Another aim of the present invention is to provide a process for the preparation of a pharmaceutical dosage form according to the invention which is effective in costs and/or time.

Further aims of the present invention become apparent to the one skilled in the art by description hereinbefore and in the following and by the examples.

**Summary ~~of the Invention~~**

~~In one aspect t~~The present disclosure~~invention~~ provides a pharmaceutical composition comprising a SGLT-2 inhibitor and a partner drug as a active pharmaceutical ingredients and one or more excipients. In one embodiment~~aspect~~, a pharmaceutical compositions according to the invention is a solid pharmaceutical composition, for example a solid pharmaceutical composition for oral administration.

In one embodiment~~aspect~~, partner drugs to be combined with the SGLT-2 inhibitor within the pharmaceutical compositions according to this disclosure~~invention~~ are biguanides (e.g. metformin such as metformin hydrochloride).

A preferred partner drug within the meaning of this invention is metformin, particularly metformin hydrochloride (1,1-dimethylbiguanide hydrochloride or metformin HCl).

In general, pharmaceutical excipients which may be used may be selected from the group consisting of one or more fillers, one or more binders or diluents, one or more lubricants, one or more disintegrants, and one or more glidants, one or more film-coating agents, one or more plasticizers, one or more pigments, and the like.

In one aspect, there is provided a solid pharmaceutical dosage form comprising the SGLT-2 inhibitor 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-(*(S)*-tetrahydrofuran-3-yloxy)-benzyl]-benzene, the partner drug metformin hydrochloride, and one or more pharmaceutical excipients, wherein the SGLT-2 inhibitor is present in a dosage range from about 1 mg to about 25 mg, and wherein metformin hydrochloride is present in a dosage range from about 100 mg to about 1500 mg, and wherein the pharmaceutical excipients are selected from the group consisting of one or more fillers selected from the group consisting of microcrystalline cellulose (MCC); D-mannitol, corn starch and pregelatinized starch; a binder selected from the group consisting of copovidone.

The pharmaceutical compositions (tablets) of this invention comprise usually a binder.

In more detail, the pharmaceutical compositions (tablets) of this disclosure~~invention~~ comprise usually one or more fillers (e.g. D-mannitol, corn starch and/or pregelatinized starch and/or microcrystalline cellulose), a binder (e.g. copovidone), a lubricant (e.g. magnesium stearate, sodium stearyl fumarate), and a glidant (e.g. colloidal anhydrous silica).

Suitably the pharmaceutical excipients used within this disclosure~~invention~~ are conventional materials such as D-mannitol, corn starch, microcrystalline cellulose, pregelatinized starch as a filler, copovidone as a binder, magnesium stearate or sodium stearyl fumarate as a lubricant,

colloidal anhydrous silica as a glidant, hypromellose as a film-coating agent, propylene glycol as a plasticizer, titanium dioxide, iron oxide red/yellow/black or mixture thereof as a pigment, and talc, etc.

A typical composition according to the present disclosure~~invention~~ comprises the binder copovidone (also known as copolyvidone or Kollidon VA64).

Further, a typical composition according to the present disclosure~~invention~~ comprises the filler corn starch, the binder copovidone, the lubricant magnesium stearate, and the glidant colloidal anhydrous silica.

Further, a typical composition according to the present disclosure~~invention~~ comprises the filler microcrystalline cellulose, the binder copovidone, the lubricant magnesium stearate or sodium stearyl fumarate, and the glidant colloidal anhydrous silica and optionally the desintegrant crospovidone or croscarmellose sodium.

Thus, in particular, the present disclosure~~invention~~ is directed to a pharmaceutical composition (especially an oral solid dosage form, particularly a tablet) comprising a SGLT-2 inhibitor, metformin hydrochloride and one or more pharmaceutical excipients, particularly one or more fillers, one or more binders, one or more glidants, and/or one or more lubricants.

In more particular, the present disclosure~~invention~~ is directed to a pharmaceutical composition (especially an oral solid dosage form, particularly a tablet) comprising a SGLT-2 inhibitor, metformin hydrochloride, copovidone as binder and one or more further pharmaceutical excipients.

