# PHARMACEUTICAL COMBINATION, COMPOSITION, AND COMBINATION FORMULATION CONTAINING GLUCOKINASE ACTIVATOR AND PPAR RECEPTOR ACTIVATOR, AND PREPARATION METHODS AND USES THEREOF

## PRIORITY APPLICATION

**[0001]** This application claims the priority of the Chinese patent application No. 201810556685.6 filed on May 31, 2018, the entire disclosure of which is incorporated herein by reference.

## TECHNICAL FIELD

**[0002]** The present disclosure relates to a pharmaceutical combination, a composition and a fixed dose combination (FDC) formulation comprising a glucokinase activator (GKA) drug and a partner drug, to a preparation method thereof and to a use thereof in the treatment of some diseases.

**[0003]** More specifically, the present disclosure relates to a pharmaceutical combination, a pharmaceutical composition, or an oral solid formulation of a fixed dose combination comprising a glucokinase activator drug and a partner drug, and a preparation method thereof. The present disclosure also relates to the use of a pharmaceutical combination, a pharmaceutical composition or a fixed dose combination formulation comprising a glucokinase activator for the treatment and/or prevention of one or more diseases and medical disorders, including but not limited to type I diabetes, type II diabetes, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, impaired glucose tolerance, impaired fasting blood glucose, obesity and hypertension. In addition, the present disclosure also relates to a method for treating and/or preventing one or more diseases and medical disorders, comprising administering a therapeutically effective amount of the pharmaceutical combination, pharmaceutical composition or fixed dose combination formulation disclosed herein to a subject in need thereof.

## BACKGROUND

**[0004]** Diabetes mellitus has become a prevalent disease worldwide, with 425 million patients over the world, and 120 million patients in China (International Diabetes Federation, Diabetes Atlas, 2015). Type II diabetes, i.e., non-insulin dependent diabetes mellitus (NIDDM), accounts for more than 90% of the patients with diabetes. Type II diabetes is a hyperglycemic, chronic, metabolic dysfunction resulting from an imbalance of blood glucose homeostasis in

compressor;

(6) mixing the mixture in step (3) in advance, and then rolled with a roller if processing the mixture in step (4) by a roller compressor; if necessary, sizing the granules on a suitable grinder to obtain granules of the required size;

(7) in a suitable mixer, adding optional diluent(s) to the granules obtained in step (6) to improve the compression performance;

(8) adding optional disintegrant(s) (e.g., croscarmellose sodium, crospovidone, or sodium starch glycolate) into the mixture in step (7);

(9) adding optional lubricant(s) or glidant(s) into the mixture in step (8);

(10) filling the mixture of lubricated granules in step (9) into vials, pouches or capsules, or compressing it into a tablet with a desired shape; and

(11) optionally, film-coating the tablets obtained in step (5) or step (10).

**[00122]** In one embodiment disclosed herein, the glucokinase activator in the pharmaceutical combination, pharmaceutical composition or fixed dose combination formulation disclosed herein is in the form of a solid dispersion, which can be prepared by a method selected from the group consisting of spray drying method, fluidized bed drying method, solvent method, melt extrusion method and the like.

**[00123]** One embodiment disclosed herein is a method of preparing a solid dispersion of a glucokinase activator by a spray drying method, which includes the steps of:

(1) formulating a spray drying solution, including dissolving a polymer carrier and a glucokinase activator (alternatively, HMS5552) in a solvent;

(2) spray drying, including controlling the temperature of the inlet air, the amount of the inlet air, the flow rate and pressure of the atomized airflow, the spraying speed of the solution, and the like.

**[00124]** In the embodiment disclosed herein, the solvent used in the preparation of the solid dispersion of the glucokinase activator includes but is not limited to alkanols, esters, nitriles, cycloalkanes, aromatic hydrocarbons, ketones and the like. Specifically, the solvent is selected from the group consisting of anhydrous ethanol, methanol, isopropanol, ethyl acetate, acetone, acetonitrile, isobutanol, n-hexane, benzene and toluene. The solvent can be a single solvent, a mixed solvent, or a mixture of an organic solvent and water.

**Methods and uses for treating and/or preventing diseases**

**[00125]** Another embodiment disclosed herein relates to a method or use of a composition or formulation (alternatively, a fixed dose combination pharmaceutical composition or a fixed dose combination formulation) comprising a glucokinase activator disclosed herein for the

about 0-90% of filler(s);

about 1-10% of binder(s);

about 1-10% of disintegrant(s);

about 0.1-5% of lubricant(s);

about 0-3% of glidant(s); and

about 0-5% of coating agent(s).

