PHARMACEUTICAL COMPOSITIONS COMPRISING METFORMIN AND A DPP-4 INHIBITOR OR A SGLT-2 INHIBITOR

The present ~~invention~~disclosure relates to pharmaceutical compositions containing a fixed dose combination (FDC) comprising
a DPP-4 inhibitor drug (particularly 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, also named linagliptin) and/or
a SGLT-2 inhibitor drug (particularly 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene, also named Compound "A" herein),
and
metformin (particularly metformin hydrochloride) in extended release form (metformin XR);
processes for the preparation thereof, and their use to treat certain diseases.

In particular, the present ~~invention~~disclosure relates to a pharmaceutical composition comprising a fixed dose combination of an extended release form of metformin hydrochloride, optionally seal or barrier coated, which is further coated with an immediate release form of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine (linagliptin) and/or 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene (Compound "A").

In a first aspect, there is provided a pharmaceutical composition comprising

a) an extended release core comprising metformin (particularly metformin hydrochloride) and one or more excipients;
b) an optional seal and/or barrier coating; and
c) an immediate release coating comprising at least one active pharmaceutical ingredient selected from
a DPP-4 inhibitor, preferably linagliptin, and
a SGLT-2 inhibitor, preferably 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene,
and one or more excipients.

Further, the present ~~invention~~disclosure relates to a pharmaceutical composition, particularly a solid preparation (e.g. an oral solid dosage form, such as e.g. a tablet), comprising or consisting essentially of

a) an inner extended release core comprising metformin (particularly metformin hydrochloride) and one or more excipients;
b) an optional intermediate seal and/or barrier coating; and

c) an outer immediate release coating comprising at least one active pharmaceutical ingredient selected from
a DPP-4 inhibitor, preferably linagliptin, and
a SGLT-2 inhibitor, preferably Compound "A",
and one or more excipients.

In ~~a~~ more detail~~ed aspect~~, the present ~~invention~~disclosure relates to a pharmaceutical composition, particularly a solid preparation (e.g. an oral solid dosage form, such as a tablet) of a selected dipeptidyl peptidase-4 (DPP-4) inhibitor (preferably linagliptin, particularly in immediate release form) and metformin (particularly metformin hydrochloride) in extended release form (metformin XR). In one embodiment ~~of this aspect~~, the present ~~invention~~disclosure relates to a

pharmaceutical composition, particularly a solid preparation (e.g. an oral solid dosage form, such as a tablet), comprising a fixed dose combination of an extended release form of metformin hydrochloride, optionally seal and/or barrier coated, and further coated with an immediate release form of linagliptin.

In ~~another~~ more detail~~ed aspect~~, the present ~~invention~~disclosure also relates to a pharmaceutical composition, particularly a solid preparation (e.g. an oral solid dosage form, such as a tablet) of a selected SGLT-2 inhibitor (preferably 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene, particularly in immediate release form) and metformin (particularly metformin hydrochloride) in extended release form (metformin XR). In one embodiment ~~of this aspect~~, the present ~~invention~~disclosure relates to a pharmaceutical composition, particularly a solid preparation (e.g. an oral solid dosage form, such as a tablet), comprising a fixed dose combination of an extended release form of metformin hydrochloride, optionally seal and/or barrier coated, and further coated with an immediate release form of 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene.

In ~~a further~~ more detail~~ed aspect~~, the present ~~invention~~disclosure further relates to a pharmaceutical composition, particularly a solid preparation (e.g. an oral solid dosage form, such as e.g. a tablet), comprising

a first component, part or composition comprising metformin (particularly metformin hydrochloride) in extended release form and one or more excipients, and

a second component, part or composition comprising a selected dipeptidyl peptidase-4 (DPP-4) inhibitor (preferably linagliptin), particularly in immediate release form, and one or more excipients.

In particular, the present ~~invention~~disclosure relates to a pharmaceutical composition, particularly a solid preparation (e.g. an oral solid dosage form, such as a tablet), comprising an extended release form of metformin hydrochloride, optionally seal and/or barrier coated, and further coated with an immediate release form of linagliptin.

In ~~another further~~ more detail~~ed aspect~~, the present ~~invention~~disclosure further relates to a pharmaceutical composition, particularly a solid preparation (e.g. an oral solid dosage form, such as e.g. a tablet), comprising

a first component, part or composition comprising metformin (particularly metformin hydrochloride) in extended release form and one or more excipients, and
a second component, part or composition comprising a selected SGLT-2 inhibitor (preferably 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene), particularly in immediate release form, and one or more excipients.

