PHARMACEUTICAL COMBINATION, COMPOSITION AND COMBINATION FORMULATION COMPRISING GLUCOKINASE ACTIVATOR AND DPP-IV INHIBITOR, AND PREPARATION METHOD AND USE 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, diabetic cognitive dysfunction, memory dysfunction, senile dementia, 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

combination formulation), the second active ingredient is linagliptin, and the dose (alternatively, a unit dose) of linagliptin is about 1 mg to about 50 mg, alternatively about 2.5 mg, about 5 mg, about 7.5 mg or about 10 mg. The alternative dose (alternatively, a unit dose) of linagliptin is about 2.5 mg or about 5 mg. Alternatively, in the above-mentioned pharmaceutical combination, pharmaceutical composition or pharmaceutical formulation (alternatively a fixed dose combination formulation), HMS5552 exists in the form of a solid dispersion.

[00108] In the above-mentioned pharmaceutical combination, pharmaceutical composition or pharmaceutical formulation (alternatively a fixed dose combination formulation), the embodiments of the doses (alternatively, unit doses) of HMS5552 (or an isotope labeled analogue thereof or a pharmaceutically acceptable salt thereof) and linagliptin are as follows:

(1) about 25 mg of HMS5552 and about 2.5 mg of linagliptin;

(2) about 25 mg of HMS5552 and about 5 mg of linagliptin;

(3) about 50 mg of HMS5552 and about 2.5 mg of linagliptin;

(4) about 50 mg of HMS5552 and about 5 mg of linagliptin;

(5) about 75 mg of HMS5552 and about 2.5 mg of linagliptin;

(6) about 75 mg of HMS5552 and about 5 mg of linagliptin;

(7) about 100 mg of HMS5552 and about 2.5 mg of linagliptin; and

(8) about 100 mg of HMS5552 and about 5 mg of linagliptin;

alternatively, in the above-mentioned pharmaceutical combination, pharmaceutical composition or pharmaceutical formulation (alternatively a fixed dose combination formulation), HMS5552 exists in the form of a solid dispersion.

[00109] In one embodiment, the alternative dosage form of the above-mentioned pharmaceutical combination, pharmaceutical composition or pharmaceutical formulation (alternatively a fixed dose combination formulation) is a tablet.

[00110] In one embodiment, the above-mentioned tablet is a fixed dose combination tablet of the glucokinase activator (HMS5552 or an isotope labeled analogue thereof or a pharmaceutically acceptable salt thereof) and linagliptin.

[00111] In one embodiment, the pharmaceutical combination, pharmaceutical composition or pharmaceutical formulation (alternatively a fixed dose combination tablet of 25 mg

step (4) into a tablet with a desired shape, or processing the mixture in step (4) by a roller 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).

[00155] 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.

[00156] 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.

[00157] 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

about 1 to 80% of a glucokinase activator (alternatively HMS5552 or an isotope labeled analogue thereof or a pharmaceutically acceptable salt thereof), alternatively HMS5552, alternatively a solid dispersion of HMS5552, alternatively a solid dispersion comprising HMS5552 and a polymer carrier, and alternatively a solid dispersion comprising about 1:1 of HMS5552 and Eudragit L100;

about 1-50% of vildagliptin;

about 0-55% of filler(s);

about 1-25% 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).

[00227] Solution 17. 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 a glucokinase activator, alternatively HMS5552;

about 50 mg or about 100 mg of vildagliptin;

about 0-55% of filler(s);

about 1-25% 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).

[00228] Solution 18. The pharmaceutical combination, pharmaceutical composition or fixed dose combination formulation of solution 17 (the fixed dose combination formulation is alternatively a tablet of 25 mg HMS5552/50 mg vildagliptin), comprising the components with the following amounts (by weight):

- about 25 mg of HMS5552, alternatively a solid dispersion of HMS5552, alternatively a solid dispersion comprising HMS5552 and a polymer carrier, and alternatively a solid

comprising:

a film-coating substrate, such as hypromellose, hydroxypropyl methyl cellulose or a mixture thereof;

an optional plasticizer, such as polyvinyl alcohol, polyethylene glycol, propylene glycol, polysorbate or a mixture thereof;

an optional coloring agent, such as iron oxide red, iron oxide yellow or a mixture thereof;

an optional opacifier, such as titanium dioxide, and

an optional glidant.

[00255] Solution 15. The pharmaceutical combination, pharmaceutical composition or fixed dose combination formulation of solution 14, wherein the coated tablet is a film-coated tablet, and the film-coating agent is Opadry.

[00256] Solution 16. The pharmaceutical combination, pharmaceutical composition or fixed dose combination formulation of any one of solutions 1-15, comprising (by weight):

about 1 to 80% of a glucokinase activator (alternatively HMS5552 or an isotope labeled analogue thereof or a pharmaceutically acceptable salt thereof), alternatively HMS5552, alternatively a solid dispersion of HMS5552, alternatively a solid dispersion comprising HMS5552 and a polymer carrier, and alternatively a solid dispersion comprising about 1:1 of HMS5552 and Eudragit L100;

about 1-20% of saxagliptin or saxagliptin monohydrate;

about 0-90% of filler(s);

about 1-25% 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).