Typical pharmaceutical compositions of this invention may comprise in the SGLT-2 inhibitor portion (% by weight of total SGLT-2 inhibitor portion):

0.1-10 % SGLT-2 inhibitor,
0.1-3 % SGLT-2 inhibitor,
0.4-2.2 % SGLT-2 inhibitor, or
0.1-2.11 % SGLT-2 inhibitor

Typical pharmaceutical compositions of this invention may also comprise in the SGLT-2 inhibitor portion (% by weight of total SGLT-2 inhibitor portion):

0.1-10 % SGLT-2 inhibitor,
0.1-3 % SGLT-2 inhibitor,

0.4-2.2 % SGLT-2 inhibitor, or
0.1-2.12 % SGLT-2 inhibitor.

Typical pharmaceutical compositions of this invention may comprise one or more of the following amounts (% by weight of total coated tablet mass):

| | |
|---|---|
| 0.1-2.11 % | SGLT-2 inhibitor, |
| 47-88 % | metformin HCl, |
| 3.9-8.3 % | binder (e.g. copovidone), |
| 2.3-8.0 % | filler 1 (e.g. corn starch), |
| 0-4.4 % | filler 2 (e.g. pregelatinized starch), |
| 0-33 % | filler 3 (e.g. D-mannitol), |
| 0.7-1.5 % | lubricant (e.g. magnesium stearate), |
| 0.05-0.5 % | glidant (e.g. colloidal anhydrous silica), |
| 0.00-3.0 % | desintegrant (e.g. crospovidone or croscarmellose sodium). |

Typical pharmaceutical compositions of this invention may comprise one or more of the following amounts (% by weight of total coated tablet mass):

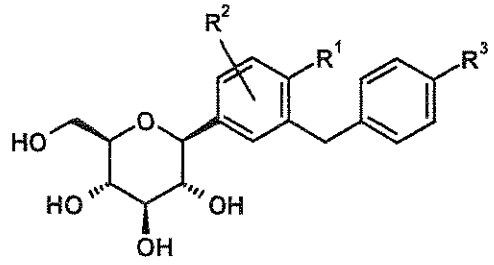
| | |
|---|---|
| 0.1-2.12 % | SGLT-2 inhibitor, |
| 47-88 % | metformin HCl, |
| 3.9-8.3 % | binder (e.g. copovidone), |
| 2.3-8.0 % | filler 1 (e.g. corn starch), |
| 0-4.4 % | filler 2 (e.g. pregelatinized starch), |
| 0-33 % | filler 3 (e.g. D-mannitol), |
| 0.7-1.5 % | lubricant (e.g. magnesium stearate), |
| 0.05-0.5 % | glidant (e.g. colloidal anhydrous silica), |
| 0.00-3.0 % | desintegrant (e.g. crospovidone or croscarmellose sodium). |

In one embodiment, the FDC formulations are chemically stable and either a) display similarity of in-vitro dissolution profiles and/or are bioequivalent to the free combination, or b) allow to adjust the in-vitro and in-vivo performance to desired levels. In a preferred embodiment the invention relates to chemically stable FDC formulations maintaining the original dissolution profiles of corresponding mono tablets of each individual entity, with a reasonable tablet size.

In one embodiment, a pharmaceutical composition of this disclosure~~invention~~ is produced using fluid bed granulation.

Further details about the FDC formulations of this disclosure~~invention~~, e.g. the ingredients, ratio of ingredients (such as e.g. ratio of SGLT-2 inhibitor, metformin hydrochloride,and/or excipients), particularly with respect to special dosage forms (tablets) used within this invention as well as their preparation, become apparent to the skilled person from the disclosure hereinbefore and hereinafter (including by way of example the following examples).

Preferably the SGLT2 inhibitor is selected from a glucopyranosyl-substituted benzene derivative of the formula (I)



I

wherein $R^1$ denotes Cl, methyl or cyano; $R^2$ denotes H, methyl, methoxy or hydroxy and $R^3$ denotes ethyl, cyclopropyl, ethynyl, ethoxy, *(R)*-tetrahydrofuran-3-yloxy or *(S)*-tetrahydrofuran-3-yloxy; or a prodrug of one of the beforementioned SGLT2 inhibitors.

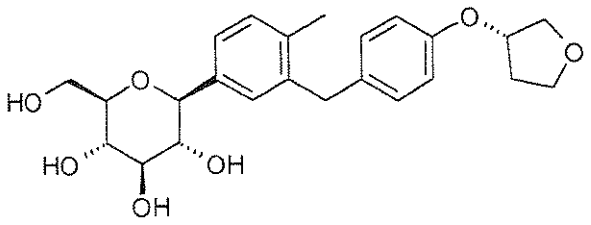
In the above glucopyranosyl-substituted benzene derivatives of the formula (I) the following definitions of the substituents are preferred.