In particular, the present ~~invention~~disclosure relates to a pharmaceutical composition, particularly a solid preparation (e.g. an oral solid dosage form, such as a tablet), comprising an extended release form of metformin hydrochloride, optionally seal and/or barrier coated, and further coated with an immediate release form of 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene.

In ~~a yet further~~ more detail~~ed aspect~~, the present ~~invention~~disclosure further relates to a pharmaceutical composition, particularly a solid preparation (e.g. an oral solid dosage form, such as e.g. a tablet), comprising or consisting essentially of

a) an inner extended release core comprising metformin (particularly metformin hydrochloride) and one or more excipients,
bi) an optional seal coating,
bii) an optional barrier coating, and
c) an immediate release coating comprising a selected dipeptidyl peptidase-4 (DPP-4) inhibitor (preferably linagliptin) and one or more excipients.

In ~~another yet further~~ more detail~~ed aspect~~, the present ~~invention~~disclosure further relates to a pharmaceutical composition, particularly a solid preparation (e.g. an oral solid dosage form, such as e.g. a tablet), comprising or consisting essentially of

a) an inner extended release core comprising metformin (particularly metformin hydrochloride) and one or more excipients,
bi) an optional seal coating,
bii) an optional barrier coating, and
c) an immediate release coating comprising a selected SGLT-2 inhibitor (preferably 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene) and one or more excipients.

Particularly, the pharmaceutical compositions of this ~~invention~~disclosure comprise an inner core formulation of metformin hydrochloride comprising a swellable and/or extended release material.

In an embodiment, the pharmaceutical compositions of this ~~invention~~disclosure comprise an inner extended release core which is a formulation (e.g. matrix formulation) comprising metformin hydrochloride, a swellable and/or extended release material, and one or more further excipients.

Particularly, the pharmaceutical compositions of this ~~invention~~disclosure comprise an outer coat of active pharmaceutical ingredient (API) (linagliptin and/or 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene) in an immediate release polymer film.

The extended-release mechanism for the metformin HCl core may be based on an expandable polymeric swelling formulation that increases gastric retention and extends drug release from the matrix.

This metformin HCl core may be then film-coated (spray-coated) with up to four layers (e.g. barrier coat layer, immediate-release active coat layer, color coat layer, final coat layer), one of which (active coat layer) contains the active pharmaceutical ingredient (API) (linagliptin or 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene), to add the immediate-release active component.

Further, the present ~~invention~~disclosure relates to a coating process (e.g. coating technology and processing conditions) and immediate release coating formulations of active pharmaceutical ingredients (API) in low doses (typically in doses of 0.5 to 25 mg) on top of tablet cores comprising active pharmaceutical ingredients (API) in high doses (typically in doses of 500 – 1500 mg) preferably, but not exclusively on extended release tablets. Anyhow, essential parts of the formulation and the process of this ~~invention~~disclosure may be also applicable to any other fixed dose combination with the described setting.

An aim of the present ~~invention~~disclosure is to provide a pharmaceutical composition comprising a combination of a selected DPP-4 inhibitor (preferably linagliptin, particularly in immediate release form), and metformin (particularly metformin hydrochloride) in extended release form.

Another aim of the present ~~invention~~disclosure is to provide a pharmaceutical composition comprising a combination of a selected SGLT-2 inhibitor (preferably 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene, particularly in immediate release form), and metformin (particularly metformin hydrochloride) in extended release form.

The objectives of the present disclosure are to identify suitable formulations and processing conditions, such as e.g. of a coat of linagliptin or of 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene on top metformin XR cores, providing adequate:

- Chemical stability of the API (particularly linagliptin) in the API film coat,
- Assay of linagliptin or 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene in the API film-coat (e.g. 95-105%),
- Content uniformity of linagliptin or 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene (e.g. RSD < 3%) in the API film-coat,
- Low defect rate of the API-film during film coating process,
- Fast dissolution of the API from the API film-coat and no changes of XR Metformin HCl dissolution, due to the API coating with immediate release of linagliptin or 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene,
- Processing aspects of coating process/technology, processing conditions and immediate release API (linagliptin or Compound "A") coating formulations (API film coat),
- Processing aspects of coating process/technology, processing conditions and immediate release API (linagliptin or Compound "A") coating formulations on top of metformin extended release tablets.

A particular objective of the present ~~invention~~disclosure is to provide a pharmaceutical composition and suitable coating process with very broad range of drug substance (linagliptin or Compound "A")/drug substance (metformin) ratio: 1:400 - 1:40. And the ratio of very low dosed API, e.g. linagliptin with 1 mg or 2.5 mg to very high dosed metformin with 1000 mg and more. And the suitable immediate release dissolution of the low dosed API with high dosed extended release metformin.

