PHARMACEUTICAL COMPOSITION FOR TREATING DIABETES

TECHNICAL FIELD

The present disclosure relates to a pharmaceutical composition for treating diabetes, and more particularly, to a pharmaceutical composition for treating diabetes comprising both metformin and an enzyme inhibitor, which enzyme plays an important role in diabetes mechanism, called a dipeptidyl peptidase 4 (hereinafter referred to as DPP-IV).

BACKGROUND ART

A DPP-IV inhibitor and metformin are pharmaceutical compounds for treating diabetes widely known in the art.

It is disclosed that each of the pharmaceutical compounds provides an antidiabetic effect through different mechanisms, and the combination of the two drugs exerts a good effect in the treatment of patients with diabetes (Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2013:6 187-95).

Furthermore, Korean Patent Publication Nos. 2014-0021049 and 2008-0056171 disclose a pharmaceutical composition comprising a DPP-IV inhibitor and metformin and its preparation method.

However, when the two drugs are administered together, the influence of each drug on stability and release pattern of the other drug is not known.

In the development of DPP-IV inhibitor/metformin combination medicine, the inventors of the present disclosure discovered the fact that when a DPP-IV inhibitor comes into contact with metformin in single formulation, their interaction affects the stability of

the DPP-IV inhibitor. In addition, the inventors of the present disclosure discovered the fact that an amount or proportion of a separating layer for inhibiting the contact between metformin and the DPP-IV inhibitor affects the stability of the DPP-IV inhibitor.

Drugs are degraded or may produce by-products harmful to patients over time. Accordingly, the development of formulations that can minimize the formation of pharmaceutically unacceptable impurities without degradation during long-term storage is urgently needed in the field to which the present disclosure pertains, especially in the field related to manufacturing of combination medicinal products.

Furthermore, in the development of combination medicinal products, drugs should achieve so suitable release to be absorbed into the body, but because each substance has different physical and chemical properties, the development of combination formulation is difficult. Even if a formulation that manifests desirable release is developed, there are problems with costs or residual solvent, making applicability difficult.

In these circumstances, the inventors of the present disclosure attempted to develop a pharmaceutical composition for treating diabetes comprising a DPP-IV inhibitor and metformin in a dosage form that improves the stability of the DPP-IV inhibitor and manifests a desirable release pattern, and perfected the present disclosure.

[RELATED LITERATURE]

(Patent Literature 1) Korean Patent Publication No. 2008-0056171

(Patent Literature 2) Korean Patent Publication No. 2014-0021049

(Non-Patent Literature 1) Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2013:6 187-95

DISCLOSURE

Technical Problem

The present disclosure is directed to providing a pharmaceutical composition for treating diabetes comprising metformin and a DPP-IV inhibitor, with high stability.

The present disclosure is further directed to providing a pharmaceutical composition for treating diabetes, with a desirable release pattern.

Technical Solution

To achieve the object, the present disclosure provides a pharmaceutical composition for treating diabetes comprising metformin and a DPP-IV inhibitor, in which the pharmaceutical composition comprises a separating layer to block the contact between the metformin and the DPP-IV inhibitor.

Advantageous Effects

As the pharmaceutical composition for treating diabetes according to the present disclosure can block the contact between the DPP-IV inhibitor and metformin, there are advantages like that the shelf-life of the composition is extended, and not only the type but also the amount of impurites reduce. Moreover, there are further advantages like that the rapid release of the DPP-IV inhibitor can be achieved and the sustained-release of metformin can be modified at the same time.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagram showing the DPP-IV inhibitor (teneligliptin) release test

results of positive control, example 2, and comparative example 1.

BEST MODE FOR CARRYING OUT THE INVENTION

Hereinafter, the present disclosure is described in detail.

The present disclosure relates to a pharmaceutical composition for treating diabetes comprising metformin; and a DPP-IV inhibitor, in which the pharmaceutical composition comprises a separating layer to block the contact between the metformin and the DPP-IV inhibitor.

Metformin is a biguanide class drug for type 2 diabetes treatment, and improves peripheral insulin sensitivity. Furthermore, metformin reduces intestinal glucose absorption, inhibits hepatic gluconeogenesis, and is associated with inhibition of fatty acid oxidation. General dosage in patients with diabetes is 250 mg to 1000 mg.

