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(54) Title: THE COMBINATION COMPRISING LINAGLIPTIN AND METFORMIN

(57) Abstract: The present invention relates to a solid oral pharmaceutical composition comprising linagliptin, metformin and at least one pharmaceutically acceptable excipient. Further the present invention provides a method for the preparation of said composition.

THE COMBINATION COMPRISING LINAGLIPTIN AND METFORMIN

Field of the Invention

The present invention relates to a solid oral pharmaceutical composition comprising linagliptin, metformin and at least one pharmaceutically acceptable excipient. Further the present invention provides a method for the preparation of said composition.

Background of the Invention

Diabetes mellitus is a group of disorders of carbohydrate metabolism in which the action of insulin is diminished or absent through altered secretion, decreased insulin activity or a combination of both factors. There are two main types of diabetes; Type 1 and Type 2:

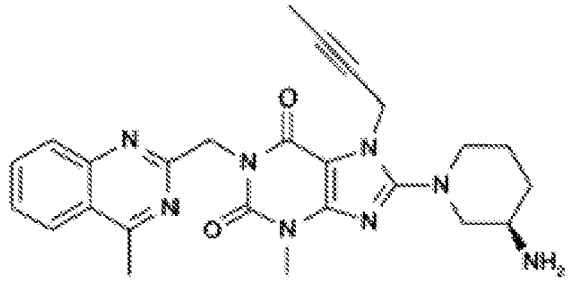
Type 1 diabetes occurs because the insulin-producing cells of the pancreas (beta cells) are damaged. In Type 1 diabetes, the pancreas makes little or no insulin, so sugar cannot get into the body's cells for use as energy. People with Type 1 diabetes must use insulin injections to control their blood glucose.

In Type 2 diabetes, the pancreas makes insulin, but it either doesn't produce enough, or the insulin does not work properly. This diabetes occurs most often in people who are over 40 years old and overweight. Type 2 diabetes may sometimes be controlled with a combination of diet, weight management, and exercise. However, treatment also may include oral glucose-lowering medications or insulin injections.

Linagliptin is used for type 2 or non-insulin dependent diabetes. It is a selective, orally administered, xanthine based dipeptidyl peptidase-4 (DPP-4) inhibitor used as an adjunct to diet and exercise to improve glycemic control. DPP-4 inhibitors work by blocking the action of DPP-4, an enzyme which destroys the hormone incretin. There are two types of incretin hormones found in the body, called glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These hormones are naturally produced by the body in response to food intake. Their function is to help the body produce more insulin only when it is needed and reduce the amount of glucose being produced by the liver when it is not needed. Linagliptin works by binding to DPP-4 and preventing it from

breaking down the GLP-1 and GIP. This increases the levels of these hormones in the body and so increases their effect on controlling blood sugar.

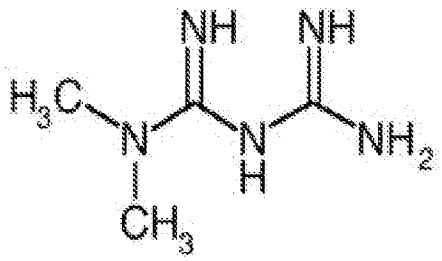
The chemical name of linagliptin is 8-[(3R)-3-aminopiperidin-1-yl]-7-but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione and its chemical structure is shown in the Formula I.



Formula I

Metformin is antidiabetics having an orally-administrated biguanide structure. Metformin hydrochloride is a white to off-white crystalline compound and it is freely soluble in water and practically insoluble in acetone, ether and chloroform. Oral doses of metformin are generally recommended in the range of 500 to 2500 mg a day and a single dose may vary from 500 to 850 mg. It is used singly or in combination with sulfonylureas, alpha-glucosidase inhibitors, or insulin.

The chemical name of metformin hydrochloride is 1,1-dimethylbiguanide hydrochloride, has the following chemical structure of Formula II.



Formula II

It has been surprisingly observed that an unexpected therapeutic benefit and especially a synergistic therapeutic benefit can be obtained in the treatment of type-2 diabetes when a combination therapy comprising linagliptin and metformin are used together.