The unit dosage strength of the metformin hydrochloride for incorporation into the fixed-dose combination of the present ~~invention~~disclosure is preferably 500, 750, 850 or 1000 milligrams, or even more (e.g. 1500 mg).

These unit dosage strengths of metformin hydrochloride represent the dosage strengths approved in the U.S. for marketing to treat Type 2 diabetes.

The unit dosage strength of linagliptin for incorporation into the fixed-dose combination of the present ~~invention~~disclosure is preferably in the range from 0.5 to 10 mg, for particular example 2.5 or 5 milligrams, or even less (e.g. 0.5 mg or 1 mg).
The unit dosage strength of 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene for incorporation into the fixed-dose combination of the present ~~invention~~disclosure is preferably in the range from 5 to 25 mg, for example 5, 10, 12.5 or 25 milligrams.

Specific embodiments of dosage strengths for linagliptin and metformin hydrochloride in the fixed-dose combinations of the present ~~invention~~disclosure are the following:
(1) 5 milligrams of linagliptin and 1000 milligrams metformin hydrochloride;
(2) 2.5 milligrams of linagliptin and 1000 milligrams metformin hydrochloride;
(3) 2.5 milligrams of linagliptin and 750 milligrams metformin hydrochloride.

Specific embodiments of dosage strengths for 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene and metformin hydrochloride in the fixed-dose combinations of the present ~~invention~~disclosure are the following:
(1) 25 milligrams of 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene and 1000 milligrams metformin hydrochloride;
(2) 12.5 milligrams of 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene and 1000 milligrams metformin hydrochloride;
(3) 12.5 milligrams of 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene and 750 milligrams metformin hydrochloride;
(4) 10 milligrams of 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene and 1000 milligrams metformin hydrochloride;
(5) 10 milligrams of 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene and 750 milligrams metformin hydrochloride;
(6) 5 milligrams of 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene and 1000 milligrams metformin hydrochloride;
(7) 5 milligrams of 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene and 750 milligrams metformin hydrochloride.

Optionally, the pharmaceutical compositions, particularly solid preparations (e.g. oral solid dosage forms, such as e.g. tablets) according to the present ~~invention~~disclosure may further comprise a color coat and/or a final coat.

In a second aspect, there is provided the pharmaceutical composition as defined herein for use in treating and/or preventing (including slowing the progression and/or delaying the onset) of metabolic diseases, especially type 2 diabetes mellitus and conditions related thereto (e.g. diabetic complications), either in type 2 diabetes patients who have not been previously treated with an antihyperglycemic agent, or in type 2 diabetes patients with insufficient glycemic control despite therapy with one or two conventional antihyperglycemic agents selected from metformin, sulphonylureas, thiazolidinediones (e.g. pioglitazone), glinides, alpha-glucosidase blockers, GLP-1 or GLP-1 analogues, and insulin or insulin analogues.

(a) Metformin part:
The first part in the present invention is a part (composition, particularly solid composition, e.g. a solid pharmaceutical composition for oral administration, e.g. tablet) comprising metformin (particularly metformin hydrochloride) in extended release form, particularly an extended release formulation of metformin.

In an embodiment, this first part is a metformin (e.g. 500 mg, 750 mg or 1000 mg metformin hydrochloride) extended release core.

Exemplary extended release formulations of metformin are disclosed in US 6,340,475; US 6,488,962; US 6,635,280; US 6,723,340; US 7780987; US 6,866,866; US 6,495,162; US 6,790,459; US 6,866,866; US 6,475,521; and US 6,660,300; the disclosures of which are incorporated herein in their entireties.

A particular extended release formulation of metformin is described in US 6,723,340, the disclosure of which is incorporated herein in its entirety.

In an embodiment, the fixed-dose combination products of the present invention comprise - as first part - an inner core matrix formulation with metformin hydrochloride dispersed therein, said matrix formulation containing an extended release material. The matrix formulation is compressed into a tablet form.

In a particular embodiment, the fixed-dose combination products of the present invention comprise - as first part - an inner core extended release formulation comprising metformin

hydrochloride, hydroxypropyl methylcellulose (hypromellose), polyethylene oxide, microcrystalline cellulose, and magnesium stearate.

In another particular embodiment, the fixed-dose combination products of the present invention comprise - as first part - an inner core extended release formulation comprising metformin hydrochloride, polyethylene oxide, low molecular weight hydroxypropyl methylcellulose (hypromellose, e.g. Methocel E5), and magnesium stearate.