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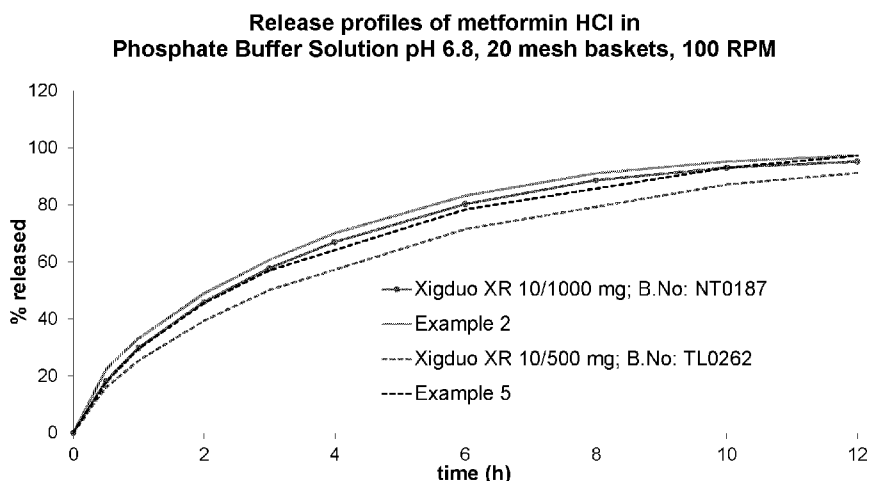


Fig. 1

(57) Abstract: The present invention relates to a bilayer tablet comprising metformin extended release formulation as the first layer and dapagliflozin formulation as the second layer, wherein both layers comprising hydroxypropyl cellulose as a binder. The invention also relates to a process for the manufacturing of the said tablet.

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Bilayer tablet formulation comprising dapagliflozin and metformin**Field of the invention**

The present invention relates to a pharmaceutical composition which is a bilayer tablet comprising metformin extended release formulation as the first layer and dapagliflozin formulation as the second layer, and optionally a film coating. The present invention preferably relates to a bilayer tablet comprising metformin extended release formulation as the first layer and dapagliflozin formulation as the second layer, wherein both layers comprising hydroxypropyl cellulose as a binder. The invention relates also to a manufacturing method for a preparation of the bilayer tablet and to a bilayer tablet for use in a method of treatment of the diseases or disorders associated with metabolic disorders or to a bilayer tablet for use in a method of treating a glucose related disorder.

Background of the invention

Diabetes is a group of metabolic disorders which is related with high glucose in plasma. Currently, there are three types of diabetes, such as type 1, type 2, and gestational diabetes. However, type 2 diabetes is known to be the most common form of the diabetes in both of the developed and developing countries.

Type 2 diabetes (non-insulin dependent diabetes, (NIDDM)) is a condition and is called as insulin resistance where the body produces insulin, but certain mechanisms prevent insulin from moving glucose into cells. Therefore, glucose level rises to the unsafe in the blood and which is called as hyperglycemia.

Sustained hyperglycemia leads to worsened insulin resistance and contributes to dysfunction in the beta cells of the pancreas. Diabetic microvascular complications and macro-vascular complications are the direct result of the degree of the sustained hyperglycemia. Thus, Type 2 diabetes is characterized by hyperglycemia and an increased risk of microvascular and macro-vascular complications.

The present invention combines two anti-hyperglycemic medicinal products with different and complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: dapagliflozin, a SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure.

This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodeling and preserve renal function. Other effects include an increase in hematocrit and reduction in body weight. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect.

Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal blood glucose, dapagliflozin has a low propensity to cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin.

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 glycemic 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 type I diabetes as adjunct therapy to adjustable insulin.

Metformin is an oral anti-hyperglycemic agent which has been widely used for improving glycemic control in patients with Type 2 diabetes for decades by being alone or combined form with other anti-hyperglycemic medications. Metformin can also be of value in the treatment of obese or overweight diabetic patients or in patients with polycystic ovary syndrome.

Metformin can be taken in high doses in the range of 500 mg to 2500 mg per day and that requires twice or three times a day dosing. However, this type of administration may cause the changes in the blood concentration of the drug and that will trigger to expose the adverse reactions and resistance to the drug.

Extended-release formulations of metformin can have advantages over immediate release-formulations, as extended-release formulations of metformin generate a more uniform maintenance of blood plasma active drug concentrations and provide better patient compliance.

Thus, an aspect of the present invention is a fixed dose combination of dapagliflozin and metformin for the treatment of the Type 2 diabetes, wherein metformin is presented in the extended-release formulation and dapagliflozin is presented in a further formulation, preferably in the immediate release formulation.

A long-standing issue for bilayer tablets is the inadequate interfacial bonding strength, which may result in bilayer tablets delamination at the interface during production or any downstream operations. If not solved, such problems can highly affect product integrity and impact drug delivery. However, during development of the bilayer tablet several aspects have to be considered, such as chemical stability of layers, physical stability of layers, layer interactions, storage stability of the bilayer tablet and its layers, beneficial packaging properties, layer formulation composition, process parameters, aspects of production (especially on industrial scale, e.g. time-effective production), adequate drug release from individual layers (e.g. absence of undesired effects and interactions among the layers in view of drug release), advantageous or acceptable tablet size, appropriate matching of the elastic modulus between adjacent layers, appropriate bilayer tablet hardness, and combinations thereof.

WO2010045656 describes a bilayer tablet comprising the sustained release metformin layer prepared by granulation of metformin with povidone and extragranular addition of ethyl cellulose and dapagliflozin layer prepared by granulation with povidone and extragranular addition of disintegrant and lubricant.

WO2011060290 describes a monolayer immediate formulation of dapagliflozin and metformin HCl.

WO2011060256 describes a bilayer tablet. WO2013130785, WO2017114227 and WO 2022066363 describe formulations comprising metformin sustained release composition coated with a coating layer including dapagliflozin.

WO 2022115053 describes a bilayer tablet, one layer representing the sustained release formulation of metformin, comprising metformin, povidone as binder, HPMC as controlled release agent, microcrystalline cellulose and silicon dioxide.

WO 2022225489 describes a two-layer tablet that does not include magnesium stearate.

However, for various reasons, there remains a need for alternative pharmaceutical compositions comprising dapagliflozin and metformin exhibiting a desired physical and chemical stability, a desired dissolution profile and which are prepared by a simple and reliable manufacturing process.

Double-layer tableting is a demanding technology in which it is essential to ensure adequate compressibility of individual layers as well as their connectivity, which ensures adequate hardness of the tablet or core, especially if these are further intended for coating. It is also important that the tablet does not undergo lamination or layering, which can occur if the layers do not connect to the appropriate extent. Inadequate hardness of the cores/tablets and lamination between layers can lead to a higher number of inadequate tablets during manufacture, leading to poorer production yields and at the same time posing a risk of inadequate appearance of the tablets if such a tablet passes all in-process controls.

Moreover, this invention relates to a combination of an extended release layer and a further layer (which is preferably an immediate release layer). Therefore, appropriate release from individual layers is also necessary, and there should be no disadvantageous interaction between the layers, e.g. the extended release layer (metformin layer) should not delay the release of the immediate release active substance (dapagliflozin layer).

Pharmaceutical composition of the present invention exhibits excellent physico-mechanical properties, chemical and physical stability, and at the same time it provides desired dissolution profile. The composition is prepared by an economical process suitable for use on an industrial scale production. It has been surprisingly found that the both layers of the pharmaceutical composition according to the present invention can be prepared by simple technological process using fluid bed granulation, which provides for efficient manufacturing process and results in excellent physical properties of the bilayer tablet.

Summary of the invention

The present invention relates to a bilayer tablet comprising metformin extended release formulation as the first layer and dapagliflozin formulation as the second layer, wherein both layers comprising hydroxypropyl cellulose (as a binder).

According to a first aspect, there is provided a pharmaceutical composition, which pharmaceutical composition is a bilayer tablet comprising: a first layer, and a second layer, said first layer being a metformin extended release layer, and said first layer comprising metformin and hydroxypropyl cellulose, said second layer comprising dapagliflozin and hydroxypropyl cellulose.

Furthermore, there is provided a pharmaceutical composition for use in a method of treating diseases or disorders associated with metabolic disorders or for use in a method of treating a glucose related disorder, especially for use in a method of treating a glucose related disorder, chronic heart failure, chronic kidney disease, and cardiovascular disease, said pharmaceutical composition being a bilayer tablet comprising: a first layer, and a second layer, said first layer being a metformin extended release layer, and said first layer comprising metformin and hydroxypropyl cellulose, said second layer comprising dapagliflozin and hydroxypropyl cellulose.

Moreover, there is provided a process for the preparation of a pharmaceutical composition which is a bilayer tablet, said process comprising:

A) preparing a phase comprising metformin, said preparing of a phase comprising metformin comprising:

A-1) dissolving hydroxypropyl cellulose in a liquid, which liquid preferably is or comprises water or an organic solvent (in particular ethanol), e.g. which liquid is water or ethanol or a mixture of water and ethanol, more preferably is or comprises water, to obtain a granulation liquid;

A-2) spraying the granulation liquid onto metformin, optionally spraying the granulation liquid onto a mixture of metformin with one or more intragranular excipients to obtain granules comprising metformin;

A-3) adding a controlled release agent, a lubricant, optionally a glidant and optionally a diluent, to the granulate obtained in step A-2) to obtain the phase comprising metformin;

B) preparing a phase comprising dapagliflozin, said preparing of a phase comprising dapagliflozin comprises:

B-1) dissolving hydroxypropyl cellulose and dapagliflozin in a liquid, which liquid preferably is or comprises water or an organic solvent, more preferably is or comprises ethanol to obtain a granulation liquid;

- B-2) preparing a mixture of one or more pharmaceutically acceptable excipients, preferably a mixture of one or more pharmaceutically acceptable excipients comprising diluent(s) and optionally glidant, to obtain a homogenous mixture of excipients;
- B-3) spraying the granulation liquid onto the mixture of one or more pharmaceutically acceptable excipients to obtain granules;
- B-4) adding one or more (extragranular) diluents, one or more (extragranular) disintegrants, optionally one or more colorants and one or more lubricants to the granules obtained in step B-3) to obtain the phase comprising dapagliflozin;
- C) bilayer tableting of metformin phase and dapagliflozin phase, thereby obtaining bilayer tablet;
- D) optionally film coating of the bilayer tablet.

In another aspect the present invention provides a method for a manufacturing of a bilayer tablet, wherein the processes for preparation of the compression mixtures for both layers comprise a fluid bed granulation process.

Brief description of the Figures

Figure 1 discloses a dissolution profile of metformin in phosphate buffer, pH 6.8, according to USP Apparatus 1 (basket) from a bilayer tablet formulation according to Example 2 in comparison to the (commercially available) reference product.

Figure 2 discloses a dissolution profile of dapagliflozin in phosphate buffer, pH 6.8, according to USP Apparatus 1 (basket) from a bilayer tablet formulation according to Example 2 in comparison to the reference product.

Figure 3 discloses tableability profile, characterized by tablet hardness achieved at different compaction pressures.

Figures 4 and 5 disclose dissolution profiles of metformin and dapagliflozin in phosphate buffer, pH 6.8, according to USP Apparatus 1 (basket) from tablet of different hardness.

Detailed description of the invention

Bilayer tablets are associated with many challenges in formulation design, manufacturing processes, quality control, and product performance. These challenges include complex weight control in individual layers and final tablet weight, inadequate layer strength, delamination or cracks at the interface, active ingredient or controlled release agent cross-contamination between layers, reduced production yields.

In tablets comprising a metformin layer and a dapagliflozin layer, a high tendency of tablet delamination or layer separation at the interface between metformin layer and dapagliflozin layer has been observed. This tendency is even increased if said layers comprise considerably divergent weight amounts of active ingredients. Thus, for a bilayer tablet having layers comprising considerably divergent weight amounts of active ingredients or having considerably divergent layer weights, there is an even higher tendency to delamination or layer separation at the interface. The present inventors have found out that the problem of providing a bilayer tablet having a good or improved physical and/or chemical stability, especially the problem of providing a bilayer tablet having an advantageous or improved resistance against delamination or layer separation, can be solved by using the same type of binder in the metformin and in the dapagliflozin layer. What is still more, the bilayer tablets of the present invention show the before-mentioned advantages, while they maintain an advantageous tablet hardness, advantageous tableability properties, an advantageous physical stability, and an advantageous or acceptable bilayer tablet volume. Furthermore, it is advantageous that the layers of the bilayer tablets of the present invention are well compatible, so that no or merely few disadvantageous chemical or physical interactions between the layers are observed. Furthermore, the bilayer tablets of the present invention are prepared with granules (especially with metformin containing granules), which show an advantageous or improved flowability (especially shorter flow times) and have as such an advantageous or improved compressibility.

The invention relates to a bilayer tablet comprising metformin extended release formulation as the first layer and dapagliflozin formulation as the second layer, wherein both layers comprising hydroxypropyl cellulose as a binder.

In particular, the present invention provides a pharmaceutical composition, which pharmaceutical composition is a bilayer tablet comprising a first layer, and a second layer, said first layer being a metformin extended release layer, and said first layer comprising metformin and hydroxypropyl cellulose, said second layer comprising dapagliflozin and hydroxypropyl cellulose.

Unless explicitly indicated otherwise, the term "metformin" as used herein is used interchangeably with "metformin or a pharmaceutically acceptable salt thereof, or a solvate of metformin or a solvate of a pharmaceutically acceptable salt of metformin, and mixtures thereof". Unless explicitly indicated otherwise, the term "dapagliflozin" as used herein encompasses "dapagliflozin (especially dapagliflozin in amorphous form) or a pharmaceutically acceptable salt thereof, or a solvate of dapagliflozin or of a pharmaceutically acceptable salt of dapagliflozin (a preferred solvate being dapagliflozin (S) propylene glycol hydrate, especially dapagliflozin (S) propylene glycol hydrate (1:1:1)), and mixtures thereof.

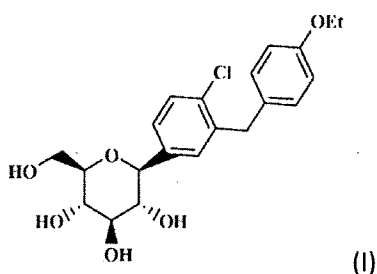
The term "solvates" encompasses hydrates and solvates comprising water and one (or more) organic solvents. Dapagliflozin can be in crystalline or amorphous form. Preferably, dapagliflozin is or comprises dapagliflozin in the amorphous form.

Metformin is preferably metformin hydrochloride. Dapagliflozin is preferably dapagliflozin in the amorphous form (especially dapagliflozin in free form in the amorphous form) or dapagliflozin (S) propylene glycol hydrate, especially dapagliflozin (S) propylene glycol hydrate (1:1:1).

Preferably, in a bilayer tablet the metformin is metformin HCl, and the dapagliflozin is dapagliflozin (S) propylene glycol hydrate or dapagliflozin in amorphous form (especially amorphous dapagliflozin in free form). Especially, in a bilayer tablet the metformin is metformin HCl, and the dapagliflozin is dapagliflozin (S) propylene glycol hydrate. Especially, in a bilayer tablet the metformin is metformin HCl, and the dapagliflozin is dapagliflozin in amorphous form.

