated with magnesium stearate (ex. 36, ex. 38, ex. 39) or sodium stearyl fumarate (ex. 37) to obtain compression mixture which was compressed into tablets.

The tablets were coated with Opadry® and yellow iron oxide by conventional coating process.

| **Example** | **Ex. 36** | **Ex. 38** |
|---|---|---|
| **Mass RSD [%]** | **0,35** | **0,34** |
| **Main compression force [kN]** | **31,1** | **28,6** |
| **Hardness [N]** | **244** | **216** |
| **Hardness RSD [%]** | **2,49** | **4,02** |
| **Friability [%]** | **0,16** | **0,21** |

**Examples 33 - 35: Dapagliflozin/Sitagliptin/Metformin film coated tablets prepared by wet granulation**

**Table 10**

| | | **Ex. 33** | **Ex. 34** | **Ex. 35** |
|---|---|---|---|---|
| Name of constituents | Function | per unit [mg] | per unit [mg] | per unit [mg] |
| **Spray Solution:** | | | | |
| Dapagliflozin propanediol monohydrate | API | 6.15 | - | - |
| Povidone K30 | binder | 91.00 | 91.00 | 91.00 |
| Ethanol. Anhydrous | solvent | q.s. | q.s. | q.s. |
| **Intragranular phase:** | | | | |
| Metformin HCl | API | 1000.00 | 1000.00 | 1000.00 |
| Dapagliflozin propanediol monohydrate | API | - | - | 6.15 |
| Sitagliptin base | API | - | - | 50.00 |
| **Extragranular phase:** | | | | |
| Sitagliptin base | API | 50.00 | 50.00 | - |
| Dapagliflozin amorphous | API | - | 5.00 | - |
| Mannitol | diluent | 55.77 | 55.77 | 55.77 |
| MCC 101 | diluent | 65.63 | 64.13 | 65.63 |
| Texapon K 12 P PH | surfactant | 6.45 | 6.45 | 6.45 |

| | | | | |
|---|---|---|---|---|
| Magnesium stearate | lubricant | 20.00 | 20.00 | 20.00 |
| **Film Coating phase:** | | | | |
| Opadry® | | 33.50 | 33.50 | 33.50 |
| Iron Oxide. Red | | 1.50 | 1.50 | 1.50 |
| Water. Purified | | q.s. | q.s. | q.s. |
| Σ (dry) | | 1330.00 | 1330.00 | 1330.00 |

**Ex 33-35:**

Povidone K30 was added to ethanol anhydrous and mixed until a clear solution was obtained. Dapagliflozin was added (ex. 33) to the obtained solution and mixed until completely dissolved. The dapagliflozin-binder solution (ex. 33) or binder solution (ex. 34, 35) was sprayed onto the metformin, dapagliflozin (ex. 35) and sitagliptin (ex. 35) by top spraying process to obtain dry granulate, which was sieved through sieve with mesh 800 to obtain uniform granules. The granules were blended with sitagliptin (ex. 33-34), dapagliflozin (ex. 34), mannitol, micro-crystalline cellulose type PH 101 and sodium lauryl sulfate to obtain a mixture which was further lubricated with magnesium stearate to obtain compression mixture which was compressed into tablets. The tablets were coated with Opadry® and red iron oxide by conventional coating process.

**Example 36**

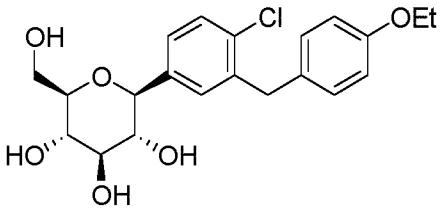
Figures 3 and 4 show that dapagliflozin Film Coated Tablets prepared by wet granulation or prepared by dry granulation have an advantageous dissolution profile. Figure 3 shows that a composition with amorphous dapagliflozin prepared by dry granulation retains excellent dissolution profile, also after a storage under accelerated conditions at 40°C/75% RH for 3 months. This confirms that dapagliflozin in the composition is physically and chemically stable. In particular, Figure 4 shows dissolution of dapagliflozin from Dapagliflozin film-coated tablets in 0.1 M hydrochloric acid and pertains to the following Examples:

- Dapagliflozin 10 mg film-coated tablets (B.No: Ex. 5)
- Dapagliflozin 10 mg film-coated tablets (B.No: Ex. 5A)
- Dapagliflozin 10 mg film-coated tablets (B.No: Ex. 10A)
- Dapagliflozin 10 mg film-coated tablets (B.No: Ex. 10B)
- Dapagliflozin 10 mg film-coated tablets (B.No: Ex. 6)

Figure 5 pertains to Dapagliflozin/Metformin Film Coated Tablets. The dissolution profiles show that the compositions comprising metformin and dapagliflozin according to the invention, using ethanol as a granulation solvent, are insensitive to the use of different binders. The dissolution profile of dapagliflozin and of metformin is similar irrespective of the type of the binder used.

## Claims

1. A pharmaceutical composition for oral administration comprising at least one active ingredient which at least one active ingredient is or comprises dapagliflozin of formula 1




formula 1

in one or more crystalline or amorphous forms or co-crystal complex or a hydrate or a solvate thereof or one or more polymorph forms or any mixtures thereof and at least one pharmaceutically acceptable excipient selected from the group comprising

- at least one binder,
- at least one diluent,
- at least one disintegrant,
- at least one glidant and
- at least one lubricant.

2. The pharmaceutical composition according to claim 1 wherein the dapagliflozin is dapagliflozin of formula 1 or a co-crystal complex or a hydrate or a solvate thereof or a mixture thereof.

3. The pharmaceutical composition according to claim 1 or 2, wherein the dapagliflozin is or comprises dapagliflozin in amorphous form, or
wherein the dapagliflozin is or comprises dapagliflozin in crystalline form, or
wherein the dapagliflozin is a mixture comprising dapagliflozin in crystalline form and dapagliflozin in amorphous form.

4. The pharmaceutical composition according to any one of claims 1 to 3 further comprising metformin or one or more pharmaceutically acceptable salts thereof.

5. The pharmaceutical composition according to any one of claims 1 to 3 further comprising sitagliptin or one or more pharmaceutically acceptable salts thereof.

6. The pharmaceutical composition according to any one of claims 1 to 3 further comprising metformin or one or more pharmaceutically acceptable salts thereof and sitagliptin or one or more pharmaceutically acceptable salts thereof.

7. The pharmaceutical composition according to any one of the preceding claims wherein dapagliflozin is in amorphous form.

8. The pharmaceutical composition according to any one of the preceding claims wherein dapagliflozin is dapagliflozin propylene glycol hydrate.

9. The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition comprises dapagliflozin containing granules prepared by dry granulation, the dapagliflozin in the pharmaceutical composition being dapagliflozin which is predominantly in amorphous form, especially dapagliflozin wherein at least 70 % of the dapagliflozin in the pharmaceutical composition is amorphous dapagliflozin.

10. The pharmaceutical composition according to any one of the preceding claims, wherein the at least one active ingredient is or comprises dapagliflozin in amorphous form, and wherein the at least one pharmaceutically acceptable excipient comprises at least one diluent which is or comprises microcrystalline cellulose and lactose.

11. The pharmaceutical composition according to any one of the preceding claims, wherein the pharmaceutical composition is or comprises granules comprising dapagliflozin, said granules comprising dapagliflozin being prepared by wet granulation, preferably fluid bed granulation, using a solvent which is or comprises ethanol, and wherein the pharmaceutical composition comprises microcrystalline cellulose and lactose, said pharmaceutical composition being further characterized in that

(i) the weight ratio of microcrystalline cellulose to lactose is from 4 : 1 to 1:2, preferably 3:1 to 1:1, or

said pharmaceutical composition being further characterized in that

(ii) the granules comprising dapagliflozin prepared by wet granulation, preferably fluid bed granulation, comprise microcrystalline cellulose and lactose, the weight ratio of microcrystalline cellulose to lactose in said granules comprising dapagliflozin being from 1 : 2 to 2:1, preferably 1.5:1 to 1:1.