**[00156]** Solution 18. The pharmaceutical combination, pharmaceutical composition, or fixed dose combination formulation of solution 16, wherein the doses (alternatively, unit doses) of the ingredients are (by weight):

about 25 mg, about 50 mg, about 75 mg or about 100 mg of the glucokinase activator, or alternatively HMS5552;

about 2 mg, about 4 mg or about 8 mg of rosiglitazone;

about 0-90% of filler(s);

about 1-25% of binder(s);

about 0-15% of disintegrant(s);

about 0.1-10% of lubricant(s);

about 0-3% of glidant(s); and

about 0-5% of coating agent(s).

**[00157]** Solution 19. The pharmaceutical combination, pharmaceutical composition, or fixed dose combination formulation of solution 18 (the fixed dose combination formulation is alternatively a tablet of 25 mg HMS5552/4 mg rosiglitazone or a corresponding amount of rosiglitazone maleate) comprises the components with the following amounts (by weight):

- about 25 mg of HMS5552, alternatively a solid dispersion of HMS5552, alternatively a solid dispersion containing HMS5552 and a polymer carrier, or alternatively a solid dispersion containing about 1:1 of HMS5552 and Eudragit L100;
- about 4 mg of rosiglitazone or a corresponding amount of rosiglitazone maleate;
- about 0-75% of filler(s);
- about 2-8% of binder(s);
- about 1-5% of disintegrant(s);
- about 0.5-3% of lubricant(s);
- about 0-0.5% of glidant(s); and
- about 0-5% of coating agent(s).

**[00158]** Solution 20. The pharmaceutical combination, pharmaceutical composition, or fixed dose combination formulation of solution 18 (the fixed dose combination formulation is alternatively a tablet of 50 mg HMS5552/4 mg rosiglitazone or a corresponding amount of

**[00190]** Solution 18. The pharmaceutical combination, pharmaceutical composition, or fixed dose combination formulation of solution 16, wherein the doses (alternatively, unit doses) of the ingredients are (by weight):

about 25 mg, about 50 mg, about 75 mg or about 100 mg of the glucokinase activator, or alternatively HMS5552;

about 15 mg, about 30 mg, or about 45 mg of pioglitazone or an amount of pioglitazone hydrochloride that can obtain said amount of pioglitazone;

about 0-90% of filler(s);

about 1-25% of binder(s);

about 0-15% of disintegrant(s);

about 0.1-10% of lubricant(s);

about 0-3% of glidant(s); and

about 0-5% of coating agent(s).

**[00191]** Solution 19. The pharmaceutical combination, pharmaceutical composition, or fixed dose combination formulation of solution 18 (the fixed dose combination formulation is alternatively a tablet of 25 mg HMS5552/15 mg pioglitazone or a corresponding amount of pioglitazone hydrochloride) comprises the components with the following amounts (by weight):

- about 25 mg of HMS5552, alternatively a solid dispersion of HMS5552, alternatively a solid dispersion containing HMS5552 and a polymer carrier, or alternatively a solid dispersion containing about 1:1 of HMS5552 and Eudragit L100;
- about 15 mg of pioglitazone or a corresponding amount of pioglitazone hydrochloride;
- about 0-90% of filler(s);
- about 1-25% of binder(s);
- about 1-8% of disintegrant(s);
- about 0.5-3% of lubricant(s);
- about 0-0.5% of glidant(s); and
- about 0-5% of coating agent(s).

**[00192]** Solution 20. The pharmaceutical combination, pharmaceutical composition, or fixed dose combination formulation of solution 18 (the fixed dose combination formulation is alternatively a tablet of 50 mg HMS5552/15 mg pioglitazone or a corresponding amount of pioglitazone hydrochloride) comprises the components with the following amounts (by weight):

- about 50 mg of HMS5552, alternatively a solid dispersion of HMS5552, alternatively a solid dispersion containing HMS5552 and a polymer carrier, or alternatively a solid dispersion

improving blood glucose control and/or reducing fasting plasma glucose, postprandial plasma glucose and/or glycosylated hemoglobin HbA1c.