A dipeptidyl peptidase-IV (hereinafter DPP-IV) inhibitor is known as being effective in treating diabetes, especially type 2 diabetes, and its general dosage is 25 to 100 mg.

The mechanism of DPP-IV inhibitors is as follows:

Incretin hormones are secreted after eating, and glucagon like peptide-1 (hereinafter, GLP-1) and gastric inhibitory peptide (hereinafter, GIP) are now known as the incretin hormone. Incretin augments the secretion of insulin dependent on blood sugar level. DPP-IV inactivates incretin in vivo. Accordingly, DPP-IV inhibitors have an antidiabetic effect by preventing the reduction in serum insulin level.

The term "metformin" as used herein includes metformin or its pharmaceutically acceptable salt, its crystalline form, hydrate, solvate, diastereomer or enantiomer.

Furthermore, the term "DPP-IV inhibitor" as used herein includes a DPP-IV inhibitor or its pharmaceutically acceptable salt, its crystalline form, hydrate, solvate, diastereomer or enantiomer.

Furthermore, the term "DPP-IV inhibitor" as used herein includes its active metabolite and prodrug, for example, active metabolite and prodrug of the DPP-IV inhibitor. The "metabolite" is an active derivative of the DPP-IV inhibitor produced by metabolism of the DPP-IV inhibitor, and the "prodrug" is a compound that is metabolized into the DPP-IV inhibitor, or metabolized into the same metabolite(s) as the DPP-IV inhibitor.

The DPP-IV inhibitor is known in the art. For example, the DPP-IV inhibitor includes Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Anagliptin, teneligliptin, Alogliptin, Gemigliptin, and Dutogliptin, and the most preferable DPP-IV inhibitor of the present disclosure is teneligliptin.

An advantage of teneligliptin is that teneligliptin achieves a desirable reduction effect in blood sugar level only with once daily administration.

In the present disclosure, the "pharmaceutically acceptable salt" refers to salts produced using an organic or inorganic acid or a base that is not toxic or less toxic. The organic acid includes, for example, formate, acetate, propionate, lactate, butyrate, isobutyrate, trifluoroacetate, malate, maleate, malonate, fumarate, succinate, monoamide succinate, glutamate, tartrate, oxalate, citrate, glycolate, glucuronate, ascorbate, benzoate, phthalate, salicylate, anthranilate, dichloroacetate, aminooxyacetate, benzenesulfonate, p-toluenesulfonate and methanesulfonate, and the inorganic acid includes, for example, hydrochlorate, bromate, sulfate, phosphate, nitrate, carbonate, and borate. Preferably, the

pharmaceutically acceptable salt may be in the form of hydrochlorate or acetate, and more preferably hydrochlorate.

The acid addition salt is produced by a general salt production method, including a) directly mixing the compound with acid, b) dissolving one of the compound and acid in a solvent or a solvent comprising water and mixing them, or c) positioning the compound in acid in a solvent or a solvent comprising water and mixing them.

Aside from the above, alternative salt includes gamma-amino butyrate, gabapentin, pregabalin, nicotinate, adipate, hemi-malonate, cysteinate, acetylcysteinate, methionate, arginate, lycinate, ornithinate, and aspartate.

The pharmaceutically acceptable base addition salt includes, but is not limited to, salts of sodium, potassium, calcium, ammonium, magnesium or organic amino.

The direct pharmaceutical interaction between the DPP-IV inhibitor and the metformin has not been known so far. The inventors first discovered that the stability of a drug may be affected due to the difference in physical·chemical properties between the two drugs.

Specifically, the inventors of the present disclosure found out the fact that the stability of the DPP-IV inhibitor significantly reduced when the DPP-IV inhibitor and the metformin physically contact each other, compared to when they do not physically contact each other.

In an embodiment of the present disclosure, after preparing a pharmaceutical composition comprising the DPP-IV inhibitor and the metformin, as a result of measuring the stability of the two active ingredients, a much lower amount of impurities were measured in the case in which the two active ingredients are physically separated by a

separating layer than the case in which the two active ingredients are not separated. Furthermore, it was predicted that the shelf-life would be extended by 300% or greater when compared control (see experimental example 1).