The layer comprising metformin (also referred to herein as first layer) preferably comprises metformin (e.g. metformin HCl) in an amount in the range of from about 250 mg to about 1250 mg, more preferably in an amount in the range of from about 500 mg to about 1000 mg, especially about 500 mg or about 1000 mg, calculated as metformin HCl.

In an embodiment of the present invention, the layer comprising dapagliflozin (especially the immediate release layer comprising dapagliflozin) comprises dapagliflozin in an amount in the range of from about 1 mg to about 12 mg, more preferably in an amount in the range of from about 2.5 mg to about 10 mg, especially in an amount of about 2.5 mg, about 5 mg or about 10 mg, calculated as dapagliflozin in free form. Dapagliflozin in free form being the compound of formula (I):



Preferably, the bilayer tablet of the present invention can comprise metformin (e.g. metformin HCl) and dapagliflozin (e.g. dapagliflozin (S) propylene glycol hydrate or dapagliflozin in amorphous form) in the following amounts (per bilayer tablet): 2.5 mg dapagliflozin and 1000 mg metformin, 5 mg dapagliflozin and 500 mg metformin, 5 mg dapagliflozin and 1000 mg metformin, 10 mg dapagliflozin and 500 mg metformin and 10 mg dapagliflozin and 1000 mg metformin, the amount of metformin

(e.g. metformin HCl) being calculated as metformin HCl and the amount of dapagliflozin being calculated as dapagliflozin in free form.

In particular, the second layer comprising dapagliflozin and hydroxypropyl cellulose can be an immediate release layer. This provides the advantage that the bilayer tablet not only provides two different active ingredients, but also provides at least two different release profiles adapted to the respective active ingredients present in the pharmaceutical composition.

A "metformin extended release layer" preferably refers to a layer (especially a layer present in a bilayer tablet) which releases the metformin (e.g. metformin HCl) slowly (i.e. over an extended period of time) following administration. Plasma concentration of the drug is thereby maintained at a therapeutic level for a prolonged period of time (e.g. for at least 4 hours, such as from about 4 to about 24 hours, in particular from about 8 to about 12 hours).

In a preferred embodiment, a metformin extended release layer (which can be in particular present in a pharmaceutical composition comprising a metformin extended release layer) has dissolution properties such that the metformin (present in the metformin layer) dissolves over a time period of at least 6 hours, especially a time period of at least 8 hours, further especially a time period of at least 10 hours, such as a time period of from about 6 to about 24 hours, in particular from about 8 to about 12 hours. Metformin release can be determined *in vitro* using dissolution test procedure applying apparatus 1 - baskets (preferably apparatus 1 - baskets, 20-mesh size), 900 mL of aqueous Phosphate buffer solution pH 6.8 at 37 °C and, preferably at rotation speed of 100 RPM, in particular using dissolution test procedure apparatus 1 - baskets, 20-mesh size and 900 mL of aqueous Phosphate buffer solution pH 6.8 at 37 °C and rotation speed of 100 RPM. Apparatus 1 (baskets) can be in an embodiment the apparatus 1 described in the United States Pharmacopeia, e.g. 29th Edition.

The term "metformin extended release" is also abbreviated herein as "metformin XR".

A "dapagliflozin immediate release layer" preferably refers to a layer (especially a layer present in a bilayer tablet) which releases the dapagliflozin (preferably dapagliflozin is dapagliflozin (S) propylene glycol hydrate or dapagliflozin in amorphous form) immediately following administration. In a preferred embodiment, a dapagliflozin immediate release layer has dissolution properties such that after 45 minutes at least 80 % by weight, more preferably at least 90 % by weight, of the dapagliflozin present in the dapagliflozin immediate release layer is dissolved. In an embodiment, a dapagliflozin immediate release layer has dissolution properties such that after 5 minutes at least 80 % by weight of dapagliflozin is dissolved. Dapagliflozin dissolution can be determined *in vitro* using dissolution test procedure applying apparatus 1 - baskets (preferably apparatus 1 - baskets, 20-mesh size), 900 mL of

aqueous Phosphate buffer solution pH 6.8 at 37 °C and, preferably at rotation speed of 100 RPM, in particular using dissolution test procedure applying apparatus 1 – baskets, 20-mesh size and 900 mL of aqueous Phosphate buffer solution pH 6.8 at 37 °C and rotation speed of 100 RPM.

In particular, the first layer of the bilayer tablet can be a layer comprising

- granule(s) comprising metformin, and hydroxypropyl cellulose (HPC), and optionally one or more further pharmaceutically acceptable excipients; and
- an extra-granular phase comprising one or more pharmaceutically acceptable excipients.

The first layer comprises granule(s) comprising metformin, and HPC; said granule(s) comprising metformin, and HPC can be also referred to herein as "first layer internal phase granule(s)" comprising metformin, and HPC.

Preferably, the granule(s) comprising metformin, and HPC are prepared by wet granulation, especially fluid bed granulation.

Furthermore, the second layer of the bilayer tablet can be preferably a layer comprising

- granule(s) comprising dapagliflozin, and hydroxypropyl cellulose (HPC), and optionally one or more further pharmaceutically acceptable excipients; and
- an extra-granular phase comprising one or more pharmaceutically acceptable excipients.

The second layer comprises granule(s) comprising dapagliflozin, and HPC; said granule(s) comprising dapagliflozin, and HPC can be also referred to herein as "second layer internal phase granule(s)" comprising dapagliflozin, and HPC. Preferably, the granule(s) comprising dapagliflozin, and HPC are prepared by wet granulation, especially fluid bed granulation.

A particularly advantageous embodiment of the pharmaceutical composition of the present invention is a bilayer tablet, wherein the first layer is a layer comprising

- granule(s) comprising metformin, and hydroxypropyl cellulose, and optionally one or more further pharmaceutically acceptable excipients; and
- an extra-granular phase comprising one or more pharmaceutically acceptable excipients, and

wherein the second layer is a layer comprising

- granule(s) comprising dapagliflozin, and hydroxypropyl cellulose, and optionally one or more further pharmaceutically acceptable excipients; and
- an extra-granular phase comprising one or more pharmaceutically acceptable excipients.

The granule(s) comprising metformin, and hydroxypropyl cellulose can be prepared by fluid bed granulation, or the granule(s) comprising dapagliflozin and hydroxypropyl cellulose can be prepared

by fluid bed granulation. Preferably, both the granule(s) comprising dapagliflozin, and HPC, and the granule(s) comprising metformin, and HPC are prepared by wet granulation, more preferably fluid bed granulation.

Optionally, one or both of the first layer and the second layer may comprise further granule(s) which can consist of pharmaceutical excipient(s) or can comprise active ingredients and pharmaceutical excipient(s). Optionally, the first layer is free of dapagliflozin or comprises not more than 1 wt.-%, especially not more than 0.1 wt.-% of dapagliflozin, based on the total weight of the first layer, and the second layer is free of metformin or comprises not more than 1 wt.-%, especially not more than 0.1 wt.-% of metformin, based on the total weight of the second layer.

Pharmaceutically acceptable excipients which can be present in the first layer (e.g. in (internal phase) granule(s) or extragranularly) or in the second layer (e.g. in (internal phase) granule(s) or extragranularly) or both in first and second layer, include but are not limited to disintegrants, binders, diluents, lubricants, glidants, controlled release agents, stabilizers, antioxidants, osmotic agents, colorants, plasticizers, and mixtures thereof. Particularly suitable pharmaceutical excipients and their properties may be e.g. found in texts such as Handbook of Pharmaceutical Excipients, Edited by R.C. Rowe, P.J. Sheskey & M.E. Quinn, Sixth Edition (Published by Pharmaceutical Press, a Division of Royal Pharmaceutical Society of Great Britain). The terms "colorants" and "colouring agent" are used interchangeably in the present application.

Both the first layer and the second layer comprise hydroxypropyl cellulose. Optionally, one or both of first layer and the second layer (especially one or more of granule(s) of first layer, granule(s) of second layer, extragranular phase of first layer, extragranular phase of second layer) may further comprise binder(s) (other than hydroxypropyl cellulose), such as in particular selected from polyvinylpyrrolidone, hydroxypropyl methylcellulose, methylcellulose, and sodium carboxymethyl cellulose, glycol, sucrose, dextrose, corn syrup, polysaccharides (including acacia, tragacanth, guar, alginates and starch), corn starch, pregelatinized starch, modified corn starch, gelatine, polyethylene, polyethylene glycol, and combinations thereof.

Diluent(s), which can be present in the first or second layer or both in first and second layer (especially which can be present in one or more of granule(s) of first layer, granule(s) of second layer, extragranular phase of first layer, extragranular phase of second layer), include, but are not limited to, microcrystalline cellulose, calcium phosphate, starches (in particular corn starch), pregelatinized starch, dextrin, dextrose, mannitol, polydextrose, sucrose, lactose (preferably anhydrous or monohydrate, especially crystalline lactose), glucose, cellulose, polysaccharides (including dextrans and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), cyclodextrins, calcium carbonates,

magnesium carbonates, coprocessed multifunctional excipients such as fructose and starch (commercially available as Advantose FS 95), microcrystalline cellulose and guar gum (commercially available as Avicel CE15), lactose and cellulose (commercially available as Cellactose and Microcelac), or mixtures thereof.

Disintegrant(s), which can be present in the first or second layer or both in first and second layer (especially which can be present in one or more of granule(s) of first layer, granule(s) of second layer, extragranular phase of first layer, extragranular phase of second layer), include, but are not limited to, sodium carboxymethylcellulose, calcium carboxymethylcellulose, starches (e.g. maize starch, wheat starch, potato starch), croscarmellose sodium, crospovidone, modified starches (sodium starch glycolate, pregelatinized starch), low-substituted hydroxypropyl cellulose (comprising from 5 to 16% by weight of hydroxypropyl groups), crosslinked CMC-Na (e.g. Ac-Di-Sol), alginic acid, sodium alginate, guar gum, gellan gum, Xanthan SM, polacrillin potassium, or any mixtures thereof.

Lubricant(s), which can be present in the first or second layer or both in first and second layer (especially which can be present in one or more of granule(s) of first layer, granule(s) of second layer, extragranular phase of first layer, extragranular phase of second layer) include, but are not limited to lubricants such as stearic acid, magnesium stearate, calcium stearate, sodium lauryl sulphate, hydrogenated vegetable oil, hydrogenated castor oil, sodium stearyl fumarate, talc, macrogols, polyethylene glycol, magnesium lauryl sulphate, sodium benzoate, magnesium oxide, magnesium silicate, hydrogenated vegetable oils, waxes, glyceryl behenate, or combinations thereof.

The bilayer tablet of the present invention can further comprise antioxidant(s).

The bilayer tablet of the present invention can further comprise one or more controlled release agents, especially for controlling the release of the metformin from the metformin extended release layer. The one or more controlled release agents can be one or more polymers. The one or more controlled release agents can be one or more polymers (especially hydrophilic polymer(s), in particular hydrophilic polymer(s) (providing modified release)). The one or more controlled release agents can be one or more polymers and can be preferably selected from the group comprising alkyl celluloses, and hydroxyalkyl alkyl celluloses, in particular methyl cellulose (MC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), methyl hydroxyethyl cellulose (MHEC), hydroxypropyl methyl cellulose (HPMC); sodium carboxymethyl cellulose (NaCMC); polymers based on at least one of acrylate and methacrylate; cellulose acetate phthalate (CAP); hydroxypropyl methylcellulose phthalate (HPMCP); hydroxypropyl methylcellulose acetate succinate (HPMC-AS); polyvinyl acetate phthalate (PVAP); sodium alginate; polyethylene oxides (especially one of Polyethylene Oxide WSR N10, WSR N80, WSR N750, and combinations thereof); polyelectrolytes (e.g., alginate, carrageenan, carboxymethyl

cellulose, gum arabic, pectin and xanthan gum; and combinations thereof. More preferably, the controlled release agent is or comprises hydroxypropyl methyl cellulose. Most preferably, the controlled release agent is hydroxypropyl methyl cellulose. Polyethylene oxides can be polyethylene oxides having about 2000 to about 8500 repeating units, preferably having about 2200 to 7000 repeating units.

The bilayer tablet of the present invention can further comprise one or more glidants, which can be selected from the group of talc and silicon dioxide (especially colloidal silicon dioxide), magnesium carbonate, magnesium lauryl sulphate, calcium silicate, talc, and combinations thereof

The bilayer tablet may further comprise a coating. The coating of the bilayer tablets is beneficial as it increases the ease of swallowing. The bilayer tablets of the present invention provide the advantage of having hardness which facilitates an application of a coating.

The pharmaceutical compositions disclosed herein can further comprise one or more colorants, preferably selected from dyes and pigments, e.g. one or more iron oxides. Said dyes and pigments can be titan free.

In particular, the first layer can comprise metformin, and hydroxypropyl cellulose, and can further comprise a controlled release agent, a lubricant, optionally a glidant and optionally a diluent.

The metformin extended release layer preferably comprises hydroxypropyl cellulose (as a binder), hydroxypropyl methyl cellulose (as a controlled release agent), magnesium stearate (as a lubricant), optionally a glidant and optionally a diluent. The metformin extended release layer more preferably comprises hydroxypropyl cellulose (as a binder), hydroxypropyl methyl cellulose (as a controlled release agent), magnesium stearate (as a lubricant), optionally silicon dioxide (as a glidant) and optionally microcrystalline cellulose (as a diluent).

In an embodiment of the present invention, the layer comprising dapagliflozin (especially the immediate release layer comprising dapagliflozin) and HPC further comprises one or more of the following additional excipients: one or more diluents, preferably two or more diluents, one or more binders (said one or more binders being binders other than hydroxypropyl cellulose (HPC)), one or more disintegrants, one or more lubricants, one or more glidants, one or more colorants, and combinations thereof.

In particular, the second layer can comprise dapagliflozin, hydroxypropyl cellulose, and further comprises a diluent (preferably at least one, more preferably at least two diluents), a disintegrant, a lubricant and optionally a glidant and optionally a colorant. Especially, the second layer comprises dapagliflozin, hydroxypropyl cellulose, and further comprises microcrystalline cellulose and isomalt,

sodium croscarmellose, magnesium stearate, and optionally talc or silicon dioxide. The second layer comprising dapagliflozin and hydroxypropyl cellulose is preferably a dapagliflozin immediate release layer.

Dapagliflozin immediate release layer preferably comprises hydroxypropyl cellulose (as a binder), one or two diluents, a disintegrant, a lubricant and optionally a glidant and optionally a colorant. Preferably, dapagliflozin layer comprises hydroxypropyl cellulose (as a binder), microcrystalline cellulose and isomalt (as diluents), sodium croscarmellose (as a disintegrant), magnesium stearate (as a lubricant) and at least one of talc and silicon dioxide (as a glidant).