**[00206]** The following examples further describe and illustrate embodiments within the scope of the present disclosure. However, the present invention is not limited to the examples, and various modifications and substitutions made on the basis of the technology disclosed herein are within the protection scope of the present invention.

**Examples**

**Preparation of the combination tablet of the glucokinase activator**

**[00207]** The chemicals used in the present disclosure can be purchased from companies such as Shin-Etsu Japan, Evonik Germany, J.T. Baker US, SCR China, Ashland US, FMC US, JRS Germany, Colorcon US, Capsugel, BASF, Zhenxing China, and the like. A producing equipment, analytical testing instrument and the like can be purchased from companies such as Sartorius, Nikon, Sympatec, Bruker, Gea Niro, Korsch, Erweka, Agilent, Quadro Engineering, Canada; Waters, US; TA, US; SOTAX, Switzerland; Mettler Toledo Instrument Newark, DE.

**I. Preparation of the solid dispersion of the glucokinase activator**

**1.1 Preparation of the solution of the solid dispersion used for spray drying**

**Example 1A (weight ratio of active ingredients to polymer carriers is 1:9)**

**[00208]** 6.75g Eudragit L100 (Evonik Germany) was weighed, and added to anhydrous ethanol (J.T.Baker) under stirring. After it was completely dissolved, 0.75g of the compound HMS5552 was added. Stirring was continued after adding sufficient amount of anhydrous ethanol to obtain 50 ml solution.

**Example 2A (weight ratio of active ingredients to polymer carriers is 3:7)**

**[00209]** 5.25g Eudragit L100 (Evonik Germany) was weighed, and added to anhydrous ethanol (J.T.Baker) under stirring. After it was completely dissolved, 2.25g of the compound HMS5552 was added. Stirring was continued after adding sufficient amount of anhydrous ethanol to obtain 50 ml solution.

**Example 3A (weight ratio of active ingredients to polymer carriers is 5:5)**

**[00210]** 3.75g Eudragit L100 (Evonik Germany) was weighed, and added to anhydrous ethanol (J.T.Baker) under stirring. After it was completely dissolved, 3.75g of the compound HMS5552 was added. Stirring was continued after adding sufficient amount of anhydrous ethanol to obtain 50 ml solution.

**mg/15 mg)**

| Formula composition | Unit formula amount/mg | % (w/w) |
|---|---|---|
| Pioglitazone hydrochloride* | 15.91 | 5.30 |
| HMS5552 solid dispersion** | 200.00 | 66.67 |
| Microcrystalline cellulose | 63.09 | 21.03 |
| Hydroxypropyl cellulose | 9.00 | 3.00 |
| Croscarmellose sodium | 9.00 | 3.00 |
| Magnesium stearate | 3.00 | 1.00 |
| Total weight of a tablet core | 300.00 | 100.00 |
| Opadry | 9.00 | 3.00 |
| Total weight of a coated tablet | 309.00 | - |

*15.91 mg of pioglitazone hydrochloride was equivalent to 15 mg of pioglitazone free base anhydrate.

**200.00 mg of the HMS5552 solid dispersion contained 100 mg of HMS5552.

**2.2 Preparation of the combination tablet by fluidized bed wet granulation**

**[00228]** The HMS5552 solid dispersion prepared according to the above preparation examples of the solid dispersion of the glucokinase activator and the partner drug were added into a fluidized bed granulator. The optional filler (e.g., microcrystalline cellulose) was added. The prepared solution of the binder (e.g., polyvinylpyrrolidone) was sprayed into the mixture in the fluidized bed during 20 to 60 minutes for granulation, and then drying was continued in a fluidized bed dryer (with the inlet air temperature of 40-60°C). Then, the dried material was ground using a grinder to obtain granules of suitable size. After grinding, the microcrystalline cellulose or silicified microcrystalline cellulose (for the formulation comprising an extragranular filler) was added to the granules, and the mixture was mixed in a barrel mixer. Then, the lubricant (magnesium stearate) and/or optional glidant (micronized silica gel) were added to the mixture and mixed well additionally. The lubricated mixture was compressed with a rotary tablet press to obtain tablets (plain tablets, uncoated tablet cores) of different tablet weights and tablet shapes corresponding to different strengths. Optionally, the obtained tablets were film-coated, and the weight increased by about 3%, thereby obtaining film-coated tablets.

**[00229] Example 7B A combination tablet of HMS5552 + rosiglitazone (dose strength: 25 mg/4 mg)**