US patent publication 2011206766 discloses pharmaceutical composition comprising linagliptin and metformin HCl and one or more pharmaceutical excipients, and a nucleophilic and/or basic agents for stabilizing said linagliptin against degradation. Furthermore, the patent discloses use of a basic amino acid L-arginine, which may be suitable for stabilizing.

In the prior art, there are combinations comprising linagliptin and metformin, the combinations uses many ways to overcome the problem of chemical degradation of free base of linagliptin, for example; using basic amino acid as stabilizer. But the process and formulation described in the prior art are complex, time consuming and costs are high.

Thus, still a need for a physically and chemically stable composition.

In the present invention, it has been found surprisingly that physically and chemically stable pharmaceutical composition comprising linagliptin and metformin that overcomes above mentioned problem without using stabilizer.

Detailed description of the Invention

The present invention is aimed to obtain a stable combination formulation with synergistic effect for use in the treatment of type-2 diabetes so, this invention provides more effective treatment and at the same time, provide therapeutic effect in a shorter time.

The present invention is aimed to ensure good content uniformity without the addition of significant side effect.

Another object of the present invention is to eliminate problems and bringing additional advantages to the relevant prior art.

Another object of this present invention is to provide stable dosage form with desired dissolution profiles.

The term “combination” means that when drugs are administered together, a combined action is obtained which is higher than the individual actions of the respective drugs when they are used separately. On the other hand, using a lower dose of each drug to be combined according to the present invention will reduce the total dosage. These are advantageous in terms of patients to be treated.

The term "linagliptin" as used throughout the specification refers to not only linagliptin, but also its other pharmaceutically acceptable salt, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs or pharmaceutically acceptable prodrugs thereof.

The linagliptin is present as amorphous linagliptin, crystalline linagliptin having polymorphic form A, crystalline linagliptin having polymorphic form B and crystalline linagliptin having polymorphic form C or mixtures of thereof.

The term "metformin" as used throughout the specification refers to not only metformin, but also its other pharmaceutically acceptable salt, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs or pharmaceutically acceptable prodrugs thereof.

In this present invention, combining more than one molecule in one dosage form increases the patient’s compliance. However, while this combination is increasing the patients’ quality of life, combining more than one molecule in one dosage form also reduces side effects.

In one embodiment of the present invention, the solid oral pharmaceutical composition comprises linagliptin and metformin.

One embodiment according to this present invention, preferably crystalline linagliptin having polymorphic form A and/or crystalline linagliptin having polymorphic form B is used form of linagliptin. The amount of linagliptin in the total composition is between 0.05% and 10.0%, preferably 0.05% and 5.0% or 5.0% and 8.0% or 8.0% and 10.0% by weight.

One embodiment according to this present invention, a pharmaceutically acceptable polymorphs of metformin is used and the amount of metformin in the total composition is between 70.0% and 90.0%, preferably 70.0% and 75.0% or 75.0% and 81.0% or 81.0% and 90.0% by weight.

In one embodiment of the present invention, the pharmaceutically acceptable excipients are selected from disintegrants, binders, fillers, lubricants, coating agents or mixtures thereof.

The advantages of the present invention are even more significant, as the problem of homogeneity is even more likely to occur when two active substances are incorporated in one final dosage form, especially when two actives is used very different regarding the amount. Improved content uniformity efficiently contributes to a marked increase in bioavailability. Improved content uniformity also favors to avoid toxicity in the otherwise possible event that the amount of drug substance would be too high.

Linagliptin is used small proportion that can lead to considerable problems during the manufacture of the composition with regard to the uniformity of the content of active agent in the individual composition units. Because of problems uniformity of the content, the active substance may interact with several excipients. It reflects that content uniformity play important role in the dissolution of the drug. Using the right disintegrant is ensured uniformity of the content.

Suitable disintegrants are selected from the group comprising sodium starch glycolate, low-substituted hydroxypropyl cellulose, cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethylcellulose, alginates, gums, cross-linked calcium carboxymethylcellulose, sodium carboxymethylcellulose, ion-exchange resins or mixtures thereof.

A sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredient should be used to form solid oral dosage forms provided herein. However, disintegrants can be mixed with other excipient to increase effective disintegration of the tablet into smaller fragments.