In a preferred embodiment, at least one or preferably both of first and second layer can comprise a hydroxypropyl cellulose having a weight-average molecular weight in the range of from 40,000 to 140,000 g/mol, preferably in the range of from 75,000 to 85,000 g/mol, especially of about 80,000 g/mol; weight-average molecular weight can be determined using size exclusion chromatography. Types of hydroxypropyl cellulose which can be used as a binder in at least one or preferably both of first and second layer can be in particular one or more of hydroxypropyl cellulose EF, EXF, SSL, I, JF. The preferred type of hydroxypropyl cellulose used as a binder in both layers is hydroxypropyl cellulose EF. The bilayer tablet may further comprise a coating, especially a film coating. Optionally, two or more coatings can be present. Particularly suitable coatings are film-forming polymers, such as, for example, those from the group of polyvinyl alcohol, polymethacrylates and derivatives thereof, cellulose derivatives, especially hydroxypropyl methylcellulose (HPMC), dextrans, starches, natural gums, such as, for example, gum arabic, xanthans, alginates. The coating may be applied to the bilayer tablet as solution(s) or suspension(s) by means of the various pharmaceutical conventional method known to the skilled person working in the present field of the art, such as film coating. The coating can be for example applied as solution or suspension which, in addition to any film-forming polymer present, may further comprise one or more adjuvants, such as e.g. one or more of plasticisers, surfactants, hydrophilizers, dyes and pigments. In a preferred embodiment, the coating is a film coating comprising partially hydrolysed polyvinyl alcohol, calcium carbonate, polyethylene glycol (PEG), and talc.

In an embodiment of the pharmaceutical composition of the present invention, the first layer can comprise metformin (preferably metformin HCl) in an amount of preferably 40 to 90 wt.-%, based on the total weight of the first layer, and hydroxypropyl cellulose in an amount of 1 to 10 wt.-%, based on the total weight of the first layer, and optionally further comprises a controlled release agent, a lubricant, optionally a glidant and optionally a diluent.

In an embodiment of the pharmaceutical composition of the present invention, the first layer comprises metformin in an amount of 50 to 90 wt.-%, preferably 70 to 80 wt.-%, based on the total

weight of the first layer, and hydroxypropyl cellulose in an amount of 3 to 10 wt.-%, preferably 3.5 to 7 wt.-%, based on the total weight of the first layer, and optionally further comprises a controlled release agent, a lubricant, optionally a glidant and optionally a diluent; wherein preferably said first layer comprises metformin (preferably metformin HCl) in an amount of from 800 to 1200 mg, especially in an amount of 1000 mg. Optionally, in this embodiment of the pharmaceutical composition of the present invention, the pharmaceutical composition can comprise metformin in a (total) amount of from 800 to 1200 mg, especially in a (total) amount of 1000 mg, preferably metformin HCl in a (total) amount of from 800 to 1200 mg, more preferably metformin HCl in a (total) amount of 1000 mg.

In a preferred embodiment, the first layer comprises 1000 mg metformin (preferably metformin HCl) which is comprised in an amount of 50 to 90 wt.-%, preferably 70 to 80 wt.-%, based on the total weight of the first layer, and

hydroxypropyl cellulose in an amount of 3 to 10 wt.-%, preferably 3.5 to 7 wt.-%, based on the total weight of the first layer. Optionally, the first layer further comprises a controlled release agent, a lubricant; further optionally, the first layer further comprises a controlled release agent, a lubricant and a diluent.

In a preferred embodiment, the first layer comprises 1000 mg metformin (preferably metformin HCl), which is comprised in an amount of 50 to 90 wt.-%, preferably 70 to 80 wt.-%, based on the total weight of the first layer, and

hydroxypropyl cellulose in an amount of 3 to 10 wt.-%, preferably 3.5 to 7 wt.-%, based on the total weight of the first layer,

a controlled release agent (preferably hydroxypropyl methylcellulose) in an amount in the range of from 6 to 22 wt.-%, preferably 9 to 19 wt.-%, based on the total weight of the first layer, and a lubricant, preferably in an amount in the range of from 0.2 to 1 wt.-%, preferably 0.4 to 0.8 wt.-%, based on the total weight of the first layer, and optionally a diluent.

A first layer, which comprises metformin in an amount of from 800 to 1200 mg, preferably in an amount of 1000 mg, can be preferably a first layer which comprises metformin HCl in an amount of from 800 to 1200 mg, preferably in an amount of 1000 mg metformin HCl.

In another aspect, the first layer comprises 500 mg metformin (preferably metformin HCl) which is comprised in an amount of 40 to 60 wt.-%, preferably 45 to 55 wt.-%, based on the total weight of the first layer, and

hydroxypropyl cellulose in an amount of 1 to 7 wt.-%, preferably 2 to 5 wt.-%, based on the total weight of the first layer. Optionally, the first layer further comprises a controlled release agent, a lubricant; further optionally, the first layer further comprises a controlled release agent, a lubricant, and a

diluent; still further optionally, the first layer further comprises a controlled release agent, a lubricant, a glidant and a diluent.

In particular, the first layer can comprise 500 mg metformin (preferably metformin HCl), which is comprised in an amount of 40 to 60 wt.-%, preferably 45 to 55 wt.-%, based on the total weight of the first layer, and hydroxypropyl cellulose in an amount of 1 to 7 wt.-%, preferably 2 to 5 wt.-%, based on the total weight of the first layer, a controlled release agent (preferably hydroxypropyl methylcellulose) in an amount in the range of from 20 to 50 wt.-%, preferably 30 to 40 wt.-%, based on the total weight of the first layer, and a lubricant, preferably in an amount in the range of from 0.2 to 1 wt.-%, preferably 0.4 to 0.8 wt.-%, based on the total weight of the first layer, and optionally a diluent.

In another aspect, the first layer can comprise 500 mg metformin (preferably metformin HCl), which is comprised in an amount of 40 to 60 wt.-%, preferably 45 to 55 wt.-%, based on the total weight of the first layer, and

hydroxypropyl cellulose in an amount of 1 to 7 wt.-%, preferably 2 to 5 wt.-%, based on the total weight of the first layer,

a controlled release agent (preferably hydroxypropyl methylcellulose) in an amount in the range of from 20 to 50 wt.-%, preferably 30 to 40 wt.-%, based on the total weight of the first layer,

a diluent (preferably microcrystalline cellulose) in an amount in the range of from 1 to 20 wt.-%, preferably 5 to 15 wt.-%, based on the total weight of the first layer,

a glidant (preferably silicon dioxide) in an amount in the range of from 0.2 to 2 wt.-%, preferably 0.5 to 1.5 wt.-%, based on the total weight of the first layer, and

a lubricant, preferably in an amount in the range of from 0.2 to 1 wt.-%, preferably 0.4 to 0.8 wt.-%, based on the total weight of the first layer.

Preferably, a first layer comprising 500 mg metformin is a first layer comprising 500 mg metformin HCl.

The controlled-release agent can be present intragranularly or extragranularly (especially extragranularly) in the first layer. Lubricant can be preferably present extragranularly in the first layer. HPC can be present intragranularly in the first layer. In an embodiment, HPC can be present intragranularly (in the granules comprising metformin) in the first layer, but is not present extragranularly in the first layer. In an embodiment, HPC can be present intragranularly in first and second layer, but is not present extragranularly in first and second layer.

In a preferred embodiment, the first layer comprises granule(s) comprising metformin and HPC, which granule(s) comprise metformin in an amount of 82 to 98 wt.-%, preferably 88 to 97 wt.-%, based on the total weight of the granule(s) comprising metformin and HPC (present in the first layer), and hydroxypropyl cellulose in an amount of 3 to 10 wt.-%, preferably 4 to 7 wt.-%, based on the total weight of the granule(s) comprising metformin and HPC (present in the first layer), and optionally one or more further pharmaceutically acceptable excipients.

In a preferred embodiment, the layer comprising dapagliflozin and HPC further comprises two or more diluents (especially three or more diluents), which can be preferably selected from microcrystalline cellulose, isomalt, lactose (especially crystalline lactose), dextrate, calcium phosphate, starch (especially corn starch), pregelatinized starch, dextrin, dextrose, mannitol, polydextrose, sucrose, and combinations thereof. Especially, the layer comprising dapagliflozin and HPC can further comprise two or more diluents comprising at least one of microcrystalline cellulose, isomalt, lactose (especially crystalline lactose), dextrate, calcium phosphate, starch (especially corn starch), pregelatinized starch, dextrin, dextrose, mannitol, polydextrose, sucrose, and combinations thereof. Further especially, the layer comprising dapagliflozin and HPC can further comprise two or more diluents comprising at least two of microcrystalline cellulose, isomalt, lactose (especially crystalline lactose), dextrate, calcium phosphate, starch (especially corn starch), pregelatinized starch, dextrin, dextrose, mannitol, polydextrose, sucrose, and combinations thereof. Still further especially, the layer comprising dapagliflozin and HPC can further comprise three or more diluents comprising at least three of microcrystalline cellulose, isomalt, lactose (especially crystalline lactose), dextrate, calcium phosphate, starch (especially corn starch), pregelatinized starch, dextrin, dextrose, mannitol, polydextrose, sucrose, and combinations thereof.

In an embodiment of the present invention, the diluent (in the second layer comprising dapagliflozin) is or comprises microcrystalline cellulose, and isomalt. In an embodiment, microcrystalline cellulose is both present in the granules comprising dapagliflozin and extragranularly in the second layer.

In an embodiment of the present invention, the second layer (comprising dapagliflozin) comprises diluent in an amount in the range of from about 75% by weight to about 95% by weight (relative to the total weight of the layer comprising dapagliflozin), preferably in an amount in the range of from about 75% by weight to about 92% by weight, more preferably in an amount in the range of from about 80% by weight to about 90% by weight, each relative to the total weight of the layer comprising dapagliflozin. In particular, the second layer (comprising dapagliflozin) comprises diluent in an amount in the range of from about 86% by weight to about 91% by weight, especially in the range of from about 87.0 % by weight to about 90.0 % by weight, each relative to the total weight of the layer

comprising dapagliflozin. Preferably, the second layer, which comprises from 3 to 7 mg dapagliflozin, comprises diluent in an amount in the range of from about 88,5% by weight to about 90,5% by weight, especially in an amount of about 89.5% by weight (each relative to the total weight of the layer comprising dapagliflozin). Preferably, the second layer, which comprises from 8 to 12 mg dapagliflozin, comprises diluent in an amount in the range of from about 86,5% by weight to about 88,4% by weight, especially in an amount of about 87.5% by weight, each relative to the total weight of the layer comprising dapagliflozin.

In the second layer comprising dapagliflozin and HPC and diluent(s), the weight ratio HPC: diluent(s) can be in particular in the range 1:20 to 1:45, preferably 1:25 to 1:36.

The granules comprising dapagliflozin (which are present in the second layer comprising dapagliflozin) can further comprise diluent(s) in an amount in the range of from about 75% by weight to about 95% by weight, preferably in an amount in the range of from about 75% by weight to about 92% by weight, more preferably in an amount in the range of from about 82% by weight to about 92% by weight, especially in an amount in the range of from about 82% by weight to about 91% by weight, in particular in an amount in the range of from about 87% by weight to about 91% by weight (each relative to the total weight of the said granules comprising dapagliflozin), optionally said granules further comprise one or more glidant(s). Preferably, dapagliflozin is present in the granules comprising dapagliflozin (which are present in the second layer comprising dapagliflozin) in an amount in the range of from about 1% by weight to about 20% by weight, preferably in an amount in the range of from about 3% by weight to about 20% by weight, more preferably in an amount in the range of from about 2% by weight to about 10% by weight, especially in an amount in the range of from about 2% by weight to about 6% by weight (each relative to the total weight of said granules comprising dapagliflozin). In an embodiment of the pharmaceutical composition of the invention, dapagliflozin is present in the granules comprising dapagliflozin (which are present in the second layer comprising dapagliflozin) in an amount in the range of from about 1.5 % by weight to about 4.0% by weight, especially in an amount of about 2.8 % by weight (each relative to the total weight of said granules comprising dapagliflozin), and the pharmaceutical composition comprises a total amount of from 3 to 7 mg (especially about 5 mg) dapagliflozin. In an embodiment of the pharmaceutical composition of the invention, dapagliflozin is present in the granules comprising dapagliflozin (which are present in the second layer comprising dapagliflozin) in an amount in the range of from about 4.0 % by weight to about 7.0% by weight, especially in an amount of about 5.5 % by weight (each relative to the total weight of said granules comprising dapagliflozin), and the pharmaceutical composition comprises a total amount of from 8 to 12 mg (especially about 10 mg) dapagliflozin.

Preferably, in the granules comprising dapagliflozin, HPC, and optionally glidant (which granules are present in the layer comprising dapagliflozin (second layer)), diluent(s) are present in an amount in the range of from about 75% by weight to about 92% by weight (relative to the total weight of the said granules comprising dapagliflozin), preferably in an amount in the range of from about 82% by weight to about 91% by weight. In particular, in the granules comprising dapagliflozin, HPC, and optionally glidant, the weight ratio HPC: diluent(s) can be in the range 1:20 to 1:45, preferably 1:25 to 1:36. In this embodiment, preferably glidant is talc.

The granules comprising dapagliflozin, HPC, and optionally glidant (which granules are present in the layer comprising dapagliflozin) are preferably prepared by wet granulation, most preferably prepared by fluid bed granulation. As liquid used for wet granulation, preferably fluid bed granulation, a liquid which is or comprises water or an organic solvent, more preferably is or comprises ethanol, especially is ethanol, can be used.

The granules comprising metformin and HPC (which granules are present in the first layer comprising metformin) are preferably prepared by wet granulation, most preferably prepared by fluid bed granulation. As liquid used for wet granulation, preferably fluid bed granulation, a liquid which is or comprises water and optionally organic solvent, more preferably is or comprises water, can be used.

In an embodiment of the present invention, the layer comprising metformin and HPC further comprises one or more of the following additional excipients: (a) one or more diluents, preferably two or more diluents, (b) one or more binders (said one or more binders being binders other than hydroxypropyl cellulose (HPC)), (c) one or more disintegrants, (d) one or more lubricants, (e) one or more glidants, (f) one or more colorants, and combinations thereof.

In a preferred embodiment, the layer comprising dapagliflozin and HPC comprises granules comprising dapagliflozin and HPC, which granules further comprise two or more diluents, preferably selected from microcrystalline cellulose, isomalt, lactose (especially crystalline lactose), dextrate, calcium phosphate, starch (especially corn starch), pregelatinized starch, dextrin, dextrose, mannitol, polydextrose, sucrose, and combinations thereof. Especially, the layer comprising dapagliflozin and HPC comprises granules comprising dapagliflozin and HPC, which granules can further comprise two or more diluents comprising at least one of microcrystalline cellulose, isomalt, lactose (especially crystalline lactose), dextrate, calcium phosphate, starch (especially corn starch), pregelatinized starch, dextrin, dextrose, mannitol, polydextrose, sucrose, and combinations thereof. Further especially, the layer comprising dapagliflozin and HPC comprises granules comprising dapagliflozin and HPC, which granules can further comprise two or more diluents comprising at least two of microcrystalline cellulose, isomalt,

lactose (especially crystalline lactose), dextrate, calcium phosphate, starch (especially corn starch), pregelatinized starch, dextrin, dextrose, mannitol, polydextrose, sucrose, and combinations thereof.