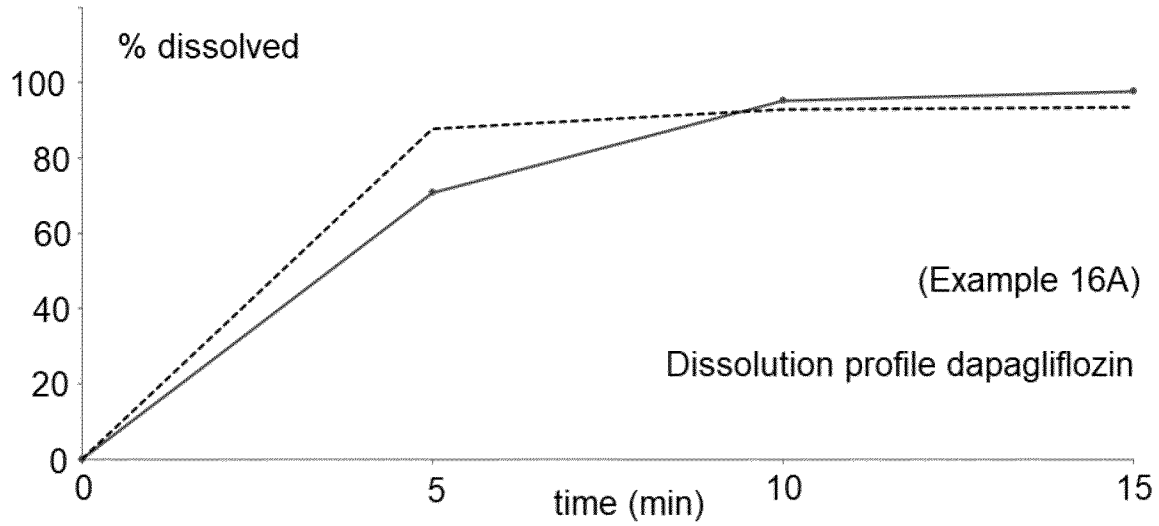
12. The pharmaceutical composition according to any one of the preceding claims, which is or comprises a compressed mixture, especially tablet, which compressed mixture comprises an extragranular phase comprising microcrystalline cellulose, and dapagliflozin containing granules, said dapagliflozin containing granules comprise dapagliflozin and microcrystalline cellulose.

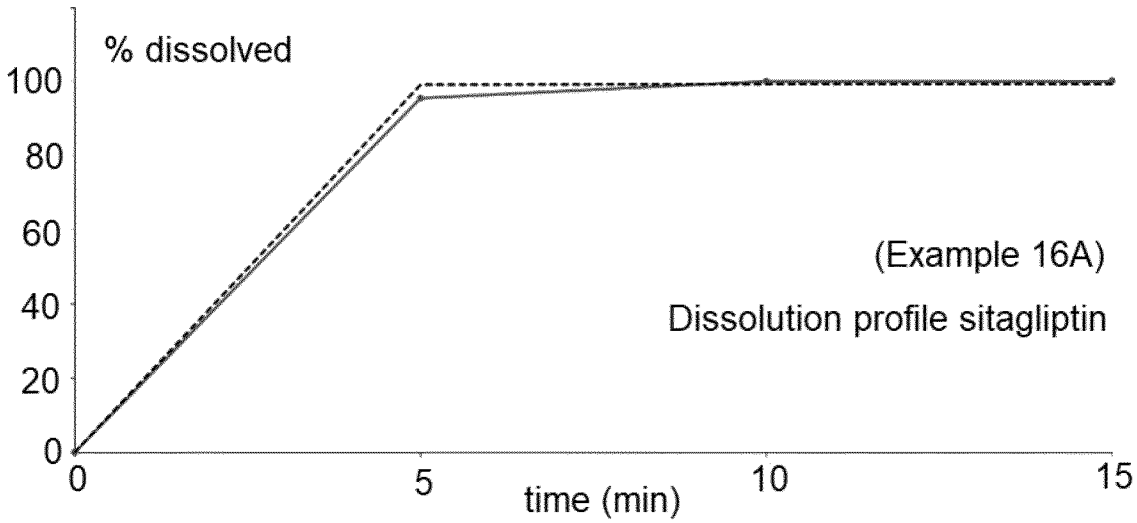
13. The pharmaceutical composition according to any one of the preceding claims, wherein the at least one pharmaceutically acceptable excipient comprises at least one binder selected from the group consisting of povidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, copovidone, and mixtures thereof, and at least one diluent.