Accordingly, in the case that the DPP-IV inhibitor and the metformin are combined into a single formulation, the presence of a separating layer is necessary to physically block the contact between the two in order to ensure the stability.

The "separating layer" refers to means that can block the contact between the DPP-IV inhibitor and the metformin, and its form encompasses all means available for oral dosage form in the art, for example, membrane, wall, and coating.

Preferably, when the pharmaceutical composition for treating diabetes according to the present disclosure is prepared in oral dosage form, the oral dosage form includes a formulation comprising an inner layer comprising the metformin, an outer layer comprising the DPP-IV inhibitor, and an intermediate layer between the inner layer and the outer layer to block the contact between the two.

In the case of the formulation, there are not only an effect in improving the stability of the DPP-IV inhibitor but also a desirable advantage in terms of release pattern, by physically blocking the contact between the metformin and the DPP-IV inhibitor.

For example, metformin has slow and incomplete gastrointestinal absorption, and absorption occurs predominantly in the upper part of the small intestine. Metformin is known to have a blood half-life of 2~6 hours. Its solubility is very high, but metformin absorption is incomplete and its half-life is short. Accordingly, the sustained release formulation is necessary to slowly release the drug, and to this end, incorporating into an inner side of the formulation rather than an outer side is advantageous for its release.

In an embodiment of the present disclosure, after preparing a pharmaceutical composition comprising the DPP-IV inhibitor and the metformin, as a result of measuring a release rate of the DPP-IV inhibitor in which rapid action is required, the release rate was much higher when the two active ingredients were separated by a separating layer than when the two active ingredients were not separated (see experimental example 2).

Accordingly, in the case that the DPP-IV inhibitor and the metformin are prepared in a single dosage form, a separating layer is needed to block the contact between the two in order to achieve desirable release pattern.

Preferably, the inner layer comprising metformin may further include swellable polymer for sustained release.

The swellable polymer may be at least one selected from the group consisting of high viscosity hydroxypropylmethylcellulose, hydroxyethylcellulose, carboxymethylcellulose sodium, cross-linked carboxymethylcellulose and its derivatives, methylcellulose, ethylcellulose and its salt or derivatives, carboxy vinyl polymer, polyvinylalcohol, polyethylene oxide (PEO), polymethacrylate polymer, and pharmaceutically acceptable biodegradable cellulose derivatives.

The swellable polymer is effective in achieving the desirable release pattern of the metformin incorporated into the inner layer.

The swellable polymer preferably has the viscosity of 1,000 to 200,000 centipoise (cps), and preferably 4,000 to 200,000 centipoise (cps) to achieve good release characteristics.

In the specification, the viscosity of all polymers was measured in 2 wt% aqueous solution using viscometer commonly used in the art.

When the viscosity of the swellable polymer is lower than 1000 centipoise or higher than 200,000 centipoise, it will be difficult to achieve desirable release pattern due to the pharmacokinetic behavior of the metformin.

Furthermore, the high viscosity cellulose derivatives are preferably present in an amount of 20 to 50 wt% per the total weight of the pharmaceutical composition of the present disclosure to achieve desirable release pattern. The weight of the composition is dry weight.

When the swellable polymer is less than 20 wt% or more than 50 wt% per the total weight the pharmaceutical composition of the present disclosure, it will be difficult to achieve desirable release pattern due to the pharmacokinetic behavior of the metformin.

The inner layer may further comprise a pharmaceutically acceptable excipient widely known in the art. For example, the inner layer may further comprise a filler, a disintegrant, a lubricant, and a binder commonly used in the art without departing from the principles of the present disclosure.

In the case of the DPP-IV inhibitor drug, because rapid action is required, when the pharmaceutical composition of the present disclosure is prepared for oral use, incorporating it into an outer side is advantageous.

The outer layer comprising the DPP-IV inhibitor may further comprise at least one release modifying agent selected from the group consisting of hydroxypropylmethylcellulose (HPMC), carboxymethylcellulose (CMC), microcrystallinecellulose (MCC), polyvinylalcohol, methylcellulose (MC), hydroxypropylcellulose (HPC), celluloseacetate phthalate (CAP), hydroxypropylmethylcellulose phthalate (HPMCP), hydroxypropylmethylcellulose acetate

succinate (HPMCAS), and polymethacrylate polymer.