Preferably $R^1$ denotes chloro or cyano; in particular chloro.

Preferably $R^2$ denotes H.

Preferably $R^3$ denotes ethyl, cyclopropyl, ethynyl, *(R)*-tetrahydrofuran-3-yloxy or *(S)*-tetrahydrofuran-3-yloxy. Even more preferably $R^3$ denotes cyclopropyl, ethynyl, *(R)*-tetrahydrofuran-3-yloxy or *(S)*-tetrahydrofuran-3-yloxy. Most preferably $R^3$ denotes ethynyl, *(R)*-tetrahydrofuran-3-yloxy or *(S)*-tetrahydrofuran-3-yloxy.

Preferred glucopyranosyl-substituted benzene derivatives of the formula (I) are selected from the group of compounds (I.1) to (I.11):

| | |
|---|---|
| (I.11) |  1-methyl-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-4-(β-D-glucopyranos-1-yl)-benzene. |

Even more preferred glucopyranosyl-substituted benzene derivatives of the formula (I) are selected from the compounds (I.6), (I.7), (I.8), (I.9) and (I.11).

Even more preferred glucopyranosyl-substituted benzene derivatives of the formula (I) are selected from the compounds (I.8) and (I.9), or a crystalline form (I.9X) of compound (I.9).

The pharmaceutical compositions according to the disclosure~~invention~~ allow a high content uniformity and an effective production with regard to time and costs of pharmaceutical dosage forms, such as tablets and capsules. Furthermore, in one embodiment, these pharmaceutical dosage forms are in particular tablets.

Therefore in another embodiment~~aspect~~ the present disclosure~~invention~~ provides a pharmaceutical dosage form comprising a pharmaceutical composition according to the disclosure~~invention~~. In one embodiment~~aspect~~, the pharmaceutical dosage form according to the disclosure~~invention~~ is a solid pharmaceutical dosage form, for example a solid pharmaceutical dosage form for oral administration.

In another embodiment~~aspect~~, the present disclosure~~invention~~ provides a process for the preparation of a pharmaceutical dosage form according to the disclosure~~invention~~ comprising one or more granulation processes wherein the active pharmaceutical ingredient together with one or more excipients is granulated.

It can be found that a pharmaceutical composition comprising a SGLT2 inhibitor and partner drug as defined hereinafter can advantageously be used for preventing, slowing progression of, delaying or treating a metabolic disorder, in particular for improving glycemic control in patients. This opens up new therapeutic possibilities in the treatment and prevention of type 2 diabetes mellitus, overweight, obesity, complications of diabetes mellitus and of neighboring disease states.

Therefore, in another embodiment ~~first aspect~~ the present disclosure~~invention~~ provides a method for preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity and metabolic syndrome in a patient in need thereof characterized in that a pharmaceutical composition or a pharmaceutical dosage form of the present disclosure~~invention~~ is administered to the patient.

According to another embodiment~~aspect~~ of the disclosure~~invention~~, there is provided a method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c in a patient in need thereof characterized in that a pharmaceutical composition or a pharmaceutical dosage form of the present disclosure~~invention~~ is administered to the patient.

The pharmaceutical composition according to this disclosure~~invention~~ may also have valuable disease-modifying properties with respect to diseases or conditions related to impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or metabolic syndrome.

According to another embodiment~~aspect~~ of the disclosure~~invention~~, there is provided a method for preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus in a patient in need thereof characterized in that a pharmaceutical composition or a pharmaceutical dosage form of the present disclosure~~invention~~ is administered to the patient.

As by the use of a pharmaceutical composition according to this disclosure~~invention~~, an improvement of the glycemic control in patients in need thereof is obtainable, also those conditions and/or diseases related to or caused by an increased blood glucose level may be treated.

According to another embodiment~~aspect~~ of the disclosure~~invention~~, there is provided a method for preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, accute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis, in a patient in

need thereof characterized in that a pharmaceutical composition or a pharmaceutical dosage form of the present disclosure~~invention~~ is administered to the patient. In particular one or more aspects of diabetic nephropathy such as hyperperfusion, proteinuria and albuminuria may be treated, their progression slowed or their onset delayed or prevented. The term "tissue ischaemia" particularly comprises diabetic macroangiopathy, diabetic microangiopathy, impaired wound healing and diabetic ulcer. The terms "micro- and macrovascular diseases" and "micro- and macrovascular complications" are used interchangeably in this application.