In one embodiment of the present invention, the amount of disintegrant in the total composition is between 0.5% and 10.0% by weight, preferably 2.0% and 8.0% by weight, more preferably 3.0% and 6.0% by weight.

In general, linagliptin are not very stable compounds. Especially, in the solid dosage forms, amine group containing linagliptin may react with many excipients or impurities of excipients. In this invention, it has been surprisingly found that using disintegrant (especially sodium starch glycolate) ensures high stability of linagliptin in a solid oral dosage formulation and thus desired level of dissolution rate is provided.

In one embodiment of the present invention, the disintegrant is sodium starch glycolate, is also known as superdisintegrant, and the amount of sodium starch glycolate in the composition is between 2.0% and 8.0% by weight, preferably 3.0% and 6.0% by weight.

Suitable binders are selected from group comprising povidone, hydroxylpropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, carboxymethyl cellulose, polyethylene glycol, polyvinyl alcohol, polyvinyl acetate, polyvinylpyrrolidone, sugars, glucose syrups, natural gums, guar gum, tragacanth gum, pregelatinized starch, gelatins, pullulan, agar, alginate, sodium alginates, glycyrrhizin, polymetacrylates, collagen, hyaluronic acid, pectin, carrageenan, carbomer, poloxamer, polyacrylamide, aluminum hydroxide, benthonite, laponite, cetostearyl alcohol, polyoxyethylene-alkyl ethers, acacia mucilage, polydextrose, polyethylene oxide, xylitol, sucrose stearate or mixtures thereof.

According to one embodiment of the present invention, the amount of binder in the total composition is between 0.1% and 10.0% by weight.

According to one embodiment of the present invention, the binder is povidone.

Furthermore, the combination of povidone and sodium starch glycolate provides desired short disintegration time in composition.

According to one embodiment of the present invention, the weight ratio of povidone of sodium starch glycolate is between 1:5 and 5:1, preferably between 1:4 and 4:1.

Suitable fillers are selected from group comprising microcrystalline cellulose, lactose monohydrate, starch, mannitol, dibasic calcium phosphate, tribasic calcium phosphate,

trehalose, isomalt, sodium carbonate, sodium bicarbonate, calcium carbonate or mixtures thereof.

Suitable lubricants are selected from group comprising sodium stearyl fumarate, magnesium stearate, polyethylene glycol, sodium lauryl sulphate, magnesium lauryl sulphate, fumaric acid, glyceryl palmitostearate, hydrogenated natural oils, zinc stearate, calcium stearate, silica, talc, stearic acid, polyethylene glycol, paraffin or mixtures thereof.

Suitable coating agents are selected from the group comprising polymethacrylates, hydroxypropyl methylcellulose, triacetin, glycerol triacetin, talc, lactose monohydrate, hydroxypropyl cellulose, polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyvinyl alcohol-polyethylene glycol copolymers (Kollicoat® IR), ethylcellulose dispersions (Surelease®), polyvinylprolidone, polyvinylprolidone-vinyl acetate copolymer (PVP-VA), all kinds of Opadry®, pigments, dyes, titanium dioxide, macrogol, coloring agent or mixtures thereof.
Suitable coloring agents are selected from the group comprising ferric oxide, titanium dioxide, Food, Drug & Cosmetic (FD&C) dyes (such as; FD&C blue, FD&C green, FD&C red, FD&C yellow, FD&C lakes), ponceau, indigo Drug & Cosmetic (D&C) blue, indigotine FD&C blue, carmoisine indigotine (indigo Carmine); iron oxides (such as; iron oxide red, yellow, black), quinoline yellow, flaming red, carmine, carmoisine, sunset yellow or mixtures thereof.

An embodiment of this present invention, the formulation is free of basic amino acid.

In this present invention, solid oral pharmaceutical composition is in the form of tablet, capsule, pastilles, strip.

In this present invention, the solid oral pharmaceutical composition is tablet form.

An embodiment of this present invention, the solid oral pharmaceutical combination is formulated as tablets comprising compressed tablets, coated or uncoated tablets, inlay tablet, multilayer tablets, inlay tablet, mini tablets, bilayer tablet, buccal tablets, sublingual tablets, effervescent tablets, immediate release tablets, modified release tablets, film-coated tablets, orally disintegrating tablets, gastric disintegrating tablets, chewable tablet, dispersing tablet, lozenges.