The second layer comprises an extra-granular phase comprising one or more pharmaceutically acceptable excipient(s). Preferably, this extra-granular phase comprises a diluent, a disintegrant, and optionally a lubricant and optionally a colorant. More preferably, this extra-granular phase comprises a diluent, a disintegrant, and a lubricant and optionally a colorant. Especially, this extra-granular phase can comprise a diluent in the range of about 80 to 92 wt.%, preferably in the range of about 84 to 90 wt.%, a disintegrant, in the range of about 4 to 10 wt.%, preferably in the range of about 6 to 9 wt.%, each based on the total weight of the extra-granular phase of the second layer, and optionally a lubricant and optionally a colorant.

Preferably, the pharmaceutical composition is an oral pharmaceutical composition. The term bi-layer tablet as used herein, encompasses also tablets comprising more than two layers, e.g. three layers. Optionally, the first layer and the second layer are separated by a layer (e.g.) consisting of one or more excipients separating first and second layer. Preferably, in the bilayer tablet, first and second layer are in direct contact.

In a preferred embodiment, the weight ratio of the total weight of the first layer to the total weight of the second layer is in the range of from 1:2 to 1:6, more preferably in the range of from 1:3 to 1:5, (e.g. in the range of from 1:3.5 to 1:5), even more preferably in the range of from 1:3.2 to 1:4.6.

Preferably, in the bilayer tablets of the present invention, the first layer is a compressed compression mixture which is obtainable by subjecting a compression mixture comprising

- granule(s) comprising metformin, and hydroxypropyl cellulose, and optionally one or more further pharmaceutically acceptable excipients; and

- an extra-granular phase comprising one or more pharmaceutically acceptable excipients, to compression, preferably the metformin containing granules being granules prepared by wet granulation, more preferably by fluid bed granulation, and

said second layer is a compressed compression mixture which is obtainable by subjecting a compression mixture comprising

- granule(s) comprising dapagliflozin, and hydroxypropyl cellulose, and optionally one or more further pharmaceutically acceptable excipients; and

- an extra-granular phase comprising one or more pharmaceutically acceptable excipients, to compression, preferably the dapagliflozin containing granules being granules prepared by wet granulation, more preferably by fluid bed granulation.

Wet granulation and fluid bed granulation are procedures known in the present field of the art. As used herein, the term wet granulation encompasses fluid bed granulation.

In particular, fluid bed granulation can comprise spraying a solution or suspension, said solution or suspension preferably comprising a binder, especially HPC, said solution or suspension comprising optionally further pharmaceutically acceptable excipients and optionally active ingredient, on active ingredient (e.g. metformin or dapagliflozin) in a fluidised bed, thereby performing a fluid bed granulation to obtain granules. Preferably, said solution or suspension comprises water or organic solvent, more preferably water and optionally organic solvent.

Moreover, fluid bed granulation can comprise spraying a solution or suspension, comprising a binder, preferably HPC, on metformin or a mixture of metformin with one or more pharmaceutically acceptable excipients in a fluidised bed, thereby performing a fluid bed granulation to obtain granules.

Furthermore, fluid bed granulation can comprise spraying a solution or suspension, said solution or suspension preferably comprising a binder, especially HPC and optionally one or more further binders and dapagliflozin, on a mixture comprising pharmaceutically acceptable excipients in a fluidised bed, thereby performing a fluid bed granulation to obtain granules. Preferably, said solution or suspension comprises water or an organic solvent, preferably comprises organic solvent, more preferably comprises ethanol.

In another aspect the present invention, there is provided a method for a manufacturing of a bilayer tablet, wherein the processes for preparation of the compression mixtures for both layers comprise a fluid bed granulation process.

Another aspect of the invention relates to a process for the preparation of a pharmaceutical composition which is a bilayer tablet, especially to a process for the preparation of a pharmaceutical composition as described above, the process comprising:

A) preparing a phase comprising metformin, said preparing of a phase comprising metformin comprising:

A-1) dissolving hydroxypropyl cellulose (as a binder) in a liquid, which liquid preferably is or comprises water or an organic solvent (in particular ethanol), e.g. which liquid is water or ethanol or a mixture of water and ethanol, more preferably is or comprises water, to obtain a granulation liquid;

A-2) spraying the granulation liquid onto metformin, optionally spraying the granulation liquid onto a mixture of metformin with one or more intragranular excipients to obtain granules comprising metformin;

A-3) adding a controlled release agent, a lubricant, optionally a glidant and optionally a diluent, to the granulate obtained in step A-2) to obtain the phase comprising metformin;

B) preparing a phase comprising dapagliflozin, said preparing of a phase comprising dapagliflozin comprises:

B-1) dissolving hydroxypropyl cellulose (as a binder) and dapagliflozin in a liquid, which liquid preferably is or comprises water or an organic solvent, more preferably is or comprises ethanol to obtain a granulation liquid;

B-2) preparing a mixture of one or more pharmaceutically acceptable excipients, preferably a mixture of one or more pharmaceutically acceptable excipients comprising diluent(s) and optionally glidant, to obtain a homogenous mixture of excipients;

B-3) spraying the granulation liquid onto the mixture of one or more pharmaceutically acceptable excipients to obtain granules;

B-4) adding one or more (extragranular) diluents, one or more (extragranular) disintegrants, optionally one or more colorants and one or more lubricants to the granules obtained in step B-3) to obtain the phase comprising dapagliflozin;

C) bilayer tableting of metformin phase and dapagliflozin phase, thereby obtaining bilayer tablet;

D) optionally film coating of the bilayer tablet.

In preferred embodiments, the metformin and dapagliflozin phases are prepared by wet granulation; preferably metformin phase is prepared by aqueous wet granulation and dapagliflozin phase is prepared by wet granulation using an organic solvent. Preferably, the metformin and dapagliflozin phases are prepared by fluid bed granulation.

Moreover, the present invention pertains to a bilayer tablet which is obtainable by the processes disclosed herein, especially by the process comprising steps A) to D) as defined herein, further especially by the process as defined in appended process claim (claim 14).

In a preferred process for the preparation of a pharmaceutical composition which is a bilayer tablet, step A-2 is:

A-2) spraying the granulation liquid onto a mixture of metformin with one or more intragranular excipients, said one or more intragranular excipients comprising hydroxypropyl cellulose, to obtain granules comprising metformin and hydroxypropyl cellulose.

Moreover, a bilayer tablet of the present invention can comprise a first layer comprising granules comprising metformin, said granules comprising metformin being obtainable according to steps A-1 to A-2 as defined supra.

Furthermore, a bilayer tablet of the present invention can comprise a second layer comprising granules comprising dapagliflozin, said granules comprising dapagliflozin being obtainable according to steps B-1 to B-3 as defined supra.

As evidenced in the examples section the composition according to the present invention is characterized by improved flow times. The wet granulation of metformin using hydroxypropyl cellulose provides for flowable granulate and flowable mixture for compression, which is evidenced by shorter flow times and lower Hausner ratios in contrast to the composition known from the prior art.

The Hausner ratio is defined as the ratio of a powder's tapped bulk density to its poured (loose) bulk density. This ratio can be applied to provide an index of the flow character of a powder (Table 1 below).

Table 1: Powder flowability based on the Hausner ratio

Flow character	Hausner ratio
Excellent	1.00 – 1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 – 1.45
Very poor	1.46 – 1.59
Very, very poor	> 1.60

The metformin granules and the mixture for compression exhibits good or fair flow character, whereas the composition according to the prior art exhibits only passable or even poor flowability. Compositions of the prior art therefore often have the disadvantage of requiring comparatively high compression forces and/or of showing a disadvantageously low tablet hardness. In contrast thereto, bilayer tablets of the present invention provide an advantageous hardness, even without applying high compression forces.

If the mass of the first layer is considerably higher than the mass of the second layer, the variation of the first layer can significantly influence the variation of second layer that contains a low dose of dapagliflozin.

Hausner ratio is also connected with compressibility since it represents the ratio between untapped bulk volume and (final) tapped bulk volume of powder material (European Pharmacopeia 11.5, "2.9.34. Bulk Density of Powders"). Hausner ratio is an indirect measure of the property of a bulk material to

reduce its volume under mechanical influence. It is also a measure of the ability to compress and of the interaction between the particles.

The granules comprising metformin (which are used for preparing the first layer) can e.g. have a Hausner ratio in the range of from 1.00 to 1.59, preferably in the range of from 1.00 to 1.45, more preferably in the range of from 1.00 to 1.34, especially of from 1.12 to 1.25, further especially of from 1.12 to 1.18.

Moreover, the phase comprising metformin prepared in step A) of the process of the present invention can comprise metformin granules, which have a Hausner ratio in the range of 1.00 to 1.59, preferably in the range of from 1.00 to 1.45, more preferably in the range of from 1.00 to 1.34, especially of from 1.12 to 1.25, further 1.12 to 1.18. The phase comprising metformin prepared in step A) of the process of the present invention can have a Hausner ratio in the range of 1.00 to 1.59, preferably in the range of from 1.00 to 1.45, more preferably in the range of from 1.00 to 1.34, especially of from 1.12 to 1.25, further 1.12 to 1.18. Furthermore, the granules obtained in step A-2) of the process of the present invention can have a Hausner ratio in the range of 1.00 to 1.59, preferably in the range of from 1.00 to 1.45, more preferably in the range of from 1.00 to 1.34, especially of from 1.12 to 1.25, further 1.12 to 1.18. Further, the granule(s) comprising metformin and HPC, and optionally one or more further pharmaceutically acceptable excipients, which are present in the compression mixture comprising granule(s) comprising metformin and HPC, and optionally one or more further pharmaceutically acceptable excipients can have a Hausner ratio in the range of 1.00 to 1.59, preferably in the range of from 1.00 to 1.45, more preferably in the range of from 1.00 to 1.34, especially of from 1.12 to 1.25, further 1.12 to 1.18. The compression mixture comprising granule(s) comprising metformin and HPC, and optionally one or more further pharmaceutically acceptable excipients can have a Hausner ratio in the range of 1.00 to 1.59, preferably of from 1.00 to 1.45, more preferably in the range of from 1.00 to 1.34, especially of from 1.12 to 1.25, further 1.12 to 1.18.

The Hausner ratio (H) is the ratio of untapped bulk volume to final tapped bulk volume:

$$H = \frac{\text{untapped bulk volume}}{\text{final tapped bulk volume}}$$

The determinations of the untapped bulk volume and final tapped bulk volume, respectively, can be performed according to European Pharmacopeia 11.5, "2.9.34. Bulk Density of Powders", "METHOD 1: MEASUREMENT IN A GRADUATED CYLINDER".

It is evidenced by Example 3, table 4, that with the pharmaceutical composition according to the present invention a wide varieties of tablet hardness can be achieved and that different tablet hardness does not influence the dissolution profile of the active ingredients from the tablets.

The pharmaceutical compositions of the present invention are for use in a method of treating diseases or disorders associated with metabolic disorders, especially for use in a method of treating or preventing a glucose related disorder, chronic heart failure, chronic kidney disease, and cardiovascular disease.

The pharmaceutical compositions are for use in methods for the treatment or prevention (including delay in the progression or onset of) of "glucose-related disorders". As used herein, the term "glucose related disorder" encompasses any disorder which is characterized by or is developed as a consequence of elevated glucose levels. Glucose-related disorders shall include diabetes mellitus (in particular type 1 or type 2 diabetes mellitus), insulin resistance, delayed wound healing, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glucose, postprandial hyperglycemia, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, hypertension, hypercholesterolemia, mixed dyslipidemia, fatty liver, nonalcoholic fatty liver disease, and combinations thereof.

Furthermore, the pharmaceutical compositions are for use in a method of treating diseases or disorders associated with metabolic disorders. As used herein, the term "diseases or disorders associated with metabolic disorders" encompasses any disorder which is characterized by or is developed as a consequence of a metabolic disorder. Diseases or disorders associated with metabolic disorders shall include "glucose-related disorders", chronic heart failure, chronic kidney disease, and cardiovascular disease.

In one embodiment, the pharmaceutical compositions of the present invention are for use 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 2 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; and
- 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 present invention is illustrated in more detail below by the following non-limiting examples:

Examples**Example 1, Comparative Example**

Process	Name of the ingredient	Strength	Function
		10/1000	
		mg/unit	
METFORMIN LAYER			
Intragranular			
High shear granulation	Metformin hydrochloride	1000.00	Active ingredient
	Na-carboxymethylcellulose	50.00	Binder
	Magnesium stearate	5.00	Glidant
	Water, purified ¹	q.s.	Solvent
Metformin granules total		1055.00	-
Extragranular			
Blending 1	Hydroxypropyl methylcellulose K100M	235.00	Controlled-release agent
	Colloidal Silicon Dioxide	13.00	Glidant
	Magnesium stearate	2.00	Lubricant
Metformin compression mixture / 1 st layer total		1305.00	-
DAPAGLIFLOZIN LAYER			
Intragranular			
Roller compaction	Dapagliflozin	10	Active ingredient
	Lactose Anhydrous	48	Diluent
	Microcrystalline Cellulose 302	222.5	Diluent
	Crospovidone	6.00	Disintegrant
	Colloidal Silicon Dioxide	2.25	Glidant
	Magnesium stearate	1.50	Lubricant
Dapagliflozin granules total		290.25	-
Extragranular			
Blending 2	Crospovidone	6.00	Disintegrant
	Colloidal Silicon Dioxide	2.25	Glidant
	Magnesium stearate	1.50	Lubricant
Dapagliflozin compression mixture / 2 nd layer total		300.000	-
Bilayer tablet core total		1605.000	
FILM COATING			
Coating	Opadry II	40.000	Coating mixture
Modified-release tablet total		1645.000	-

Bilayer tablets prepared by HSM granulation with Na-carboxymethylcellulose as a binder according to WO2011060256, Example 7.

Metformin granulation

Metformin HCl, 0.5% magnesium stearate, and sodium carboxymethyl cellulose were combined and mixed into a high shear granulator for one minute. Purified water, using a nozzle, was added with stirring for one minute. The wet granulated material was passed through a mill and then dried until the moisture content was 1.0% or less. The dried material containing metformin HCl, 0.5% magnesium

stearate, and sodium carboxymethyl cellulose was passed through a mill and discharged into polyethylene-lined drums to provide milled metformin lg bulk granulation.

Metformin compression mixture preparation

Metformin (milled lg bulk granulation), hydroxypropyl methylcellulose 2208 USP (100,000 centipoise) (Methocel K100M Premium), and silicon dioxide were added to a bin blender and mixed for 120 revolutions. Magnesium stearate was added, and after 60 revolutions, the material was discharged into polyethylene-lined drums to provide reduced mass metformin extended release lg bulk granulation.

Dapagliflozin granulation

Dapagliflozin was blended with microcrystalline cellulose, anhydrous lactose, a portion of croscopvidone, and a portion of silicon dioxide in a suitable tumble mixer and passed through a suitable conical mill. A portion of magnesium stearate (screened) was blended into the mixture and then compacted using an appropriate roller compactor. The compacted mixture was reduced to form granules.

Dapagliflozin compression mixture preparation

The granules were blended with the remaining amount of croscopvidone and silicon dioxide in a suitable tumble mixer. The granules were then blended with the remaining amount of magnesium stearate in a suitable tumble mixer.