By the administration of a pharmaceutical composition according to this disclosure~~invention~~ and due to the activity of the SGLT2 inhibitor excessive blood glucose levels are not converted to insoluble storage forms, like fat, but excreted through the urine of the patient. Therefore, no gain in weight or even a reduction in body weight is the result.

According to another embodiment~~aspect~~ of the disclosure~~invention~~, there is provided a method for reducing body weight or preventing an increase in body weight or facilitating a reduction in body weight in a patient in need thereof characterized in that a pharmaceutical composition or a pharmaceutical dosage form of the present disclosure~~invention~~ is administered to the patient.

The pharmacological effect of the SGLT2 inhibitor in the pharmaceutical composition according to this disclosure~~invention~~ is independent of insulin. Therefore, an improvement of the glycemic control is possible without an additional strain on the pancreatic beta cells. By an administration of a pharmaceutical composition according to this disclosure~~invention~~ a beta-cell degeneration and a decline of beta-cell functionality such as for example apoptosis or necrosis of pancreatic beta cells can be delayed or prevented. Furthermore, the functionality of pancreatic cells can be improved or restored, and the number and size of pancreatic beta cells increased. It may be shown that the differentiation status and hyperplasia of pancreatic beta-cells disturbed by hyperglycemia can be normalized by treatment with a pharmaceutical composition according to this disclosure~~invention~~.

According to another embodiment~~aspect~~ of the disclosure~~invention~~, there is provided a method for 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 in a patient in need thereof characterized in that a pharmaceutical composition or a pharmaceutical dosage form of the present disclosure~~invention~~ is administered to the patient.

By the administration of a pharmaceutical composition according to the present disclosure~~invention~~, an abnormal accumulation of fat in the liver may be reduced or inhibited. Therefore, according to another embodiment~~aspect~~ of the present disclosure~~invention~~, there is provided a method for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of liver fat in a patient in need thereof characterized in that an SGLT2 inhibitor as defined hereinbefore and hereinafter is administered to the patient. Diseases or conditions which are attributed to an abnormal accumulation of liver fat are particularly selected from the group consisting of general fatty liver, non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), hyperalimentation-induced fatty liver, diabetic fatty liver, alcoholic-induced fatty liver or toxic fatty liver.

As a result thereof, another embodiment~~aspect~~ of the disclosure~~invention~~ provides a method for maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance in a patient in need thereof characterized in that a pharmaceutical composition or a pharmaceutical dosage form of the present disclosure~~invention~~ is administered to the patient.

According to another embodiment~~aspect~~ of the disclosure~~invention~~ there is provided the use of a pharmaceutical composition or a pharmaceutical dosage form of the present disclosure~~invention~~ for the manufacture of a medicament for

- preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity and metabolic syndrome; or
- improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c; or
- preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus; or
- preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, accute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis; or

- reducing body weight or preventing an increase in body weight or facilitating a reduction in body weight; or
- 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; or
- preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of liver fat; or
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance;

in a patient in need thereof characterized in that the SGLT2 inhibitor is administered, as defined hereinbefore and hereinafter.

According to another embodimentaspect of the disclosureinvention, there is provided the use of a pharmaceutical composition or a pharmaceutical dosage form of the present disclosureinvention according to the present disclosureinvention for the manufacture of a medicament for a therapeutic and preventive method as described hereinbefore and hereinafter.

**Definitions**

The term **"active ingredient"** of a pharmaceutical composition according to the present invention means the SGLT2 inhibitor according to the present invention. An "active ingredient is also sometimes referred to herein as an "active substance".

The term **"body mass index"** or **"BMI"** of a human patient is defined as the weight in kilograms divided by the square of the height in meters, such that BMI has units of $kg/m^2$.

The term **"overweight"** is defined as the condition wherein the individual has a BMI greater than or 25 $kg/m^2$ and less than 30 $kg/m^2$. The terms "overweight" and "pre-obese" are used interchangeably.

The term **"obesity"** is defined as the condition wherein the individual has a BMI equal to or greater than 30 $kg/m^2$. According to a WHO definition the term obesity may be categorized as follows: the term "class I obesity" is the condition wherein the BMI is equal to or greater than 30 $kg/m^2$ but lower than 35 $kg/m^2$; the term "class II obesity" is the condition wherein the BMI is equal to or greater than 35 $kg/m^2$ but lower than 40 $kg/m^2$; the term "class III obesity" is the condition wherein the BMI is equal to or greater than 40 $kg/m^2$.