The outer layer may further comprise a pharmaceutically acceptable excipient widely known in the art. For example, the outer layer may further include a filler, a disintegrant, a lubricant, and a binder commonly used in the art without departing from the principles of the present disclosure.

The intermediate layer blocking the contact between the DPP-IV inhibitor and the metformin may further comprise at least one aqueous polymer selected from the group consisting of hydroxypropylmethylcellulose (HPMC), carboxymethylcellulose (CMC), polyvinylalcohol, and hydroxypropylcellulose (HPC). The intermediate layer may further comprise a plasticizer, a lubricant, a coating aid, and a filler commonly used in the art without departing from the principles of the present disclosure.

The intermediate layer is preferably about 2 to 5 wt% per the total weight of the pharmaceutical composition for treating diabetes according to the present disclosure. The weight of the composition is dry weight.

According to an embodiment of the present disclosure, when the intermediate layer is present in an amount of less than 2 wt% per the total weight of the pharmaceutical composition of the present disclosure, the DPP-IV inhibitor and the metformin are not completely separated, resulting in stability degradation of the DPP-IV inhibitor, and when the intermediate layer is present in an amount of greater than 5 wt%, the stability of the DPP-IV inhibitor also degrades.

The pharmaceutical composition for treating diabetes according to the present disclosure may be prepared in oral or non-oral dosage form, but oral dosage form is more desirable. Advantages of oral dosage form are simple and convenient administration,

improved patient compliance, and production and management cost savings.

The pharmaceutical composition that can be orally administered includes all oral forms that can be recognized by those skilled in the art, for example, tablets, granules, pellets, beads, powders, suspensions, capsules, troches and powders, and the tablets include non-coated tablets, film coated tablets, sugar coated tablets, enteric coated tablets, multi-layered tablets, chewable tablets, sublingual tablets, and buccal tablets.

The present disclosure further provides a preparation method of a pharmaceutical composition for treating diabetes, comprising i) preparing an inner layer comprising metformin; ii) preparing an intermediate layer by coating a surface of the inner layer with at least one aqueous polymer selected from the group consisting of hydroxypropylmethylcellulose (HPMC), carboxymethylcellulose (CMC), and hydroxypropylcellulose (HPC); and iii) preparing an outer layer comprising a DPP-IV inhibitor on a surface of the intermediate layer, and preferably, the preparation method is performed in accordance with the description relating to the pharmaceutical composition.

Hereinafter, examples are described in detail to particularly explain the present disclosure. However, the present disclosure is not limited to the examples.

EXAMPLE

Examples 1 to 3 – Preparation of pharmaceutical compositions for treating diabetes (coating tablets for oral use) according to the present disclosure

a. Preparation of metformin inner layer

The inner layers of examples 1 to 3 were prepared according to the composition

and amounts listed in Table 1.

[Table 1]

Composition	Amount (mg)
Metformin hydrochloride	1000
Hydroxypropylmethylcellulose (100,000 cps)	313
Carboxymethylcellulose sodium	50
Polyvinylpyrrolidone K-30	40
Magnesium stearate	15

Specifically, metformin hydrochloride, hydroxypropylmethylcellulose 100,000 centipoise (cps) (measured in 2 wt% aqueous solution), carboxymethylcellulose sodium and polyvinylpyrrolidone K-30 were uniformly mixed in a mixer, a predetermined amount of water was added to obtain wet granules, and granules obtained by passing the wet granules through 14 mesh sieve were dried in a fluidized bed dryer. Magnesium stearate was added to the dried granules, and they were mixed to obtain granules with high flowability and compactability. Subsequently, a metformin inner layer (non-coated tablets) was obtained according to a general tableting method.

b. Preparation of intermediate layer

A coating solution for preparing an intermediate layer for blocking the contact between the metformin and a DPP-IV inhibitor was prepared according to the composition and amounts listed in Table 2.