Bilayer tableting

A bilayer tablet press was with the metformin XR formulation in the first hopper and the SGLT2 inhibitor formulation that is dapagliflozin granulation (2.5 mg, 5 mg or 10 mg strength) in the second hopper. The tablet press was set to obtain the target weight for the first layer (metformin XR). The second hopper was opened and the tablet press was adjusted to obtain the target tablet weight of dapagliflozin and metformin XR bilayer tablets. Once the target weight was obtained the press was adjusted to obtain the target hardness. Once the hardness was obtained, the manufactured tablets were periodically monitored regarding the weight of the first layer, and the weight, hardness, gauge and friability of the whole tablet.

Film coating

The collected bilayer tablets were film coated with Opadry® II PVA (polyvinyl alcohol).

Example 2

Process	Name of the ingredient	Strength	Function
		10/1000	
		mg/unit	
METFORMIN LAYER			
Intragranular			
Fluid bed granulation 1	Metformin hydrochloride	1000.000	Active ingredient
	Hydroxypropyl Cellulose	63.000	Binder
	Water (purified) ¹	q.s.	Solvent
Metformin granules total		1063.000	-
Extragranular			
Blending 1	Hydroxypropyl methylcellulose K100M	235.000	Controlled-release agent
	Magnesium stearate	7.000	Lubricant
Metformin compression mixture / 1 st layer total		1305.000	-
DAPAGLIFLOZIN LAYER			
Intragranular			
Fluid bed granulation 2	Dapagliflozin propanediol monohydrate *)	12.300	Active ingredient
	Cellulose, microcrystalline PH102	110.860	Diluent
	Izomalt GaleniQ 721	47.510	Diluent
	Hydroxypropyl Cellulose	8.700	Binder
	Talc	1.500	Glidant
	Ethanol, absolute ¹	q.s.	Solvent
Dapagliflozin granules total		180.870	-
Extragranular			
Blending 2	Cellulose, microcrystalline PH200	104.080	Diluent
	Croscarmellose sodium	9.000	Disintegrant
	Iron oxide, yellow (E172)	0.050	Colouring agent/Colorant
	Magnesium stearate	6.000	Lubricant
Dapagliflozin compression mixture / 2 nd layer total		300.000	-
Bilayer tablet core total		1605.000	
FILM COATING			
Coating	Opadry TF titanium free PVA coating mixture	39.000	Coating mixture
	Iron oxide, yellow (E172)	1.000	Colouring agent/Colorant
	Water(purified) ¹	q.s.	Solvent
Modified-release tablet total		1645.000	-

*) In the present Examples, as "Dapagliflozin propanediol monohydrate" dapagliflozin (S) propylene glycol hydrate is used.

1) The solvent is removed from the composition during the process.

Metformin granulation

Purified water or Absolute ethanol or mixture of the two was weighed into a stainless-steel vessel. Hydroxypropyl cellulose was slowly added to purified water during mixing. Dispersion was mixed as long that the clear dispersion is produced.

Metformin hydrochloride was crushed and sieved. The granulation liquid was sprayed onto metformin hydrochloride by top spraying process in fluid bed granulator. The process parameters were adjusted to achieve sufficient mixing of the product and target temperature of the product during spraying of about 28 - 40°C. After finished spraying, drying of the granulate is performed, until prescribed LOD (< 1 %) was achieved. Dry granulate was sieved.

Metformin compression mixture preparation

Hydroxypropyl methylcellulose K100M was optionally sieved. Magnesium stearate was sieved through a 0.8 mm mesh sieve. Hydroxypropyl methylcellulose K100M was firstly added to the metformin granulate and blended for approx. 200 revolutions. Then sieved magnesium stearate was added and blended for further 30 revolutions.

Dapagliflozin granulation

Absolute ethanol was poured into a stainless-steel vessel. Dapagliflozin propanediol monohydrate was slowly added to absolute ethanol during mixing. Then, hydroxypropyl cellulose was slowly added during mixing. Dispersion was mixed as long that the clear dispersion was produced.

The granulation liquid was sprayed onto powders of cellulose, microcrystalline PH102, Izomalt GaleniQ 721 and talc by top spraying process in fluid bed granulator. The process parameters were adjusted to achieve sufficient mixing of the product and temperature of the product during spraying of about 18 - 28°C. After spraying, wet granulate was dried until the temperature of granulate reaches 36 °C.

Dry granulate was sieved using a conical sieving device.

Dapagliflozin compression mixture preparation

Cellulose, microcrystalline PH200 and Croscarmellose sodium were optionally sieved. Cellulose, microcrystalline PH200, Croscarmellose sodium and triturate of Iron oxide, yellow (E172) were added to the dapagliflozin granulate and blended for approx. 200 revolutions. Then sieved magnesium stearate was added and blended for further 30 revolutions.

Bilayer tableting

The compression mixtures were compressed into tablets using an automatic rotary bilayer tableting machine. The first layer contains metformin and the second layer contains dapagliflozin. Firstly, the tablet press was set to obtain the target weight for the first layer. The second hopper was opened and the tablet press was adjusted to obtain the target bilayer tablet weight of dapagliflozin and metformin XR.

Film coating

The collected bilayer tablets were film coated with a coating mixture based on PVA (polyvinyl alcohol) that does not contain titanium dioxide (Opadry® coating mixture).

Example 3

The results of different analysis measured during the process for manufacturing of the tablet, and the results of analysis of the final tablet are provided in the following tables.

Table 2: Results of IPC (in-process control) analysis of metformin granulates with Na carboxymethylcellulose (Comparative Example 1) and HPC (Example 2) as a binder

	<i>Comparative Example 1</i>	<i>Example 2</i>
LOD of metformin granulate (105°C, 5 min, 2 g)	0,60%	0,39%
≤ 71 µm	11,2	0
≤ 125 µm	27,1	0,4
≤ 250 µm	53,2	31,2
≤ 500 µm	99,2	99,7
≤ 710 µm	100	100
Flow time (s)	27	18,2
Bulk angle (°)	42,4	30,4
Bulk V (mL/g)	1,8	2,36
Tap V (mL/g)	1,28	1,94
Hausner's ratio	1,41	1,22

Table 3 Results of IPC analysis of metformin tablet mixtures made from granulates with Na carboxy methylcellulose (Comparative Example 1) and HPC (Example 2) as a binder.

MIXTURE	Comparative Example 1	Example 2
<i>Type of granulate</i>	<i>HSM met</i>	<i>FBD met</i>
Mixture LOD (105°C, 5 min, 2g)	1,25	0,98
≤ 71 µm	7	6,6
≤ 125 µm	21,3	18,5
≤ 250 µm	43,6	60,4
≤ 500 µm	93,1	99,4
≤ 710 µm	99,4	100
Flow time (s)	63	16,6
Bulk angle (°)	37,2	33,6
Bulk V (mL/g)	1,86	2,16
Tap V (mL/g)	1,48	1,84
Hausner's ratio	1,26	1,17

Table 4: Comparison of parameters of bilayered tablets prepared from tableting mixtures of granulates with Na carboxy methylcellulose (Comparative Example 1) and HPC (Example 2) as a binder

Tableting	Comparative Example 1	Example 2
Observations	Friable tablet cores, capping	No problems observed
Total weight (mg)	1603,5	1608,2
RSD of mass (%)	0,48	0,43
Compression force (kN)	34,5	23,6
Hardness (N)	196	264

The results above show that FBD granulation using hydroxypropyl cellulose as a binder yields more flowable (substantially shorter flow times) and already primarily more compressible granulate (more favorable Hausner ratio) with a lower proportion of the powder fraction (better granulation). Also, the metformin tablet mixture of Example 2 is more flowable and more compressible, which further indicates the superiority of the composition according to the invention in comparison to the prior art. Moreover, these findings are reflected also by bilayer tableting process, where the composition according to the invention needs lower compression forces and achieves higher tablet hardness. The tablets are not friable and no capping is observed in contrast to the composition disclosed in the prior art. These superior features can be attributed to a very good compressibility of the compression mixture and interfacial adhesion between adjacent layers and the mechanical integrity of the solid dosage form.

Hardness or Resistance to crushing of tablets (2.9.8. European Pharmacopeia) is a test intended to determine, under defined conditions, the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing. Measuring tablet hardness (breaking force) plays a vital role in defining dosage form with optimum physical characteristics and testing whether produced dosage form meets the defined specifications in manufacturing. Testing tablet hardness is more than ensuring the mechanical integrity of produced tablets during subsequent processes (i.e. film coating). Together with friability, hardness is a defining physical characteristic for a tablet. High hardness values may indicate for example, longer disintegration and dissolution times, compromising the speed of drug delivery. On the other hand, if hardness is too low, then friability may be also high, giving rise to poor product stability and compromised dose uniformity. By examining correlations between hardness, dissolution and friability, a dosage form with optimum characteristics can be produced.

Superior compressibility is also shown by a wide tabletability profile (see Table 5 and Figure 3). With composition according to Example 2, consisting of HPC in both layers, a wide variety of tablet hardness, from 250 N to 500 N, can be achieved with no negative impact on layer connectivity and with acceptable friability also for the lowest tablet hardness. In the whole range also dissolution of both, metformin and dapagliflozin, is comparable as evidenced in Figures 4 and 5.

Table 5: Tableting process characteristic for hardness challenge test for bilayer tablet composition according to Example 2

Compaction pressure 1st layer [N]	1200	1200	1100	1200	1200
Compaction pressure 2nd layer and whole tablet [kN]	39	30	26	20	12
Mass of the bilayer tablet [mg]	1604.1	1602.99	1607.61	1600.65	1611.67
Mass variation [mg]	0.40	0.33	0.47	0.45	0.55
Tablet Hardness [N]	484	445	398	342	251
Thickness of tablets [mm]	7.59 – 7.64	7.71 – 7.79	7.87 – 7.93	8.16 – 8.19	8.72 – 8.77

Example 4

The dissolution profiles of the metformin and dapagliflozin released from the tablets according to Examples 1 and 2 in comparison to the reference product Xigduo XR (ref. No. NT0187) are determined under the following dissolution conditions:

- Medium: 900 ml phosphate buffer, pH 6.8
- Method: 100 rpm, USP Apparatus I.

Figures 1, 2, 4 and 5 disclose dissolution profile of metformin or dapagliflozin released from bilayer tablets. As evidenced by the figures the composition according to the present invention exhibits dissolution profile which is identical to the reference product.

Despite the formulation according to the invention, comprising hydroxypropyl cellulose (as a binder) in both layers, shows better processability and compressibility, i.e. providing tablets with higher resistance to crushing, higher hardness and having exceptional bonding relationship between the layers, this does not affect the release of dapagliflozin, which is comparable to the release of the reference product. This is evidenced by Figure 2, which discloses dissolution profile of dapagliflozin. As evidenced by the figure the composition to the present invention exhibits dissolution profile which is identical to the reference product.

Example 5

Process	Name of the ingredient	Strength	Function
		10/500	
		mg/unit	
METFORMIN LAYER			
Intragranular			
Fluid bed granulation 1	Metformin hydrochloride	500.000	Active ingredient
	Hydroxypropyl cellulose	31.500	Binder
	Water, purified ¹	q.s.	Solvent
Metformin granules total		531.500	-
Extragranular			
Blending 1	Hydroxypropyl methylcellulose K100M	380.500	Controlled-release agent
	Cellulose, microcrystalline PH200	103.000	Diluent
	Silica, colloidal anhydrous	10.000	Glidant
	Magnesium stearate	5.000	Lubricant
Metformin compression mixture / 1 st layer total		1030.000	-
DAPAGLIFLOZIN LAYER			
Intragranular			
Fluid bed granulation 2	Dapagliflozin propanediol monohydrate *)	12.300	Active ingredient
	Cellulose, microcrystalline PH102	110.860	Diluent
	Izomalt GaleniQ 721	47.510	Diluent
	Hydroxypropyl cellulose	8.700	Binder
	Talc	1.500	Glidant
	Ethanol, absolute ¹	q.s.	Solvent
Dapagliflozin granules total		180.870	-
Extragranular			
Blending 2	Cellulose, microcrystalline PH200	104.080	Diluent
	Croscarmellose sodium	9.000	Disintegrant
	Iron oxide, yellow (E172)	0.050	Colouring agent/Colorant
	Magnesium stearate	6.000	Lubricant
Dapagliflozin compression mixture / 2 nd layer total		300.000	-
Bilayer tablet core total		1330.000	-
FILM COATING			
Coating	Opadry TF titanium free PVA coating mixture	54.950	Coating mixture
	Iron oxide, red (E172)	0.050	Colouring agent/Colorant
	Water, purified ¹	q.s.	Solvent
Modified-release tablet total		1385.000	-

*) In the present Examples, as "Dapagliflozin propanediol monohydrate" dapagliflozin (S) propylene glycol hydrate is used.

1) The solvent is removed from the composition during the process.

Metformin granulation

Purified water or Absolute ethanol or mixture of the two was weighed into a stainless-steel vessel. Hydroxypropyl cellulose was slowly added to purified water during mixing. Dispersion was mixed as long that the clear dispersion is produced.

Metformin hydrochloride was crushed and sieved. The granulation liquid was sprayed onto metformin hydrochloride by top spraying process in fluid bed granulator. The process parameters were adjusted to achieve sufficient mixing of the product and target temperature of the product during spraying of about 30 - 60°C. After finished spraying, drying of the granulate is performed, until prescribed LOD (< 1 %) was achieved. Dry granulate was sieved.

Metformin compression mixture preparation

Hydroxypropyl methylcellulose K100M was optionally sieved. Silicon dioxide was mixed with part of Cellulose, microcrystalline PH200 and sieved. Magnesium stearate was mixed with part of Cellulose, microcrystalline PH200 and sieved through a 0.8 mm mesh sieve. Hydroxypropyl methylcellulose K100M, Silicon dioxide and Cellulose, microcrystalline PH200 was firstly added to the metformin granulate and blended for approx. 200 revolutions. Then sieved Magnesium stearate (mixed with part of Cellulose, microcrystalline PH200) was added and blended for further approx. 30 revolutions.

Dapagliflozin granulation

Absolute ethanol was poured into a stainless-steel vessel. Dapagliflozin propanediol monohydrate was slowly added to absolute ethanol during mixing. Then, Hydroxypropyl cellulose was slowly added during mixing. Dispersion was mixed until clear dispersion was produced.

The granulation liquid was sprayed onto powders of Cellulose, microcrystalline PH102, Izomalt GaleniQ 721 and Talc by top spraying process in fluid bed granulator. The process parameters were adjusted to achieve sufficient mixing of the product and temperature of the product during spraying of about 10 - 30°C. After spraying, wet granulate was dried until the temperature of granulate reaches 38 °C. After drying, dry granulate was cooled until the temperature of granulate reaches below 28 °C. Dry granulate was sieved.

Dapagliflozin compression mixture preparation

Cellulose, microcrystalline PH200 and Croscarmellose sodium were optionally sieved. Magnesium stearate was mixed with part of Cellulose, microcrystalline PH200 and sieved through a 0.8 mm mesh sieve. Cellulose, microcrystalline PH200, Croscarmellose sodium and triturate of Iron oxide, yellow (E172) were added to the dapagliflozin granulate and blended for approx. 200 revolutions. Then sieved

Magnesium stearate (mixed with part of Cellulose, microcrystalline PH200) was added and blended for further approx. 40 revolutions.

