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(54) Title: PHARMACEUTICAL COMPOSITION OF LINAGLIPTIN

(57) Abstract: The present invention relates to a pharmaceutical composition comprising linagliptin and one or more pharmaceutically acceptable excipients, wherein said composition is free of mannitol. The invention further provides a process for preparing said pharmaceutical composition, and its use for treating diabetes.

PHARMACEUTICAL COMPOSITION OF LINAGLIPTIN

Field of the Invention

The present invention provides a pharmaceutical composition comprising linagliptin and one or more pharmaceutically acceptable excipients, wherein the composition is free of one or more of mannitol, copovidone, corn starch and magnesium stearate. Further, the invention relates to processes for the preparation of the composition, and its use for treating diabetes.

Background of the Invention

Linagliptin is a DPP-IV inhibitor, and is marketed under the brand name Tradjenta® for the treatment of type II diabetes. It is chemically known as 1H-purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl].

DPP-IV is an enzyme that degrades the incretin hormones such as GLP-1 (glucagon-like peptide 1) and GIP (glucose dependent insulinotropic polypeptide). Linagliptin, being a DPP-IV inhibitor blocks DPP-IV enzyme, and thus inhibits the degradation of GLP-1 and GIP, which in turn increases insulin secretion and decreases blood glucose levels.

U.S. Patent No. 7,407,955 discloses linagliptin specifically.

U.S. Publication No. 2010/0209506 discloses a pharmaceutical formulation of linagliptin with specific particle size distribution. It discloses that diluents like lactose, sucrose, and microcrystalline cellulose are observed as not being compatible with linagliptin, and mentions mannitol and pregelatinized starch as preferred diluents.

U.S. Publication No. 2012/0003313 discloses pharmaceutical formulation comprising linagliptin, a first diluent, a second diluent, a binder, a disintegrant and a lubricant. The first diluent is mannitol, the second diluent is pregelatinized starch, the binder is copovidone, the disintegrant is corn starch, and the lubricant is magnesium stearate. It discloses the need of two diluents to obtain the desired formulations. Further, it specifies that excipients like microcrystalline cellulose and lactose were observed as being incompatible with DPP-IV inhibitors.

There is still a need in the art to provide an alternative pharmaceutical composition of linagliptin having desired *in-vitro* and *in-vivo* release properties, and which is free of mannitol.

The inventors have conducted experiments and have surprisingly found that contrary to the teachings in the prior art, diluents such as microcrystalline cellulose and lactose, which have been described as being unsuitable, can be used to achieve the desired release properties.

One objective of the present invention is thus to provide an alternative pharmaceutical composition comprising linagliptin and one or more pharmaceutically acceptable excipients, wherein said composition is free of mannitol. The pharmaceutically acceptable excipients are selected from the group comprising diluents, binders, disintegrants, lubricants, or mixtures thereof. Particularly, the diluent is microcrystalline cellulose.

Another objective of the present invention is to provide an alternate pharmaceutical composition comprising linagliptin and one or more pharmaceutically acceptable excipients. The composition is free of one or more of corn starch, copovidone and magnesium stearate. In particular, the composition is free of copovidone as the binder, corn starch as the disintegrant, and magnesium stearate as the lubricant.

Another objective of the present invention is to provide an alternate pharmaceutical composition comprising linagliptin and one or more pharmaceutically acceptable excipients. The composition is free of one or more of mannitol, corn starch, copovidone and magnesium stearate.

Summary of the Invention

In a first general aspect, the present invention provides a pharmaceutical composition comprising linagliptin and one or more pharmaceutically acceptable excipients, wherein the composition is free of mannitol. The pharmaceutically acceptable excipients are selected from the group comprising diluents, binders, disintegrants, lubricants, or mixtures thereof. The diluent is selected from the group comprising microcrystalline cellulose, microcrystalline cellulose co-processed with lactose, microcrystalline cellulose co-processed with silicon dioxide, or mixtures thereof. The present invention further provides processes of preparation of said pharmaceutical composition, and its use for treating diabetes.

In a second general aspect, the present invention provides a pharmaceutical composition comprising: (i) linagliptin; (ii) one or more diluents; (iii) one or more binders; (iv) one or more disintegrants; and (v) one or more lubricants. The binder is other than copovidone, the disintegrant is other than corn starch, and the lubricant is other than magnesium stearate.