[Table 2]

Composition	Amount (mg)		
	Example 1	Example 2	Example 3
Hydroxypropylmethylcellulose 4.5cps	35.7	47.6	59.6
Polyethyleneglycol	6.8	9.1	11.3
Purified water	297.8	397.0	496.3

Specifically, polyethyleneglycol and purified water were mixed, and hydroxypropylmethylcellulose (4.5 cps) was added to the prepared polyethyleneglycol aqueous solution, and mixed until a homogeneous drug coating solution is obtained. The prepared coating solution was sprayed onto the inner layer comprising the metformin prepared in 1-a, to form an intermediate layer.

c. Completion of DPP-IV inhibitor outer layer and pharmaceutical composition of the present disclosure

Coating solutions for preparing outer layers of examples 1 to 3 were prepared according to the composition and amounts listed in Table 3.

[Table 3]

Composition	Amount (mg)
Hydroxypropylmethylcellulose (4.5 cps)	50
Polyethyleneglycol	10

Teneligliptin	31
Purified water	630

Specifically, teneligliptin, polyethyleneglycol, and hydroxypropylmethylcellulose (4.5 cps) were uniformly dispersed in purified water, and mixed until a homogeneous drug coating solution is obtained. The prepared coating solution was sprayed onto tablets having the inner layer and the intermediate layer in coating machine, and dried to prepare a pharmaceutical composition of the present disclosure.

Comparative example 1

Tablets were manufactured according to the same composition and method as examples 1 to 3, except that an intermediate layer was not formed (an intermediate layer is absent).

Comparative examples 2 and 3

Formulations were prepared according to the same composition and method as examples 1 to 3, except that a coating amount for the intermediate layer was adjusted as indicated in the following Table 4.

[Table 4]

Composition	Amount (mg)	
	Comparative example 2	Comparative example 3
Hydroxypropylmethylcellulose 4.5cps	23.8	71.5

Polyethyleneglycol	4.8	13.6
Purified water	198.5	595.6

Experimental example 1: Stability test (severe conditions)

Stability comparison testing was conducted under severe conditions according to the stability testing method described by the International Conference of Harmonization (ICH). Measurements were made at the temperature of 60℃ and relative humidity of 75% for 3 days, and their results are presented in the following Table 5.

[Table 5]

Subject	Coating amount for intermediate layer (wt%)	Days	Unknown	Impurity-6	Impurity C	Predicted shelf-life (month)
Comparative example 1	0	0	0	0	0.052	6
		3	1.222	0.588	0.368	
Comparative example 2	1.8	0	0	0	0.052	18
		3	0.522	0.195	0.29	
Example 1	2.7	0	0	0	0.052	24
		3	0.458	0.183	0.252	

Example 2	3.6	0	0	0	0.052	28
		3	0.385	0.155	0.226	
Example 3	4.4	0	0	0	0.052	24
		3	0.358	0.201	0.253	
Comparative example 3	5.3	0	0	0	0.052	18
		3	0.388	0.2	0.291	

As seen from Table 5 above, it could be seen that the concentration of impurities was higher and the predicted shelf-life under severe conditions was much shorter in the absence of intermediate layer (comparative example 1) than in the presence of intermediate layer (examples 1 to 3, comparative examples 1 and 2). Furthermore, from the fact that comparative examples 2 and 3 showed higher concentration of impurites than examples 1 to 3 and the predicted shelf-life of less than 24 months, it could be seen that an amount of intermediate layer greatly affected the stability of the DPP-IV inhibitor.

Experimental example 2: Release test of DPP-IV inhibitor

In the pharmaceutical composition comprising the DPP-IV inhibitor and the metformin, the influence of the separating layer on the release properties of the DPP-IV was measured.

Each of example 2 and comparative example 1 was tested in 900ml Tris buffered saline, pH 9.0, at 37℃ and 50 rpm according to the dissolution test method (Method II) described in USP, the effluent was collected at fixed time intervals, and the teneligliptin content was measured according to high pressure liquid chromatography described in USP.

For positive control, Tenelia tablet 20mg were used.

The results are presented in the following Table 6, and a detailed description is shown in FIG. 1.