14. The pharmaceutical composition according to any one of the preceding claims, wherein the at least one active ingredient is or comprises dapagliflozin, and sitagliptin or a pharmaceutically acceptable salt thereof, which pharmaceutical composition is free of lactose and free of calcium hydrogen phosphate, and/or
wherein the at least one pharmaceutically acceptable excipient comprises at least one diluent, preferably said at least one diluent is or comprises microcrystalline cellulose and optionally one or more further diluents.

15. A process for the preparation of a pharmaceutical composition, especially according to any one of the preceding claims, said pharmaceutical composition comprising at least one active ingredient which is or comprises dapagliflozin, which process comprises the following steps:

a) binder is added to solvent which is or comprises ethanol, optionally the binder being selected from the group consisting of povidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, copovidone, and mixtures thereof, to obtain a binder solution,
b) optionally dapagliflozin is dissolved in the obtained binder solution,
c) the dapagliflozin-binder solution obtained in step b) or the binder solution obtained in step a) is contacted with, preferably sprayed onto, a mixture comprising diluent and optionally disintegrant and optionally an active ingredient selected from sitagliptin, pharmaceutically acceptable salts of sitagliptin, metformin, and pharmaceutically acceptable salts of metformin, dapagliflozin, preferably dapagliflozin in amorphous form,
d) the obtained granules are optionally blended with at least one or all of disintegrant, glidant and diluent, and optional other excipient(s), and optional active ingredient(s), preferably selected from sitagliptin, pharmaceutically acceptable salts of sitagliptin, metformin, and pharmaceutically acceptable salts of metformin, dapagliflozin, preferably dapagliflozin in amorphous form,
e) the obtained mixture is lubricated with lubricant,
f) the obtained compression mixture is compressed into tablets,
g) optionally the obtained tablets are coated.