Preferably, the solid oral pharmaceutical combination is formulated as film coated tablet or bilayer tablet.

In this present invention, the solid oral pharmaceutical combination is tablet form. Tablet comprises of at least one type of particle, for example; mini-tablet, pellets, core, agglomerates, granules, powder, liposomes, sphericles or mixtures thereof.

According to an embodiment of this present invention, each type of particle comprises at least one active agent.

Preferably, the solid oral pharmaceutical combination is tablet-in-tablet or core-in-tablet.

In this present invention, the solid oral pharmaceutical combination is capsule form. Capsule comprises of at least one type of particle, for example; capsule, mini-tablet, pellets, agglomerates, granules, powder, liposomes, sphericles or mixtures thereof.

According to an embodiment of this present invention, the combination is mini-capsule in capsule wherein the mini capsule comprises at least one active agent. Mini-capsule is located within a capsule.

According to an embodiment of this present invention, the combination is mini-tablets in capsule wherein a mini-tablet comprises at least one active agent. Mini-tablets is located within a capsule.

According to an embodiment of this present invention, the combination is pellet in capsule wherein pellet comprises at least one active agent. Pellets are located within a capsule.

According to an embodiment of this present invention, the combination is granule in capsule wherein granule comprises at least one active agent. Granules are located within a capsule.

In this present invention, linagliptin and metformin combination are stable. The combination does not show incompatibilities, degradation problems, or extraction problems with certain excipients such as microcrystalline cellulose, sodium starch glycolate, povidone, sodium stearyl fumarate and coating agents.

In one embodiment of the invention, the composition comprises;

a) 0.05 - 10.0% by weight of linagliptin
b) 70.0 - 90.0% by weight of metformin
c) 1.0 - 10.0% by weight of microcrystalline cellulose
d) 2.0 - 8.0% by weight of sodium starch glycolate
e) 0.1 - 6.0% by weight of povidone
f) 0.1 - 4.0% by weight of sodium stearyl fumarate
g) 0.1 – 6.0% by weight of coating agent

The compositions of invention can be developed into solid oral dosage form comprising immediate release, extended release, sustained release, controlled release, modified release and delayed release or combination thereof.

It has surprisingly been found that solid dosage forms of excellent uniformity and showing improved dissolution can be obtained when metformin and linagliptin are formulated together in wet granulation process. Metformin as the first pharmaceutically active ingredient is granulated together with linagliptin as second pharmaceutically active ingredient and at least one suitable pharmaceutical excipient. Wet granulation process efficiently counteracts segregation, so it can achieve good dissolution and disintegration properties.

Process for preparing the solid oral pharmaceutical composition comprises the following steps;

a) Mixing linagliptin, metformin, microcrystalline cellulose and sodium starch glycolate
b) Granulating povidone with water-ethanol mixture (70% ethanol) on a separate tank
c) Mixing step (a) mixture and step (b) mixture
d) Drying the mixture until the humidity is less than 2.0%, then sieving the mixture
e) Then, adding sodium stearyl fumarate and mixing
f) Then, pressing to form tablet
g) Coating tablets with the coating agent

Example 1: Film coated tablet comprising linagliptin and metformin

	(%) amount (w/w)
Linagliptin	0.05%-10.0%
Metformin	70.0%-90.0%
Disintegrants	0.5%-10.0%
Fillers	1.0%-10.0%
Binders	0.1%-10.0%
Lubricant	0.1%-6.0%
Coating agent	1.0%-9.0%
Total composition	**100**

Example 2: Film coated tablet comprising linagliptin and metformin

	(%) amount (w/w)
Linagliptin	0.05%-10.0%
Metformin	70.0%-90.0%
Microcrystalline cellulose	1.0%-10.0%
Sodium starch glycolate	2.0%-8.0%
Povidone	0.1%-6.0%
Sodium stearyl fumarate	0.1%-4.0%
Coating agent	0.1%-6.0%
Total composition	**100**