[Table 6]

Time (min)	Release rate of teneligliptin		
	Positive control (%)	Example 2 (%)	Comparative example 1 (%)
10	71.6	81.1	68.7
15	92.2	88.7	78.2
30	103.3	94.2	86.8
45	103.8	95.6	88.9

As seen from Table 6 above, example 2 with an intermediate layer separating the two active ingredients teneligliptin and metformin showed a release pattern almost similar to positive control, whereas comparative example 1 with no intermediate layer showed different pattern from positive control. For more objective determination, based on the results according to Table 6, similarity factor (f2) was calculated according to the pharmaceutical equivalence test standards announced by Ministry of Food and Drug Safety (when similarity factor is greater than 50, equivalence is acknowledged), and the results are shown in the following Table 7.

[Table 7]

	Example 2	Comparative example 1
Similarity factor (f2)	54.9	43.9
Result	equivalent	non-equivalent

As seen from the above table, it could be seen that example 2 was found equivalent to positive control, whereas comparative example 1 was found non-equivalent.

5

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for treating diabetes, comprising:

metformin; and

teneligliptin,

wherein the pharmaceutical composition comprises a separating layer to block contact between the metformin and the teneligliptin, and the separating layer is present in an amount of 2 to 5 wt% per the total weight of the pharmaceutical composition .

2. The pharmaceutical composition for treating diabetes according to claim 1, wherein the metformin is incorporated into an inner layer, the teneligliptin is incorporated into an outer layer, and the separating layer constitutes an intermediate layer interposed between the inner layer and the outer layer.

3. The pharmaceutical composition for treating diabetes according to claim 2, wherein the inner layer further comprises a swellable polymer, and the swellable polymer is at least one selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, carboxymethylcellulose sodium, cross-linked carboxymethylcellulose and its derivatives, methylcellulose, ethylcellulose and its salt or derivatives, carboxy vinyl polymer, polyvinylalcohol, polyethylene oxide (PEO), polymethacrylate polymer, and pharmaceutically acceptable biodegradable cellulose derivatives.

4. The pharmaceutical composition for treating diabetes according to claim 3, wherein the swellable polymer is a polymer having viscosity of 1,000 to 200,000 centipoise (cps).

5. The pharmaceutical composition for treating diabetes according to claim 4, wherein the swellable polymer is a polymer having viscosity of 4,000 to 200,000 centipoise (cps).

6. The pharmaceutical composition for treating diabetes according to claim 3, wherein the swellable polymer is present in an amount of 20 to 50 wt% per the total weight of the pharmaceutical composition.

7. The pharmaceutical composition for treating diabetes according to claim 2, wherein the outer layer further comprises at least one release modifying agent selected from the group consisting of hydroxypropylmethylcellulose (HPMC), carboxymethylcellulose (CMC), microcrystalline cellulose (MCC), polyvinylalcohol, methylcellulose (MC), hydroxypropylcellulose (HPC), celluloseacetate phthalate (CAP), hydroxypropylmethylcellulose phthalate (HPMCP), hydroxypropylmethylcellulose acetate succinate (HPMCAS), and polymethacrylate polymer.

8. The pharmaceutical composition for treating diabetes according to claim 2, wherein the intermediate layer is at least one aqueous polymer selected from the group consisting of hydroxypropylmethylcellulose (HPMC), carboxymethylcellulose (CMC), polyvinylalcohol, and hydroxypropylcellulose (HPC).

9. The pharmaceutical composition for treating diabetes according to claim 1, wherein the pharmaceutical composition for treating diabetes is for oral use.

10. The pharmaceutical composition for treating diabetes according to claim 1, wherein the metformin is present in an amount of 250 mg to 1000 mg.

11. The pharmaceutical composition for treating diabetes according to claim 1, wherein the teneligliptin is present in an amount of 25 mg to 100mg.

12. A preparation method of a pharmaceutical composition for treating diabetes, comprising:

i) preparing an inner layer comprising metformin;

ii) preparing an intermediate layer by coating a surface of the inner layer with at least one aqueous polymer selected from the group consisting of hydroxypropylmethylcellulose (HPMC), carboxymethylcellulose (CMC), and hydroxypropylcellulose (HPC); and

iii) preparing an outer layer comprising teneligliptin on a surface of the intermediate layer.