[00257] Solution 17. 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 a glucokinase activator (alternatively HMS5552 or an isotope labeled analogue thereof or a pharmaceutically

[00289] Solution 17. 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 a glucokinase activator (alternatively HMS5552 or an isotope labeled analogue thereof or a pharmaceutically acceptable salt thereof);
- about 2.5 mg, about 5 mg, about 7.5 mg or about 10 mg of linagliptin;
- about 0-90% of filler(s);
- about 1-25% 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).

[00290] Solution 18. The pharmaceutical combination, pharmaceutical composition or fixed dose combination formulation of solution 17 (the fixed dose combination formulation is alternatively a tablet of 25 mg HMS5552/5 mg linagliptin), comprising the components with the following amounts (by weight):

- about 25 mg of HMS5552, alternatively a solid dispersion of HMS5552, alternatively a solid dispersion comprising HMS5552 and a polymer carrier, alternatively a solid dispersion comprising about 1:1 of HMS5552 and Eudragit L100;
- about 5 mg of linagliptin;
- about 0-90% 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).

[00291] Solution 19. The pharmaceutical combination, pharmaceutical composition or fixed dose combination formulation of solution 17 (the fixed dose combination formulation is alternatively a tablet of 50 mg HMS5552/5 mg linagliptin), comprising the components with

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

[00307] 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)

[00308] 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)

[00309] 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)

[00310] 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

Optionally, the obtained tablets were film-coated with Opadry® II, and the weight increased by about 3%, thereby obtaining film-coated tablets.

[00322] Example 1B a combination tablet of HMS5552 + sitagliptin (dose strength: 50 mg/50 mg)

Formula composition	Unit formula amount/mg	% (w/w)
sitagliptin phosphate monohydrate**	64.25	29.20
HMS5552 solid dispersion*	100.00	45.46
microcrystalline cellulose	40.35	18.34
hydroxypropyl cellulose	6.60	3.00
croscarmellose sodium	6.60	3.00
magnesium stearate	2.20	1.00
Total weight of tablet cores	220.00	100.00
Opadry	6.60	3.00
Total weight of coated tablets	226.60	-

*100.00 mg of the HMS5552 solid dispersion contained 50 mg of HMS5552;

**64.25 mg of sitagliptin phosphate monohydrate was equivalent to 50.0 mg of sitagliptin free base anhydrate.

[00323] Example 2B a combination tablet of HMS5552 + sitagliptin (dose strength: 75 mg/50 mg)

Formula composition	Unit formula amount/mg	% (w/w)
sitagliptin phosphate monohydrate**	64.25	24.71
HMS5552 solid dispersion*	150.00	57.69
microcrystalline cellulose	27.55	10.60
hydroxypropyl cellulose	7.80	3.00

free base anhydrate.

[00327] Example 6B a combination tablet of HMS5552 + sitagliptin (dose strength: 100 mg/50 mg)

Formula composition	Unit formula amount/mg	% (w/w)
sitagliptin phosphate monohydrate**	64.25	18.36
HMS5552 solid dispersion*	200.00	57.14
microcrystalline cellulose	61.26	17.50
hydroxypropyl cellulose	10.50	3.00
croscarmellose sodium	10.50	3.00
magnesium stearate	3.50	1.00
Total weight of tablet cores	350.00	100.00
Opadry	10.50	3.00
Total weight of coated tablets	360.50	

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

**64.25 mg of sitagliptin phosphate monohydrate was equivalent to 50.0 mg of sitagliptin free base anhydrate.

[00328] Example 7B a combination tablet of HMS5552 + linagliptin (dose strength: 25 mg/5 mg)

Formula composition	Unit formula amount/mg	% (w/w)
HMS5552 solid dispersion*	50.00	22.73
linagliptin	5.00	2.27
microcrystalline cellulose	151.80	69.00
hydroxypropyl cellulose	6.60	3.00
croscarmellose sodium	4.40	2.00
magnesium stearate	2.20	1.00
Total weight of tablet cores	220.00	100.00

croscarmellose sodium	6.00	2.00
Total weight of tablet cores	300.00	100.00
Opadry	9.00	3.00
Total weight of coated tablets	309.00	-

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

** 2.64mg of saxagliptin monohydrate was equivalent to 2.5 mg of saxagliptin free base anhydrate.

2.2 Preparation of the combination tablet by fluidized bed wet granulation

[00335] 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.

[00336] Example 14B a combination tablet of HMS5552 + saxagliptin (dose strength: 25 mg/5 mg)

Formula composition	Unit formula amount/mg	% (w/w)