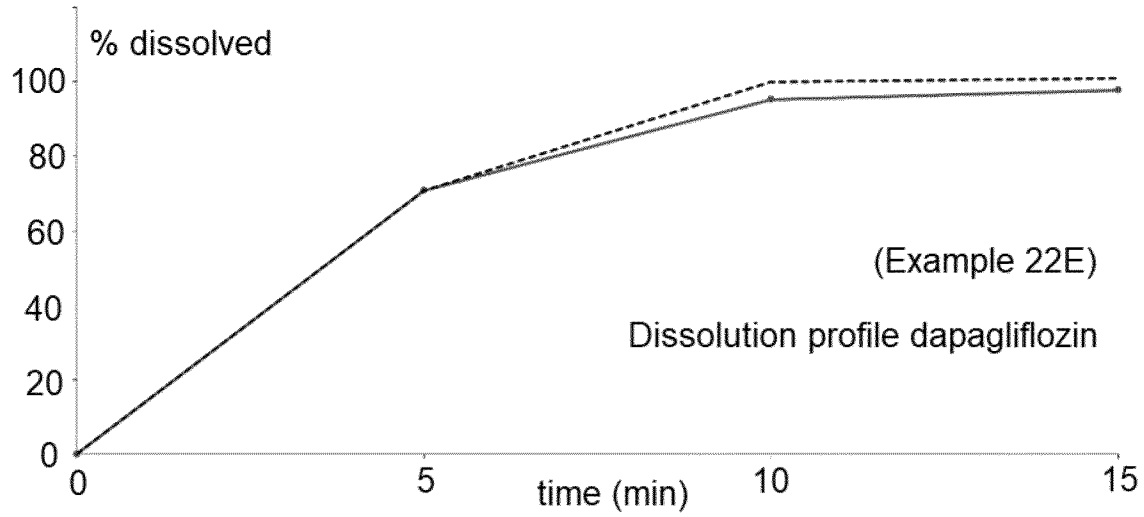


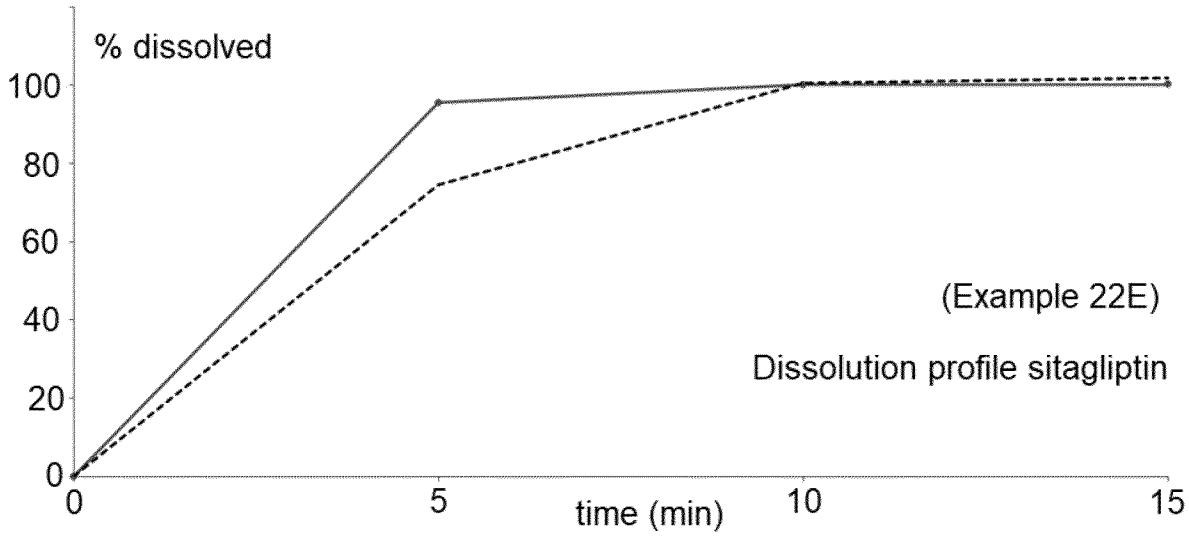




_____ Forxiga 10 mg + Januvia 100 mg film-coated tablets (B. No. X 1044C + S017289)

- - - Dapagliflozin/Sitagliptin 10/100 mg film-coated tablets (B. No. Example 16A)

**Fig. 1**




_____ Forxiga 10 mg + Januvia 100 mg film-coated tablets (B. No. X 1044C + S017289)

- - - Dapagliflozin/Sitagliptin 10/100 mg film-coated tablets (B. No. Example 22E)