Bilayer tableting

The compression mixtures were compressed into tablets using an automatic rotary bilayer tableting machine. The first layer contains metformin and the second layer contains dapagliflozin. Firstly, the tablet press was set to obtain the target weight for the first layer. The second hopper was opened and the tablet press was adjusted to obtain the target bilayer tablet weight of dapagliflozin and metformin XR.

Film coating

The collected bilayer tablets were film coated with a coating mixture based on PVA (polyvinyl alcohol) that does not contain titanium dioxide (Opadry® coating mixture).

Example 6

Additional examples based on Example 2 (HPC as a binder) were prepared, as shown below:

Additional examples (showing Excipient variations)

Pharmaceutical dosage forms, strength 10/1000 mg, Examples based on Example 2 (HPC as a binder), but with varying the amount and type of HPMC in metformin layer. Same composition just with half amount of Dapagliflozin propanediol monohydrate and Iron oxide, red instead of yellow are used for preparation of 5/1000 mg strength.

Process	Name of the ingredient	2-1	2-2	2-3	2-4	2-5	2-6
METFORMIN LAYER							
Fluid bed granulation 1	Metformin hydrochloride	1000.00	1000.00	1000.00	1000.00	1000.00	1000.00
	Hydroxypropyl Cellulose	63.00	63.00	63.00	63.00	63.00	63.00
	Water, purified / Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Blending 1	Hydroxypropyl methylcellulose K100M	235.00	185.00	135.00	/	117.5	/
	Hydroxypropyl methylcellulose K200M	/	/	/	110.00	117.5	235.00
	Magnesium stearate	7.00	7.00	7.00	7.00	7.00	7.00
Metformin compression mixture / 1 st layer total		1305.00	1255.00	1205.00	1180.00	1305.00	1305.00
DAPAGLIFLOZIN LAYER							
Fluid bed granulation 2	Dapagliflozin propanediol monohydrate *)	12.30	12.30	12.30	12.30	12.30	12.30
	Cellulose, microcrystalline PH102	110.86	110.86	110.86	110.86	110.86	110.86
	Izomalt GalenIQ 721	47.51	47.51	47.51	47.51	47.51	47.51
	Hydroxypropyl Cellulose	8.70	8.70	8.70	8.70	8.70	8.70
	Talc	1.50	1.50	1.50	1.50	1.50	1.50
	Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Blending 2	Cellulose, microcrystalline PH200	104.08	104.08	104.08	104.08	104.08	104.08
	Croscarmellose sodium	9.00	9.00	9.00	9.00	9.00	9.00
	Iron oxide, yellow (E172)	0.05	0.05	0.05	0.05	0.05	0.05
	Magnesium stearate	6.00	6.00	6.00	6.00	6.00	6.00
Dapagliflozin compression mixture / 2 nd layer total		300.00	300.00	300.00	300.00	300.00	300.00
Bilayer tablet core total		1605.00	1555.00	1505.00	1480.00	1605.00	1605.00
FILM COATING							
Coating	Opadry TF PVA	39.00	39.00	39.00	39.00	39.00	39.00
	Iron oxide, yellow (E172)	1.00	1.00	1.00	1.00	1.00	1.00

	Water, purified ¹	q.s.	q.s.	q.s.	q.s.	q.s.
Modified-release tablet total		1645.00	1595.00	1545.00	1520.00	1645.00

Pharmaceutical dosage forms, strength 10/1000 mg, Examples based on Example 2 (HPC as a binder), but with different dapagliflozin layer composition. Same composition just with half amount of Dapagliflozin propanediol monohydrate and Iron oxide, red instead of yellow are used for preparation of 5/1000 mg strength.

Process	Name of the ingredient	2-7	2-8	2-9	2-10	2-11	2-12	2-13
METFORMIN LAYER								
Fluid bed granulation 1	Metformin hydrochloride	1000.00	1000.00	1000.00	1000.00	1000.00	1000.00	1000.00
	Hydroxypropyl Cellulose	63.00	63.00	63.00	63.00	63.00	63.00	63.00
	Water, purified/ Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Blending 1	Hydroxypropyl methylcellulose K100M	235.00	235.00	235.00	235.00	235.00	235.00	235.00
	Magnesium stearate	7.00	7.00	7.00	7.00	7.00	7.00	7.00
Metformin compression mixture / 1 st layer total		1305.00	1305.00	1305.00	1305.00	1305.00	1305.00	1305.00
DAPAGLIFLOZIN LAYER								
Fluid bed granulation 2	Dapagliflozin propanediol monohydrate *)	12.30	12.30	12.30	12.30	12.30	12.30	12.30
	Cellulose, microcrystalline PH102	/	110.86	110.86	110.86	110.86	110.86	148.30
	Cellulose, microcrystalline PH101	110.86	/	/	/	/	/	/
	Izomalt GalenIQ 721	47.51	47.51	47.51	/	/	49.01	/
	Lactose, crystalline	/	/	/	47.51	/	/	/
	Dextrate Emdex	/	/	/	/	47.51	/	/
	Hydroxypropyl Cellulose	8.70	8.70	8.70	8.70	8.70	8.70	8.70
	Talc	1.50	1.50	1.50	1.50	1.50	/	/
	Ethanol, absolute	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Blending 2	Cellulose, microcrystalline PH200	/	104.08	104.08	104.08	104.08	104.08	/
	Cellulose, microcrystalline PH102	104.08	/	/	/	/	/	65.65
	Croscarmellose sodium	9.00	/	9.00	9.00	9.00	9.00	10.00
	Crospovidone	/	9.00	/	/	/	/	/
	Iron oxide, yellow (E172)	0.05	0.05	0.05	0.05	0.05	0.05	0.05

	Magnesium stearate	6.00	6.00	/	6.00	6.00	6.00	6.00	5.00
	Na-stearyl fumarate	/	/	6.00	/	/	/	/	/
Dapagliflozin compression mixture / 2 nd layer total									
		300.00	300.00	300.00	300.00	300.00	300.00	300.00	250.00
Bilayer tablet core total									
		1605.00	1605.00	1605.00	1605.00	1605.00	1605.00	1605.00	1555.00
FILM COATING									
Coating	Opadry TF PVA	39.00	39.00	39.00	39.00	39.00	39.00	39.00	39.00
	Iron oxide, yellow (E172)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Water, purified ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Modified-release tablet total	1645.00	1645.00	1645.00	1645.00	1645.00	1645.00	1645.00	1595.00

Pharmaceutical dosage forms, strength **10/500 mg**, Examples based on Example 2 (HPC as a binder).

Same composition just with half amount of Dapagliflozin propanediol monohydrate and double amount of Iron oxide, red are used for preparation of **5/500 mg strength**. All changes in dapagliflozin layer (Examples 2-7 – 2-13) apply also for these strengths (10/500 mg and 5/500 mg).

Process	Name of the ingredient	2-14	2-15	2-16	2-17	2-18	2-19	2-20	2-21
METFORMIN LAYER									
Fluid bed granulation 1	Metformin hydrochloride	500.00	500.00	500.00	500.00	500.00	500.00	500.00	500.00
	Hydroxypropyl Cellulose	31.50	31.50	31.50	31.50	31.50	31.50	31.50	31.50
	Water, purified / Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Hydroxypropyl methylcellulose K100M	399.50	399.50	399.50	399.50	200.00	399.50	399.50	399.50
Blending 1	Hydroxypropyl methylcellulose K200M	/	/	/	/	199.50	/	/	/
	Cellulose, microcrystalline PH200	104.00	/	99.00	/	104.00	/	/	/
	Cellulose, microcrystalline PH102	/	104.00	/	/	/	/	/	/
	Pregelatinized Starch (StarCap 1500)	/	/	/	/	/	104.00	/	/
	Dextrate Emdex	/	/	/	/	/	/	104.00	/
	Maltodextrin	/	/	/	/	/	/	/	104.00
	Magnesium stearate	5.00	5.00	10.00	5.00	5.00	5.00	5.00	5.00
Metformin compression mixture / 1 st layer total									
		1040.00	1040.00	1040.00	936.00	1040.00	1040.00	1040.00	1040.00
DAPAGLIFLOZIN LAYER									

Fluid bed granulation 2	Dapagliflozin propanediol monohydrate *)	12.30	12.30	12.30	12.30	12.30	12.30	12.30	12.30
	Cellulose, microcrystalline PH102	110.86	110.86	110.86	110.86	110.86	110.86	110.86	110.86
	Izomalt GalenIQ 721	47.51	47.51	47.51	47.51	47.51	47.51	47.51	47.51
	Hydroxypropyl Cellulose	8.70	8.70	8.70	8.70	8.70	8.70	8.70	8.70
	Talc	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Blending 2	Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Cellulose, microcrystalline PH200	104.08	104.08	104.08	104.08	104.08	104.08	104.08	104.08
	Croscarmellose sodium	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00
	Iron oxide, yellow (E172)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
	Magnesium stearate	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
Dapagliflozin compression mixture / 2 nd layer total		300.00	300.00	300.00	300.00	300.00	300.00	300.00	300.00
Bilayer tablet core total		1340.00	1340.00	1236.00	1340.00	1340.00	1340.00	1340.00	1340.00
FILM COATING									
Coating	Opadry TF PVA	37.97	37.97	37.97	37.97	37.97	37.97	37.97	37.97
	Iron oxide, red (E172)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
	Water, purified ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Modified-release tablet total		1378.00	1378.00	1274.00	1378.00	1378.00	1378.00	1378.00	1378.00

Pharmaceutical dosage forms, strength 10/1000 mg, Examples based on Example 2 (HPC as a binder), with varying the type of extended-release agent. All these extended release agent scan be used also for other strengths (5/1000 mg, 10/500 mg and 5/500 mg)

Process	Name of the ingredient	2-22	2-23	2-24	2-25
METFORMIN LAYER					
Fluid bed granulation 1	Metformin hydrochloride	1000.00	1000.00	1000.00	1000.00
	Hydroxypropyl Cellulose	63.00	63.00	63.00	63.00
	Water, purified / Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.
Blending 1	Hydroxypropyl Cellulose JF/GF/MF	235.00	/	/	/
	Polyethylene Oxide WSR N10 / WSR N80/ WSR N750	/	235.00	/	/
	Xanthan Gum	/	/	235.00	/
	Sodium Alginate	/	/	/	235.00

	Magnesium stearate	7.00	7.00	7.00	7.00
	Metformin compression mixture / 1 st layer total	1305.00	1305.00	1305.00	1305.00
DAPAGLIFLOZIN LAYER					
Fluid bed granulation 2	Dapagliflozin propanediol monohydrate *)	12.30	12.30	12.30	12.30
	Cellulose, microcrystalline PH102	110.86	110.86	110.86	110.86
	Izomalt GaleniQ 721	47.51	47.51	47.51	47.51
	Hydroxypropyl Cellulose	8.70	8.70	8.70	8.70
	Talc	1.50	1.50	1.50	1.50
	Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.
Blending 2	Cellulose, microcrystalline PH200	104.08	104.08	104.08	104.08
	Croscarmellose sodium	9.00	9.00	9.00	9.00
	Iron oxide, yellow (E172)	0.05	0.05	0.05	0.05
	Magnesium stearate	6.00	6.00	6.00	6.00
	Dapagliflozin compression mixture / 2 nd layer total	300.00	300.00	300.00	300.00
	Bilayer tablet core total	1605.00	1605.00	1605.00	1605.00
FILM COATING					
Coating	Opadry TF PVA	39.00	39.00	39.00	39.00
	Iron oxide, yellow (E172)	1.00	1.00	1.00	1.00
	Water, purified ¹	q.s.	q.s.	q.s.	q.s.
	Modified-release tablet total	1645.00	1645.00	1645.00	1645.00

1) The solvent is removed from the composition during the process.

*) In the present Examples, as "Dapagliflozin propanediol monohydrate" dapagliflozin (S) propylene glycol hydrate is used.

Example 2-26 corresponds to Example 2-11, except that instead of dextrate calcium phosphate is used. Example 2-27 corresponds to Example 2-11, except that instead of dextrate sucrose is used. Example 2-28 corresponds to Example 2-11, except that instead of dextrate polydextrose is used. Example 2-29 corresponds to Example 2-11, except that instead of dextrate mannitol is used. Example 2-30 corresponds to Example 2-11, except that instead of dextrate dextrose is used. Example 2-31 corresponds to Example 2-11, except that instead of dextrate dextrin is used. Example 2-32 corresponds to Example 2-11, except that instead of dextrate pregelatinized starch is used. Example 2-33 corresponds to Example 2-11, except that instead of dextrate corn starch is used.

Example 2-34 corresponds to Example 2-21, except that instead of maltodextrin calcium polydextrose is used. Example 2-35 corresponds to Example 2-21, except that instead of maltodextrin calcium sucrose is used.

Example 7

Additional examples based on Example 5 (HPC as a binder) were prepared, as shown below:

Additional examples (showing Excipient variations)

Pharmaceutical dosage forms, strength 10/500 mg, Examples based on Example 5 (HPC as a binder), but with varying the amount and type of HPMC in metformin layer. Same composition just with half amount of Dapagliflozin propanediol monohydrates and Iron oxide, red instead of yellow are used for preparation of 5/500 mg strength.

Process	Name of the ingredient	5-1	5-2	5-3	5-4	5-5	5-6
METFORMIN LAYER							
Fluid bed granulation 1	Metformin hydrochloride	500.00	500.00	500.00	500.00	500.00	500.00
	Hydroxypropyl Cellulose	31.50	31.50	31.50	31.50	31.50	31.50
	Water, purified / Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Hydroxypropyl methylcellulose K100M	380.50	330.50	280.50	/	190.5	/
Blending 1	Hydroxypropyl methylcellulose K200M	/	/	/	280.50	190.0	380.50
	Cellulose, microcrystalline PH200	103.00	103.00	103.00	103.00	103.00	103.00
	Silica, colloidal anhydrous	10.00	10.00	10.00	10.00	10.00	10.00
	Magnesium stearate	5.00	5.00	5.00	5.00	5.00	5.00
Metformin compression mixture / 1 st layer total		1030.00	980.00	930.00	930.00	1030.00	1030.00
DAPAGLIFLOZIN LAYER							
Fluid bed granulation 2	Dapagliflozin propanediol monohydrate *)	12.30	12.30	12.30	12.30	12.30	12.30
	Cellulose, microcrystalline PH102	110.86	110.86	110.86	110.86	110.86	110.86
	Izomalt GalenIQ 721	47.51	47.51	47.51	47.51	47.51	47.51
	Hydroxypropyl Cellulose	8.70	8.70	8.70	8.70	8.70	8.70
	Talc	1.50	1.50	1.50	1.50	1.50	1.50
	Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Blending 2	Cellulose, microcrystalline PH200	104.08	104.08	104.08	104.08	104.08	104.08
	Croscarmellose sodium	9.00	9.00	9.00	9.00	9.00	9.00
	Iron oxide, yellow (E172)	0.05	0.05	0.05	0.05	0.05	0.05
	Magnesium stearate	6.00	6.00	6.00	6.00	6.00	6.00
Dapagliflozin compression mixture / 2 nd layer total		300.00	300.00	300.00	300.00	300.00	300.00
Bilayer tablet core total		1605.00	1555.00	1505.00	1480.00	1605.00	1605.00
FILM COATING							
Coating	Opadry TF PVA	54.95	54.95	54.95	54.95	54.95	54.95

	Iron oxide, red (E172)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
	Water, purified ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Modified-release tablet total		1385.00	1335.00	1285.00	1285.00	1285.00	1385.00	1385.00	1385.00

Pharmaceutical dosage forms, strength 10/500 mg, Examples based on Example 5 (HPC as a binder), but with different dapagliflozin layer composition. Same composition just with half amount of Dapagliflozin propandiol monohydrates and Iron oxide, red instead of yellow are used for preparation of 5/500 mg strength.