In a third general aspect, the present invention provides a pharmaceutical composition comprising (i) linagliptin; (ii) one or more diluents; (iii) one or more binders; (iv) one or more disintegrants; and (v) one or more lubricants. The composition is free of one or more of mannitol, copovidone, corn starch, and magnesium stearate. In another embodiment, the composition is free of mannitol and includes a binder other than copovidone, a disintegrant other than corn starch and a lubricant other than magnesium stearate.

Detailed Description of the Invention

Various embodiments and variants of the present invention are described hereinafter.

A first aspect of the present invention provides a pharmaceutical composition comprising linagliptin and one or more pharmaceutically acceptable excipients, wherein said composition is free of mannitol.

According to one embodiment of the present invention, the pharmaceutically acceptable excipients are selected from one or more of diluents, binders, disintegrants, lubricants, or mixtures thereof.

According to another embodiment of the present invention, the diluent is selected from one or more of microcrystalline cellulose, microcrystalline cellulose co-processed with lactose, microcrystalline cellulose co-processed with silicon dioxide, or mixtures thereof.

According to another embodiment of the present invention, the composition further comprises one or more additional antidiabetic agents.

According to another embodiment, the process for the preparation of pharmaceutical composition of the present invention comprises the steps of:

(i) blending linagliptin and one or more pharmaceutically acceptable excipients; and

(ii) directly compressing the blend into tablets.

According to yet another embodiment, the process for the preparation of pharmaceutical composition of the present invention comprises the steps of:

(i) blending linagliptin and one or more pharmaceutically acceptable excipients;
(ii) preparing a granulation fluid by dispersing a binder in a solvent;
(iii) granulating the blend obtained in step (i) with the granulation fluid obtained in step (ii) to obtain granules; and
(iv) lubricating the granules obtained in step (iii), and then compressing them into tablets.

According to yet another embodiment, the present invention provides a method of treating diabetes by administering the pharmaceutical composition comprising linagliptin and one or more pharmaceutically acceptable excipients, wherein said composition is free of mannitol.

According to one embodiment, the present invention provides a method of treating diabetes by administering the pharmaceutical composition comprising linagliptin and one or more pharmaceutically acceptable excipients, wherein said composition is free of mannitol, and wherein the pharmaceutical composition further comprises one or more additional antidiabetic agents selected from one or more of biguanides (*e.g.*, metformin), thiazolidinediones (*e.g.*, pioglitazone), sulfonylureas (*e.g.* glipizide, gliclazide, glibenclamide/glyburide and glimepiride), insulin, or mixtures thereof.

According to one embodiment, the present invention provides a method of treating diabetes by administering to a patient in need thereof the pharmaceutical composition comprising linagliptin and one or more pharmaceutically acceptable excipients, wherein said composition is free of mannitol, and wherein the pharmaceutical composition of the present invention is administered sequentially or simultaneously with one or more additional antidiabetic agents selected from one or more of biguanides (*e.g.*, metformin), thiazolidinediones (*e.g.*, pioglitazone), sulfonylureas (*e.g.*, glipizide, gliclazide, glibenclamide/glyburide and glimepiride), insulin, or mixtures thereof.

A second aspect of the present invention provides a pharmaceutical composition comprising: (i) linagliptin; (ii) one or more diluents; (iii) one or more binders; (iv) one or more disintegrants; and (v) one or more lubricant.

According to another embodiment, the present invention provides a pharmaceutical composition comprising: (i) linagliptin; (ii) one or more diluents; (iii) one or more binders; (iv) one or more disintegrants; and (v) one or more lubricants. The binder is other than copovidone.

According to another embodiment, the present invention provides a pharmaceutical composition comprising: (i) linagliptin; (ii) one or more diluents; (iii) one or more binders; (iv) one or more disintegrants; and (v) one or more lubricants. The disintegrant is other than corn starch.

According to yet another embodiment, the present invention provides a pharmaceutical composition comprising: (i) linagliptin; (ii) one or more diluents; (iii) one or more binders; (iv) one or more disintegrants; and (v) one or more lubricants. The lubricant is other than magnesium stearate.

In another embodiment, the present invention provides a pharmaceutical composition comprising: (i) linagliptin; (ii) one or more diluents; (iii) one or more binders; (iv) one or more disintegrants; and (v) one or more lubricants. The binder is other than copovidone, the disintegrant is other than corn starch, and the lubricant is other than magnesium stearate.