**Fig. 2**

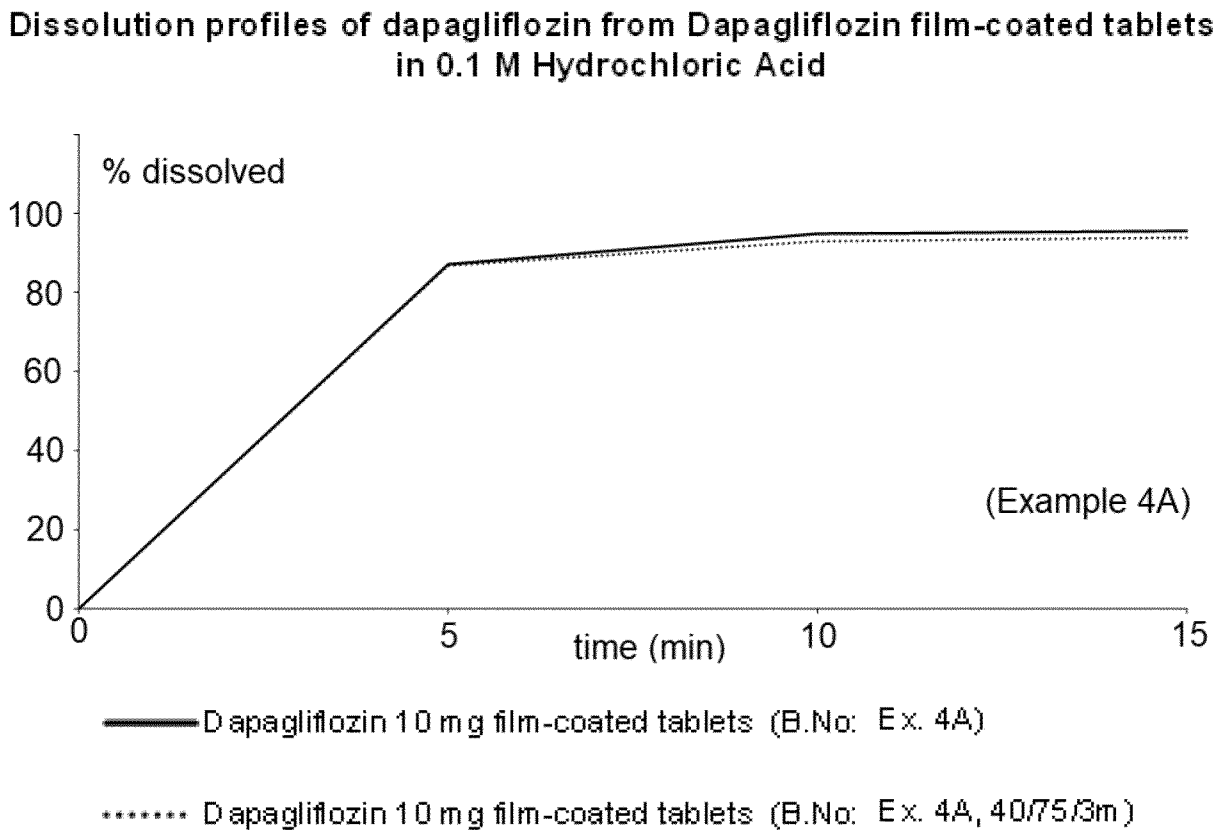

Dissolution profiles of dapagliflozin from Dapagliflozin film-coated tablets in 0.1 M Hydrochloric Acid
% dissolved
100
80
60
40
20
0
0
5
10
15
time (min)
(Example 4A)
Dapagliflozin 10 mg film-coated tablets (B.No: Ex. 4A)
Dapagliflozin 10 mg film-coated tablets (B.No: Ex. 4A, 40/75/3m)