Process	Name of the ingredient	5-7	5-8	5-9	5-10	5-11	5-12	5-13
METFORMIN LAYER								
Fluid bed granulation 1	Metformin hydrochloride	500.00	500.00	500.00	500.00	500.00	500.00	500.00
	Hydroxypropyl Cellulose	31.50	31.50	31.50	31.50	31.50	31.50	31.50
	Water, purified/ Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Blending 1	Hydroxypropyl methylcellulose K100M	380.50	380.50	380.50	380.50	380.50	380.50	380.50
	Cellulose, microcrystalline PH200	103.00	103.00	103.00	103.00	103.00	103.00	103.00
	Silica, colloidal anhydrous	10.00	10.00	10.00	10.00	10.00	10.00	10.00
	Magnesium stearate	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Metformin compression mixture / 1 st layer total		1030.00	1030.00	1030.00	1030.00	1030.00	1030.00	1030.00
DAPAGLIFLOZIN LAYER								
Fluid bed granulation 2	Dapagliflozin propanediol monohydrate *)	12.30	12.30	12.30	12.30	12.30	12.30	12.30
	Cellulose, microcrystalline PH102	/	110.86	110.86	110.86	110.86	110.86	148.30
	Cellulose, microcrystalline PH101	110.86	/	/	/	/	/	/
	Izomalt GalenIQ 721	47.51	47.51	47.51	/	/	49.01	/
	Lactose, crystalline	/	/	/	47.51	/	/	/
	Dextrate Emdex	/	/	/	/	47.51	/	/
	Hydroxypropyl Cellulose	8.70	8.70	8.70	8.70	8.70	8.70	8.70
	Talc	1.50	1.50	1.50	1.50	1.50	/	/
Blending 2	Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Cellulose, microcrystalline PH200	/	104.08	104.08	104.08	104.08	104.08	/
	Cellulose, microcrystalline PH102	104.08	/	/	/	/	/	65.65
	Croscarmellose sodium	9.00	/	9.00	9.00	9.00	9.00	10.00

	Crospovidone	/	9.00	/	/	/	/
	Iron oxide, yellow (E172)	0.05	0.05	0.05	0.05	0.05	0.05
	Magnesium stearate	6.00	6.00	/	6.00	6.00	5.00
	Na-stearyl fumarate	/	/	6.00	/	/	/
Dapagliflozin compression mixture / 2 nd layer total							
Bilayer tablet core total		1330.00	1330.00	1330.00	1330.00	1330.00	1280.00
FILM COATING							
Coating	Opadry TF PVA	54.95	54.95	54.95	54.95	54.95	54.95
	Iron oxide, red (E172)	0.05	0.05	0.05	0.05	0.05	0.05
	Water, purified ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Modified-release tablet total		1385.00	1385.00	1385.00	1385.00	1385.00	1335.00

Pharmaceutical dosage forms, strength 10/500 mg, Examples based on Example 5 (HPC as a binder). Same composition just with half amount of
Dapagliflozin propanediol monohydrates and double amount of Iron oxide, red are used for preparation of 5/500 mg strength.

[illegible]

Fluid bed granulation 2	Dapagliflozin propanediol monohydrate *)	12.30	12.30	12.30	12.30	12.30	12.30	12.30	12.30
	Cellulose, microcrystalline PH102	110.86	110.86	110.86	110.86	110.86	110.86	110.86	110.86
	Izomalt GalenIQ 721	47.51	47.51	47.51	47.51	47.51	47.51	47.51	47.51
	Hydroxypropyl Cellulose	8.70	8.70	8.70	8.70	8.70	8.70	8.70	8.70
	Talc	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Blending 2	Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	Cellulose, microcrystalline PH200	104.08	104.08	104.08	104.08	104.08	104.08	104.08	104.08
	Croscarmellose sodium	9.00	9.00	9.00	9.00	9.00	9.00	9.00	9.00
	Iron oxide, yellow (E172)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
	Magnesium stearate	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
Dapagliflozin compression mixture / 2 nd layer total		300.00	300.00	300.00	300.00	300.00	300.00	300.00	300.00
Bilayer tablet core total		1330.00	1330.00	1227.00	1330.00	1330.00	1330.00	1330.00	1330.00
FILM COATING									
Coating	Opadry TF PVA	54.95	54.95	54.95	54.95	54.95	54.95	54.95	54.95
	Iron oxide, red (E172)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
	Water, purified ¹	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Modified-release tablet total		1385.00	1385.00	1282.00	1385.00	1385.00	1385.00	1385.00	1385.00

Pharmaceutical dosage forms, strength 10/500 mg, Examples based on Example 5 (HPC as a binder), with varying the type of extended-release agent. All these extended release agents can be used also for other strengths (5/1000 mg, 10/1000 mg and 5/500 mg)

Process	Name of the ingredient	5-22	5-23	5-24	5-25
METFORMIN LAYER					
Fluid bed granulation 1	Metformin hydrochloride	500.00	500.00	500.00	500.00
	Hydroxypropyl Cellulose	31.50	31.50	31.50	31.50
	Water, purified / Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.
Blending 1	Hydroxypropyl Cellulose JF/GF/MF	380.50	/	/	/
	Polyethylene Oxide WSR N10 / WSR N80/ WSR N750	/	380.50	/	/
	Xanthan Gum	/	/	380.50	/
	Sodium Alginate	/	/	/	380.50

	Cellulose, microcrystalline PH200	103.00	103.00	103.00	103.00
	Silica, colloidal anhydrous	10.00	10.00	10.00	10.00
	Magnesium stearate	5.00	5.00	5.00	5.00
Metformin compression mixture / 1 st layer total		1030.00	1030.00	1030.00	1030.00
DAPAGLIFLOZIN LAYER					
Fluid bed granulation 2	Dapagliflozin propanediol monohydrate *)	12.30	12.30	12.30	12.30
	Cellulose, microcrystalline PH102	110.86	110.86	110.86	110.86
	Izomalt GalenIQ 721	47.51	47.51	47.51	47.51
	Hydroxypropyl Cellulose	8.70	8.70	8.70	8.70
	Talc	1.50	1.50	1.50	1.50
	Ethanol, absolute ¹	q.s.	q.s.	q.s.	q.s.
Blending 2	Cellulose, microcrystalline PH200	104.08	104.08	104.08	104.08
	Croscarmellose sodium	9.00	9.00	9.00	9.00
	Iron oxide, yellow (E172)	0.05	0.05	0.05	0.05
	Magnesium stearate	6.00	6.00	6.00	6.00
Dapagliflozin compression mixture / 2 nd layer total		300.00	300.00	300.00	300.00
Bilayer tablet core total		1330.00	1330.00	1330.00	1330.00
FILM COATING					
Coating	Opadry TF PVA	54.95	54.95	54.95	54.95
	Iron oxide, red (E172)	0.05	0.05	0.05	0.05
	Water, purified ¹	q.s.	q.s.	q.s.	q.s.
Modified-release tablet total		1385.00	1385.00	1385.00	1385.00

1) The solvent is removed from the composition during the process.

*) In the present Examples, as "Dapagliflozin propanediol monohydrate" dapagliflozin (S) propylene glycol hydrate is used.

Example 5-26 corresponds to Example 5-11, except that instead of dextrate calcium phosphate is used. Example 5-27 corresponds to Example 5-11, except that instead of dextrate sucrose is used. Example 5-28 corresponds to Example 5-11, except that instead of dextrate polydextrose is used. Example 5-29 corresponds to Example 5-11, except that instead of dextrate mannitol is used. Example 5-30 corresponds to Example 5-11, except that instead of dextrate dextrose is used. Example 5-31 corresponds to Example 5-11, except that instead of dextrate dextrin is used. Example 5-32 corresponds to Example 5-11, except that instead of dextrate pregelatinized starch is used. Example 5-33 corresponds to Example 5-11, except that instead of dextrate corn starch is used.

Example 5-34 corresponds to Example 5-21, except that instead of maltodextrin calcium polydextrose is used. Example 5-35 corresponds to Example 5-21, except that instead of maltodextrin calcium sucrose is used.

Claims

1. A pharmaceutical composition, which pharmaceutical composition is a bilayer tablet comprising:
a first layer, and
a second layer,
said first layer being a metformin extended release layer, and said first layer comprising metformin and hydroxypropyl cellulose,
said second layer comprising dapagliflozin and hydroxypropyl cellulose.
2. The pharmaceutical composition according to claim 1, wherein the first layer is a layer comprising
 - granule(s) comprising metformin and hydroxypropyl cellulose, and optionally one or more further pharmaceutically acceptable excipients; and
 - an extra-granular phase comprising one or more pharmaceutically acceptable excipients.
3. The pharmaceutical composition according to any one of the preceding claims, wherein the second layer is a layer comprising
 - granule(s) comprising dapagliflozin and hydroxypropyl cellulose, and optionally one or more further pharmaceutically acceptable excipients; and
 - an extra-granular phase comprising one or more pharmaceutically acceptable excipients.
4. The pharmaceutical composition according to any one of the preceding claims, wherein the first layer is a layer comprising
 - granule(s) comprising metformin and hydroxypropyl cellulose, and optionally one or more further pharmaceutically acceptable excipients; and
 - an extra-granular phase comprising one or more pharmaceutically acceptable excipients,and
wherein the second layer is a layer comprising
 - granule(s) comprising dapagliflozin and hydroxypropyl cellulose, and optionally one or more further pharmaceutically acceptable excipients; and

- an extra-granular phase comprising one or more pharmaceutically acceptable excipients.
5. The pharmaceutical composition according to claim 4, wherein the granule(s) comprising metformin and hydroxypropyl cellulose are prepared by fluid bed granulation, and the granule(s) comprising dapagliflozin and hydroxypropyl cellulose are prepared by fluid bed granulation.
6. The pharmaceutical composition according to any one of the preceding claims, said first layer being a compressed compression mixture which is obtainable by subjecting a compression mixture comprising
- granule(s) comprising metformin and hydroxypropyl cellulose, and optionally one or more further pharmaceutically acceptable excipients; and
 - an extra-granular phase comprising one or more pharmaceutically acceptable excipients,
- to compression, preferably the metformin containing granules being granules prepared by wet granulation, more preferably by fluid bed granulation, and
- said second layer being a compressed compression mixture which is obtainable by subjecting a compression mixture comprising
- granule(s) comprising dapagliflozin and hydroxypropyl cellulose, and optionally one or more further pharmaceutically acceptable excipients; and
 - an extra-granular phase comprising one or more pharmaceutically acceptable excipients,
- to compression, preferably the dapagliflozin containing granules being granules prepared by wet granulation, more preferably by fluid bed granulation.
7. The pharmaceutical composition according to any one of the preceding claims, wherein the first layer comprises metformin and hydroxypropyl cellulose, and further comprises a controlled release agent, a lubricant, optionally a glidant and optionally a diluent.
8. The pharmaceutical composition according to any one of the preceding claims, wherein the first layer comprises metformin, hydroxypropyl cellulose, hydroxyl propyl methyl cellulose, magnesium stearate, optionally a glidant and optionally a diluent.

9. The pharmaceutical composition according to any one of the preceding claims, wherein the second layer comprises dapagliflozin, hydroxypropyl cellulose, and further comprises a diluent, a disintegrant, a lubricant and optionally a glidant and optionally a colorant.
10. The pharmaceutical composition according to any one of the preceding claims, wherein the second layer comprises dapagliflozin, hydroxypropyl cellulose, and further comprises microcrystalline cellulose and isomalt, sodium croscarmellose, magnesium stearate, and optionally talc or silicon dioxide.
11. The pharmaceutical composition according to any one of the preceding claims, wherein the second layer is a dapagliflozin immediate release layer, said second layer comprising dapagliflozin and hydroxypropyl cellulose.
12. The pharmaceutical composition according to any one of the preceding claims, wherein the first layer comprises
metformin in an amount of 50 to 90 wt.-%, preferably 70 to 80 wt.-%, based on the total weight of the first layer, and
hydroxypropyl cellulose in an amount of 3 to 10 wt.-%, preferably 3.5 to 7 wt.-%, based on the total weight of the first layer, and
optionally further comprises a controlled release agent, a lubricant, optionally a glidant and optionally a diluent.
13. The pharmaceutical composition according to claim 12, wherein the first layer comprises metformin in an amount of from 800 to 1200 mg, especially metformin in an amount of 1000 mg, preferably metformin HCl in an amount of from 800 to 1200 mg, more preferably metformin HCl in an amount of 1000 mg, and/or
wherein the pharmaceutical composition comprises metformin in an amount of from 800 to 1200 mg, especially metformin in an amount of 1000 mg, preferably metformin HCl in an amount of from 800 to 1200 mg, more preferably metformin HCl in an amount of 1000 mg.
14. The pharmaceutical composition according to any one of claims 1 to 11, wherein the first layer comprises 500 mg metformin, preferably 500 mg metformin HCl, which is comprised in an amount of 40 to 60 wt.-%, preferably 45 to 55 wt.-%, based on the total weight of the first layer, and

hydroxypropyl cellulose in an amount of 1 to 7 wt.-%, preferably 2 to 5 wt.-%, based on the total weight of the first layer,

a controlled release agent, preferably hydroxypropyl methylcellulose, in an amount in the range of from 20 to 50 wt.-%, preferably 30 to 40 wt.-%, based on the total weight of the first layer,

a diluent, preferably microcrystalline cellulose, in an amount in the range of from 1 to 20 wt.-%, preferably 5 to 15 wt.-%, based on the total weight of the first layer,

a glidant, preferably silicon dioxide, in an amount in the range of from 0.2 to 2 wt.-%, preferably 0.5 to 1.5 wt.-%, based on the total weight of the first layer, and

a lubricant, preferably in an amount in the range of from 0.2 to 1 wt.-%, preferably 0.4 to 0.8 wt.-%, based on the total weight of the first layer.