According to one embodiment, the pharmaceutical composition of the second aspect of the present invention is prepared by direct compression process, wherein said process comprises the steps of:

(i) blending linagliptin and all the excipients, except the lubricant;

(ii) lubricating the blend using the lubricant; and

(iii) directly compressing the blend into tablets.

According to another embodiment, the pharmaceutical composition of the second aspect of the present invention is prepared by wet granulation process, wherein said process comprises the steps of:

(i) preparing a granulation fluid by dispersing a binder in a solvent;

(ii) premixing linagliptin, one or more diluent, and one or more disintegrant to obtain a premix;

(iii) granulating the premix obtained in step (ii) with the granulation fluid obtained in step (i) to form a wet mass;

(iv) drying the wet mass obtained in step (iii) and then milling to obtain granules;

(v) lubricating the granules obtained in step (iv) and finally compressing into tablets; and

(vi) optionally coating the tablets obtained in step (v).

Another embodiment of the second aspect of the present invention provides a method of treating diabetes by administering a pharmaceutical composition comprising:

(i) linagliptin;

(ii) one or more diluent;

(iii) one or more binder;

(iv) one or more disintegrant; and

(v) one or more lubricant,

wherein the composition is characterized by the one or more of the binder being other than copovidone, the disintegrant being other than corn starch, and the lubricant being other than magnesium stearate.

The term "linagliptin", as used herein, refers to linagliptin and one or more pharmaceutically acceptable salts thereof, including hydrates and solvates thereof, and crystalline or amorphous forms thereof. The present invention comprises linagliptin in an amount of from about 1% to about 99% by weight of the composition. Preferably, the linagliptin is present in an amount of from about 0.01% to about 10% by weight of the composition. Linagliptin is approved at strengths of 2.5 mg and 5 mg per day. As such, a therapeutically effective amount includes, but is not limited to, about 1 mg to about 10 mg per day.

The term "about", as used herein, refers to any value which lies within the range defined by a variation of up to ±10% of the value.

The term "pharmaceutically acceptable excipients", as used herein, includes any physiologically inert additives that are routinely used in pharmaceutical dosage forms. Pharmaceutically acceptable excipients may include, but are not limited to, diluents,

binders, disintegrants, lubricants/glidants, surfactants, solubility enhancers/solubilizers, coloring agents, plasticizers, and opacifiers.

Diluents or fillers according to the first aspect of the invention are selected from the group comprising microcrystalline cellulose, co-processed microcrystalline cellulose, powdered cellulose, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, calcium carbonate, lactose monohydrate, lactose anhydrous, sucrose, sorbitol, xylitol, erythritol, kaolin, calcium silicate, maltodextrin, starch, modified starch, *e.g.*, pregelatinized starch, maize starch, corn starch, or mixtures thereof. The present invention comprises one or more diluents in an amount of from about 5% to about 90% by weight of the composition. Among the diluents, microcrystalline cellulose is the preferred diluent.

Suitable diluents or fillers according to the second aspect of the invention are selected from the group comprising mannitol, microcrystalline cellulose, co-processed microcrystalline cellulose, powdered cellulose, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, calcium carbonate, sorbitol, xylitol, erythritol, pregelatinized starch, maize starch, corn starch, or mixtures thereof. The present invention comprises one or more diluent in an amount of from about 5% to about 90% by weight of the composition.

"Microcrystalline cellulose", as used herein, refers to microcrystalline cellulose as well as its co-processed forms.

Microcrystalline cellulose is purified partially depolymerized cellulose, prepared by treating cellulose with mineral acids. It is a white, crystalline powder. Microcrystalline cellulose is highly compressible, and thus provides harder tablets at low compression pressures. It exhibits fair flowability and binding properties. Microcrystalline cellulose also has some lubricant and disintegrant properties that makes it useful in tableting. It is marketed under brand names such as Avicel®, Librawcel®, Emcocel®, and Ambicel®.

Co-processed microcrystalline cellulose refers to microcrystalline cellulose in intimate association with another component, wherein said another component is lactose, silicon dioxide, starch, sugar alcohol, gums, cellulose, calcium carbonate, or mixtures thereof. Co-processed microcrystalline cellulose is available in the market under the trade names MicroceLac®, PROSOLV® SMCC, Avicel® CE-15, and Avicel® CL-611. MicroceLac® 100 is a spray-dried compound containing 75% α-lactose monohydrate and

25% microcrystalline cellulose. It provides better tableting performance by combining the filling properties of lactose and binding capacity of microcrystalline cellulose. Through the fixed ratios of lactose and microcrystalline cellulose, it provides an excellent compressibility, possesses low aggregation tendency, imparts consistent flowability during compression, which ensures constant tablet hardness and weight consistency.