**Fig.3**

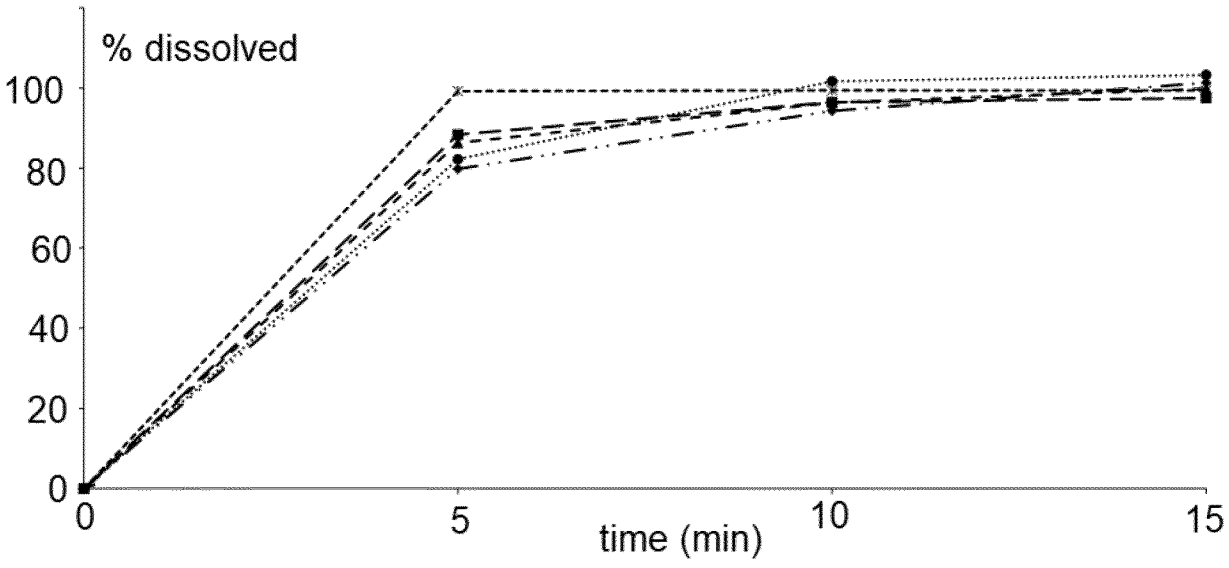
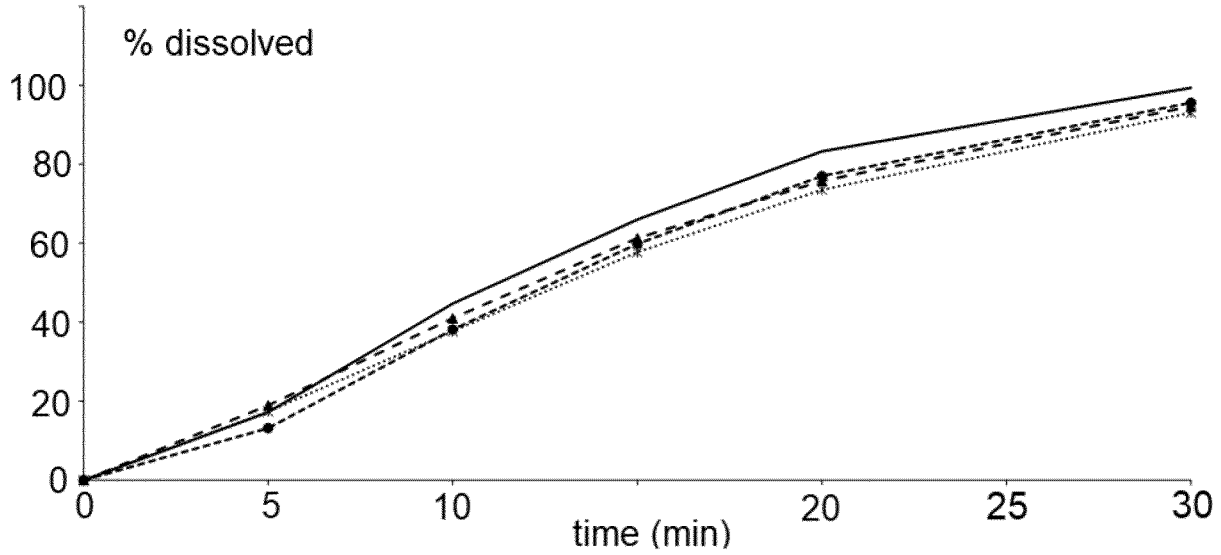

% dissolved
100
80
60
40
20
0
0
5
10
15
time (min)

**Fig. 4**

Dissolution profiles of dapagliflozin from Dapagliflozin/Metformin film-coated tablets in 0.1 M Hydrochloric Acid




Dissolution profiles of metformin from Dapagliflozin/Metformin film-coated tablets in 0.1 M Hydrochloric Acid