Example 3: Film coated tablet comprising linagliptin and metformin

	(%) amount (w/w)
Linagliptin	0.1% - 0.5%
Metformin	83.0% - 84.0%
Microcrystalline cellulose	1.0% - 2.0%
Sodium starch glycolate	5.0%
Povidone	4.0%
Sodium stearyl fumarate	1.5%
Coating agent	3.5% - 4.1%
Total composition	**100**

A process for preparing the solid oral pharmaceutical composition in example 2 and example 3 comprises the following steps:

a) Mixing linagliptin, metformin, microcrystalline cellulose and sodium starch glycolate
b) Granulating povidone with water-ethanol mixture (70% ethanol) on a separate tank
c) Mixing step (a) mixture and step (b) mixture
d) Drying the mixture until the humidity is less than 2.0%, then sieving the mixture
e) Then, adding sodium stearyl fumarate and mixing
f) Then, pressing to form tablet
g) Coating tablets with the coating agent

CLAIMS

1. A solid oral pharmaceutical composition comprising linagliptin whose total amount in the composition is 0.05% to 10.0% by weight and metformin whose total amount in the composition is 70.0% to 90.0% by weight and at least one pharmaceutically acceptable excipient.

2. The solid oral pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable excipients are selected from disintegrants, binders, fillers, lubricants, coating agents or mixtures thereof.

3. The solid oral pharmaceutical composition according to claim 2, wherein the disintegrants are sodium starch glycolate, low-substituted hydroxypropyl cellulose, cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethylcellulose, alginates, gums, cross-linked calcium carboxymethylcellulose, sodium carboxymethylcellulose, ion-exchange resins or mixtures thereof.

4. The solid oral pharmaceutical composition according to claim 3, wherein the amount of disintegrant in the total composition is between 0.5% and 10.0% by weight.

5. The solid oral pharmaceutical composition according to claim 3 or 4, wherein the disintegrant is sodium starch glycolate.

6. The solid oral pharmaceutical composition according to claim 2, wherein the binders are selected from group comprising povidone, hydroxylpropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, carboxymethyl cellulose, polyethylene glycol, polyvinyl alcohol, polyvinyl acetate, polyvinylpyrrolidone, sugars, glucose syrups, natural gums, guar gum, tragacanth gum, pregelatinized starch, gelatins, pullulan, agar, alginate, sodium alginates, glycyrrhizin, polymetacrylates, collagen, hyaluronic acid, pectin, carrageenan, carbomer, poloxamer, polyacrylamide, aluminum hydroxide, benthonite, laponite, cetostearyl alcohol, polyoxyethylene-alkyl ethers, acacia mucilage, polydextrose, polyethylene oxide, xylitol, sucrose stearate or mixtures thereof.

7. The solid oral pharmaceutical composition according to claim 6, wherein the amount of binder in the total composition is between 0.1% and 10.0% by weight.

8. The solid oral pharmaceutical composition according to claim 6 or 7, wherein the binder is povidone.

9. The solid oral pharmaceutical composition according to claim 1, wherein the formulation is free of basic amino acid.

10. The solid oral pharmaceutical composition according to any preceding claim, wherein said combination is in the form of tablet.

11. The solid oral pharmaceutical composition according to any preceding claim, wherein said combination is in the form of capsule.

12. The solid oral pharmaceutical composition according to any preceding claims, comprising;

0.05 - 10.0% by weight of linagliptin
70.0 - 90.0% by weight of metformin
1.0 - 10.0% by weight of microcrystalline cellulose
2.0 - 8.0% by weight of sodium starch glycolate
0.1 - 6.0% by weight of povidone
0.1 - 4.0% by weight of sodium stearyl fumarate
0.1 – 6.0% by weight of coating agent

13. A process for preparing the solid oral pharmaceutical composition according to claim 12, comprising the following steps:

a) Mixing linagliptin, metformin, microcrystalline cellulose and sodium starch glycolate
b) Granulating povidone with water-ethanol mixture on a separate tank
c) Mixing step (a) mixture and step (b) mixture
d) Drying the mixture, then sieving the mixture
e) Then, adding sodium stearyl fumarate and mixing
f) Then, pressing to form tablet
g) Coating tablets with the coating agent