15. The pharmaceutical composition according to any one of the preceding claims, wherein the metformin is metformin HCl, and wherein the dapagliflozin is dapagliflozin (S) propylene glycol hydrate or dapagliflozin in amorphous form.
16. Process for the preparation of a pharmaceutical composition which is a bilayer tablet, said process comprising:
 - A) preparing a phase comprising metformin, said preparing of a phase comprising metformin comprising:
 - A-1) dissolving hydroxypropyl cellulose in a liquid, which liquid preferably is or comprises water or an organic solvent, more preferably is or comprises water, to obtain a granulation liquid;
 - A-2) spraying the granulation liquid onto metformin, optionally spraying the granulation liquid onto a mixture of metformin with one or more intragranular excipients to obtain granules comprising metformin;
 - A-3) adding a controlled release agent, a lubricant, optionally a glidant and optionally a diluent to the granulate obtained in step A-2) to obtain the phase comprising metformin;
 - B) preparing a phase comprising dapagliflozin, said preparing of a phase comprising dapagliflozin comprises:
 - B-1) dissolving hydroxypropyl cellulose and dapagliflozin in a liquid, which liquid preferably is or comprises water or an organic solvent, more preferably is or comprises ethanol to obtain a granulation liquid;

- B-2) preparing a mixture of one or more pharmaceutically acceptable excipients, preferably a mixture of one or more pharmaceutically acceptable excipients comprising diluent(s) and optionally glidant, to obtain a homogenous mixture of excipients;
- B-3) spraying the granulation liquid onto the mixture of one or more pharmaceutically acceptable excipients to obtain granules;
- B-4) adding one or more diluents, one or more disintegrants, optionally one or more colorants and one or more lubricants to the granules obtained in step B-3) to obtain the phase comprising dapagliflozin;
- C) bilayer tableting of metformin phase and dapagliflozin phase, thereby obtaining bilayer tablet;
- D) optionally film coating of the bilayer tablet.
17. The pharmaceutical composition according to any one of the preceding claims for use in a method of treating diseases or disorders associated with metabolic disorders or for use in a method of treating a glucose related disorder, especially for use in a method of treating a glucose related disorder, chronic heart failure, chronic kidney disease, and cardiovascular disease.

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Figures

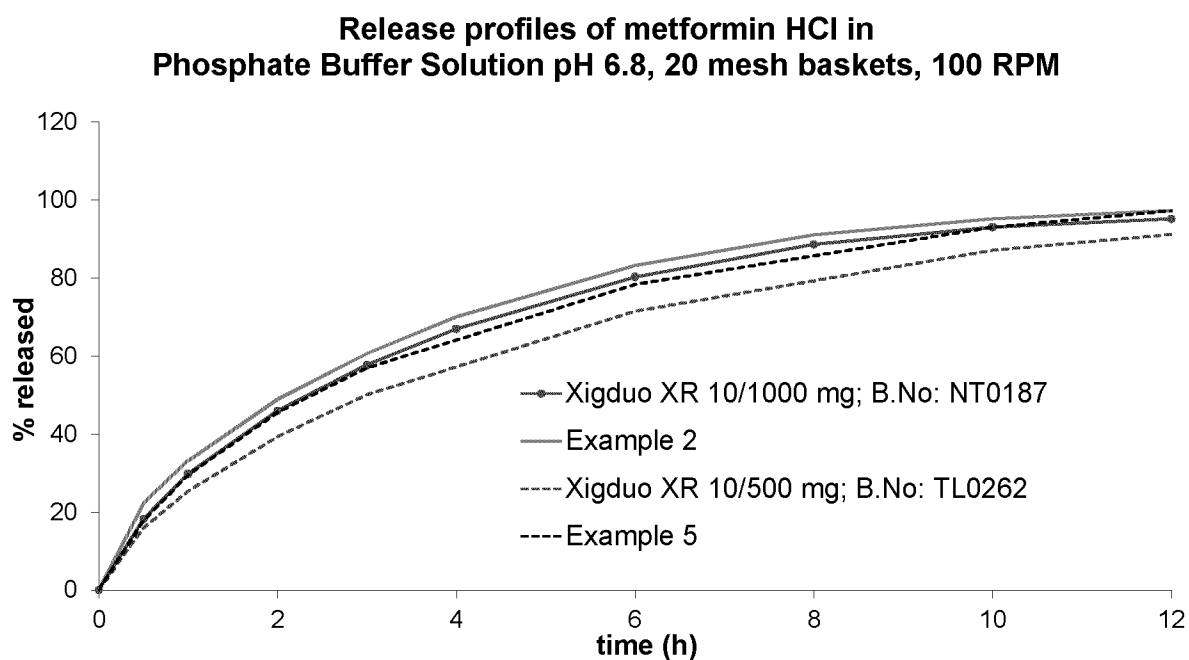


Fig. 1

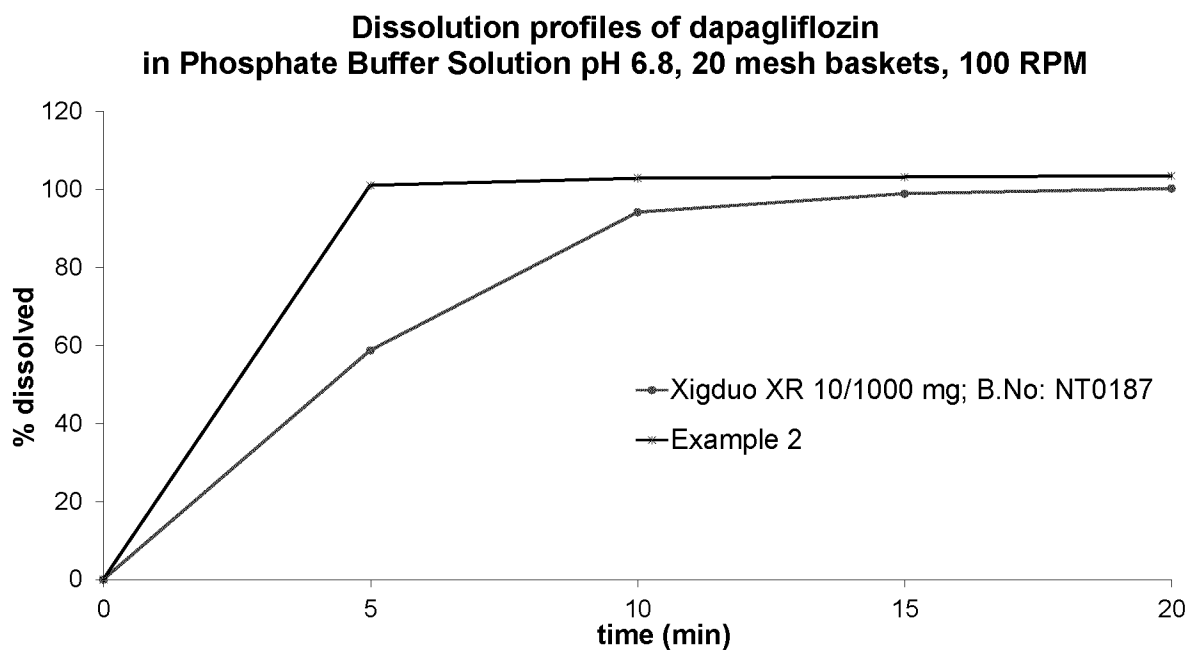


Fig. 2

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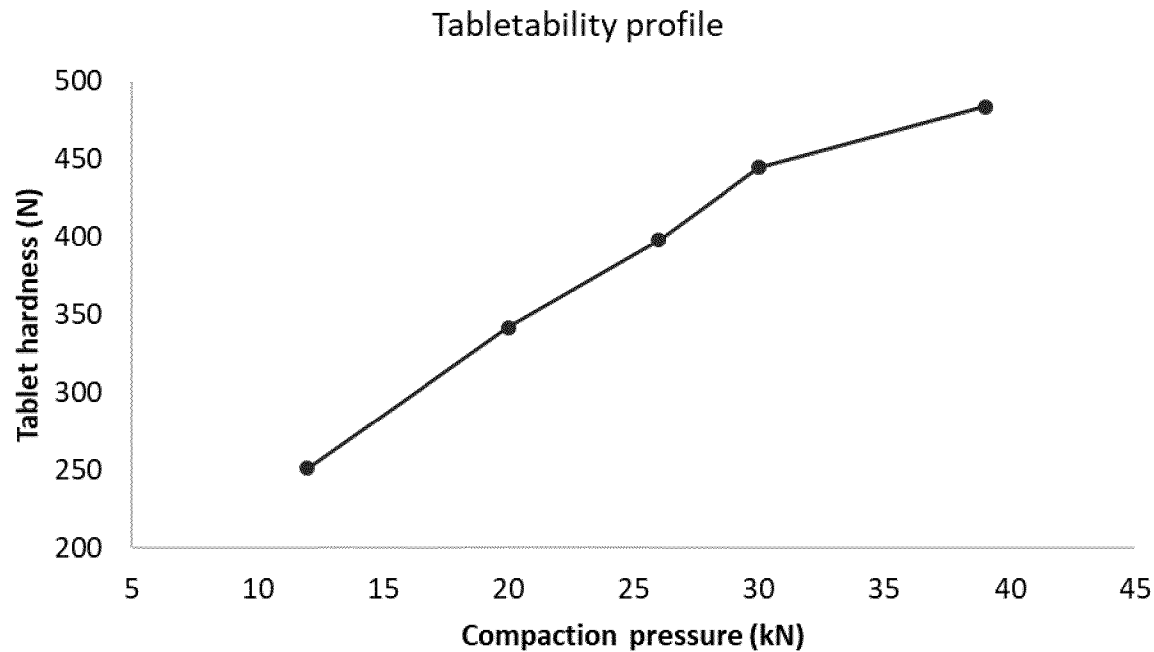


Fig. 3

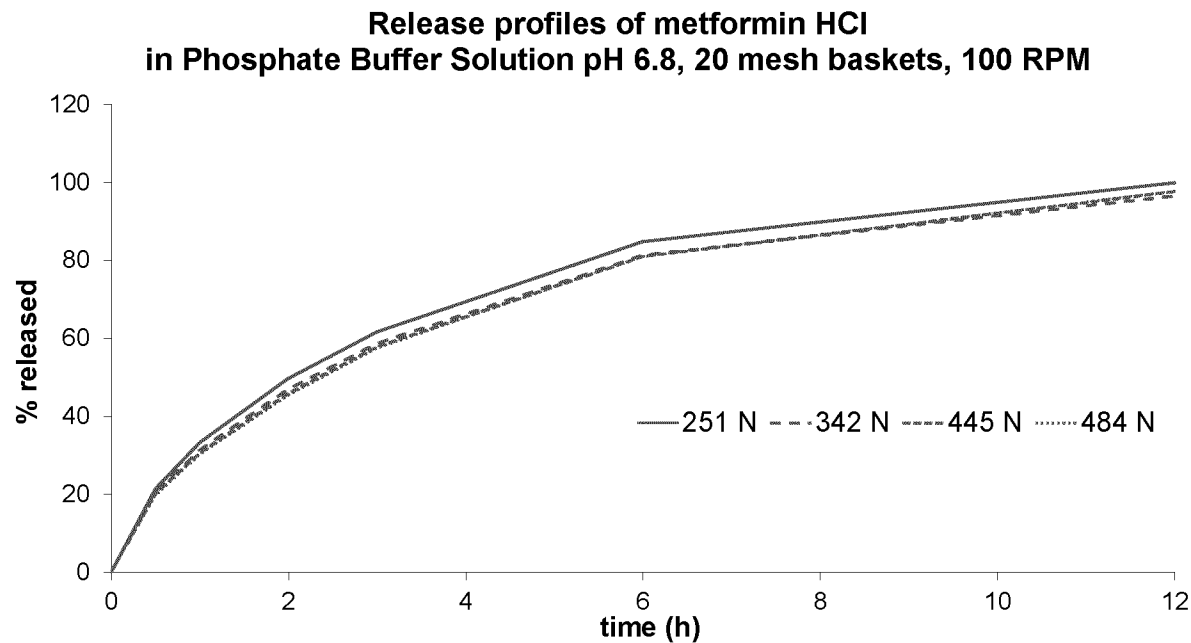
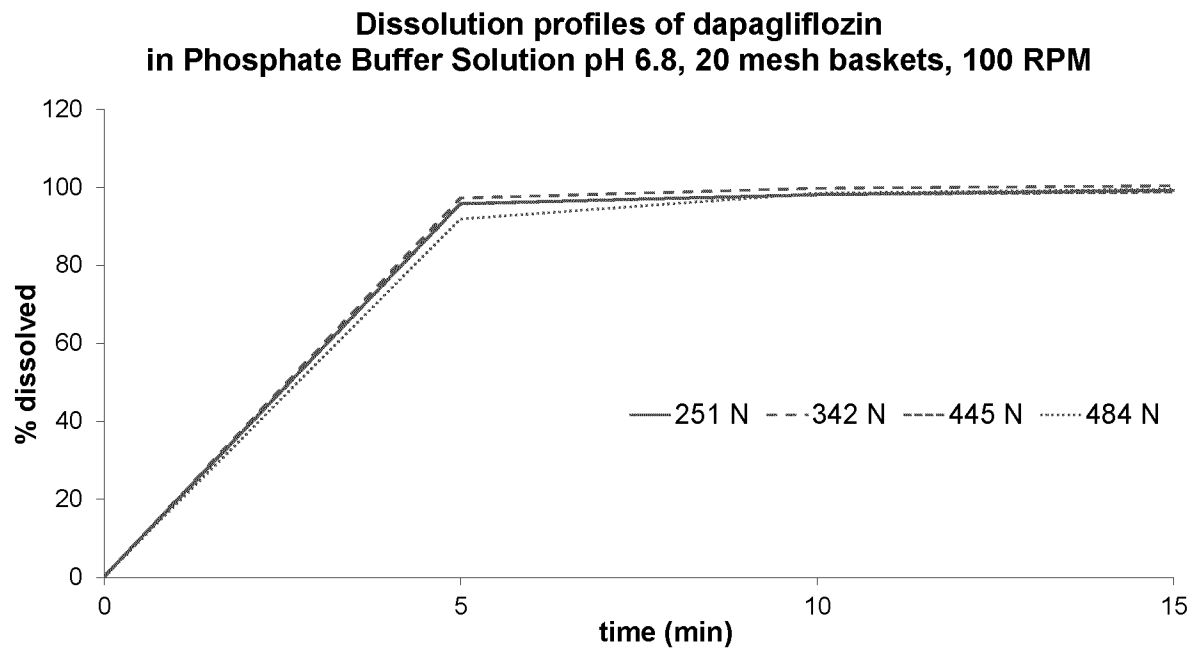


Fig. 4

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**Fig. 5**

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2024/087571

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/24 A61K31/155 A61K31/70 A61P5/48
ADD. A61K9/20

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 A61P

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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X	WO 2011/060256 A2 (BRISTOL MYERS SQUIBB CO [US]; ASTRAZENECA UK LTD [GB] ET AL.) 19 May 2011 (2011-05-19) cited in the application page 2, line 27 - page 3, line 15 page 11, line 26 - page 12, line 7 page 42, lines 5-12 example 9; table 2 claims 6, 7, 8C, 10, 11F, 13, 14C, 17, 18F, 24, 26, 28-32 -----	1-17
A	WO 2023/136797 A2 (SANOVEL ILAC SANAYI VE TICARET ANONIM SIRKETI [TR]) 20 July 2023 (2023-07-20) page 1, lines 5-9 page 4, line 13 - page 5, line 30 examples claims ----- -/-	1-17



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

21 March 2025

Date of mailing of the international search report

04/04/2025

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/087571

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

International application No

PCT/EP2024/087571

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