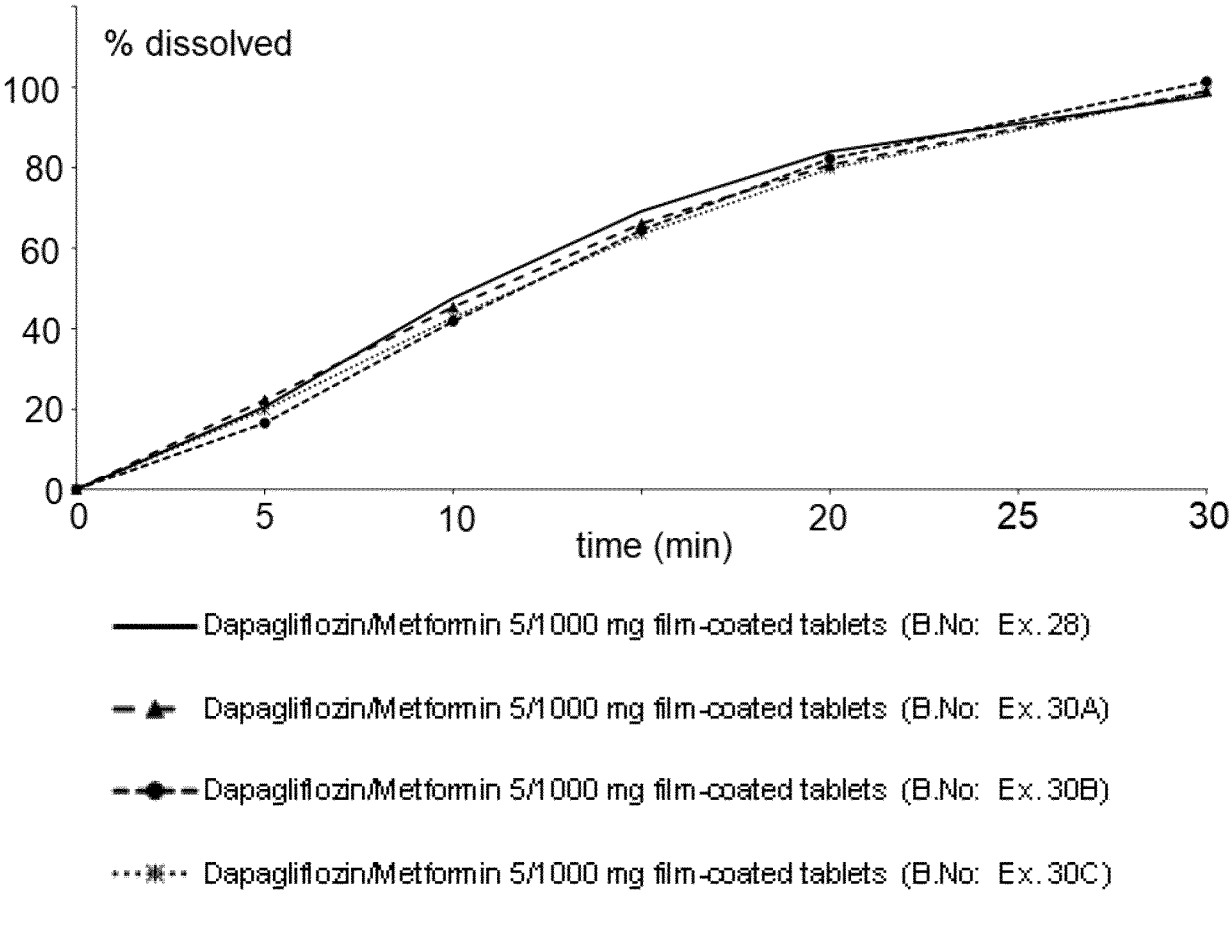



Fig. 5

# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/055688

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/155 A61K31/4985 A61K31/70
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, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 7 June 2021 | 16/06/2021 |

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

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International application No
PCT/EP2021/055688

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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