PROSOLV® SMCC is silicified microcrystalline cellulose, a combination of 98% microcrystalline cellulose and 2% colloidal silicon dioxide (SiO_2). It possesses a homogenous distribution of silicon dioxide particles on the surface which lead to an increase in the specific surface area. The increased surface area imparts enhanced flow leading to increase in production speed, and superior compaction that results in improved content uniformity. It also ensures significant reduction in numbers and levels of other excipients, and thus leads to saving of costs.

Avicel® CL-611 is co-processed microcrystalline cellulose and sodium carboxymethylcellulose.

Avicel® CE-15 is co-processed microcrystalline cellulose and guar gum.

Suitable binders are selected from the group comprising povidone, copovidone, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, ethyl cellulose, xanthan gum, gum acacia, gum arabic, tragacanth, sorbitol, dextrose, sucrose, mannitol, gelatin, pullulan, sodium alginate, propylene glycol, polyvinyl alcohol, corn syrup, methacrylates, carboxyvinyl polymers like carbomers, or mixtures thereof. The present invention comprises one or more binders in an amount of from about 1% to about 20% by weight of the composition. According to one embodiment of the second aspect of the invention, the composition has a binder that is not copovidone such that the composition is free of copovidone.

Suitable disintegrants are selected from the group comprising hydroxypropyl cellulose (L-HPC), crospovidone, croscarmellose sodium, carboxymethyl cellulose sodium, carboxymethyl cellulose calcium, sodium starch glycolate, gums, alginic acid or alginates, starch, corn starch, modified starch, carboxymethyl starch, polyacrylates, or mixtures thereof. The present invention comprises one or more disintegrants in an amount of from about 0.5% to about 50% by weight of the composition. According to one embodiment of the second aspect of the invention, the composition has a disintegrant that is not corn starch such that the composition is free of corn starch.

Suitable lubricants/glidants/antiadherents are selected from the group comprising hydrogenated vegetable oil, glyceryl behenate, glyceryl monostearate, stearic acid, sodium stearyl fumarate, sodium starch fumarate, magnesium stearate, calcium stearate, zinc stearate, aluminum silicate, talc, colloidal silicon dioxide, sucrose esters of fatty acid, waxes, silica gel, or mixtures thereof. The present invention comprises one or more lubricants in an amount from about 0.25% to about 10% by weight of the composition. According to one embodiment of the second aspect of the invention, the composition includes a lubricant that is not magnesium stearate such that the composition is free of magnesium stearate.

The pharmaceutical composition of the present invention may further contain one or more inert additives selected from the group comprising surfactants, solubility enhancers, coloring agents, plasticizers, opacifiers, and mixtures thereof.

Suitable surfactants are selected from the group comprising sodium lauryl sulfate, sodium dodecyl sulfate, ammonium lauryl sulfate, benzalkonium chloride, alkyl poly (ethylene oxide), copolymers of poly (ethylene oxide) and poly (propylene oxide) commercially called as poloxamers or poloxamines, fatty alcohols, polysorbates *e.g.*, Tween 20, Tween 80, or mixtures thereof.

Suitable solubility enhancers are selected from the group comprising polyethylene glycol, propylene glycol, glycerol, mono-alcohols, higher alcohols, dimethylsulfoxide, dimethylformamide, N, N-dimethylacetamide, N-methyl-2-pyrrolidone, N-(2-hydroxyethyl) pyrrolidone, 2-pyrrolidone, or mixtures thereof.

Coloring agents include any FDA approved color for oral use.

Suitable plasticizers are selected from the group comprising triethylcitrate, dibutyl sebacate, acetylated triacetin, tributylcitrate, glycerlotributyrate, monoglyceride, rapeseed oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin, sorbitol, diethyl oxalate, diethyl phthalate, diethyl malate, diethyl fumarate, dibutyl succinate, diethyl malonate, dioctyl phthalate, or mixtures thereof.

Suitable opacifiers are selected from the group comprising titanium dioxide, manganese dioxide, iron oxide, silicon dioxide, or mixtures thereof.

The pharmaceutical composition of the present invention can be obtained by using known conventional methods, *i.e.*, granulation or direct compression. The process to

obtain granulate includes, but is not limited to, wet granulation, fluid bed granulation, spray drying, or dry granulation.

The process for the preparation of pharmaceutical compositions of the present invention comprises granulating a blend of drug, diluent, and disintegrant using a granulation fluid prepared by dispersing a binder(s) in a solvent(s), to obtain a wet mass, drying the wet mass and milling to obtain granules, and then after lubrication compressing the granules into tablets. Alternatively, part of the diluent and the disintegrant can also be added extragranularly.

During the wet granulation process, moist granules can be wet milled, if needed, prior to final drying.

The pharmaceutical composition prepared by any of the above described processes may further be coated with a film-forming polymer and one or more pharmaceutically acceptable excipients, using techniques well known in the art, *e.g.*, spray coating in a conventional coating pan or a fluidized bed processor, or dip coating. Alternatively, the coating step can also be performed using a hot melt technique.

The film coating may contain one or more film-forming polymers and optionally one or more pharmaceutically acceptable excipients. Suitable film-forming polymers are selected from hydroxypropylmethyl cellulose, ethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, cellulose acetate, hydroxypropylmethyl cellulose phthalate, cellulose acetate trimellitate, methacrylic acid copolymers, *e.g.*, Eudragit®, polyvinylpyrrolidone, polyvinylalcohol, polyethylene glycol, or mixtures thereof. A preferred film-forming polymer is hydroxypropylmethyl cellulose. Other suitable film-forming polymers which are known in the art may also be used.

Examples of solvents used for preparing the granulation fluid or coating solution are selected from the group comprising methyl alcohol, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, acetone, acetonitrile, chloroform, methylene chloride, water, or mixtures thereof.

The pharmaceutical composition of the present invention may further include one or more additional antidiabetic agents selected from the group comprising biguanides (*e.g.*, metformin), thiazolidinediones (*e.g.*, pioglitazone), sulfonylureas (*e.g.*, glipizide, gliclazide, glibenclamide/glyburide and glimepiride), insulin, or mixtures thereof.

The pharmaceutical composition of the present invention may be administered sequentially or simultaneously with one or more additional antidiabetic agents selected from the group comprising biguanides (*e.g.*, metformin), thiazolidinediones (*e.g.*, pioglitazone), sulfonylureas (*e.g.*, glipizide, gliclazide, glibenclamide/glyburide and glimepiride), insulin, or mixtures thereof.

The pharmaceutical composition of the present invention is intended for oral use, and can be in the form of tablets, capsules, minitablets, granules, or pellets, wherein the composition can be further film coated.

The invention is further illustrated by the following examples, which are provided for illustrative purposes only and should not be construed as limiting the scope of the invention in any way.

EXAMPLES

Example 1:

Ingredients	Percent (%) w/w
Linagliptin	2.78
Dibasic calcium phosphate	22.22
Microcrystalline cellulose	58.11
Sodium starch glycolate	10.00
Hydroxypropyl cellulose	4.00
Colloidal silicon dioxide	1.39
Magnesium stearate	1.50

Procedure:

1. Linagliptin and all the excipients, except magnesium stearate, are blended in a blender.
2. The blend obtained in step 1 is lubricated using magnesium stearate.
3. The lubricated blend obtained in step 2 is compressed into tablets.

Example 2:

Ingredients	Percent (%) w/w
Linagliptin	2.78
Dibasic calcium phosphate	22.22
Microcrystalline cellulose	58.11
Sodium starch glycolate	10.00
Hydroxypropyl cellulose	4.00
Colloidal silicon dioxide	1.39
Magnesium stearate	1.50
Purified water	q.s.

Procedure:

1. A granulation fluid is prepared by dispersing hydroxypropyl cellulose in water.
2. Linagliptin, dibasic calcium phosphate, microcrystalline cellulose, and sodium starch glycolate are mixed in a mixer to obtain a premix.
3. The premix obtained in step 2 is then granulated with the granulation fluid obtained in step 1.
4. The granules obtained in step 3 are dried, screened, and blended with colloidal silicon dioxide.
5. The granules obtained in step 4 are then lubricated with magnesium stearate to obtain lubricated granules.
6. The lubricated granules obtained in step 5 are then compressed into tablets.

Alternatively, part of microcrystalline cellulose and sodium starch glycolate can also be added extragranularly.

Example 3:

Ingredients	Percent (%) w/w
Linagliptin	2.78
Silicified microcrystalline cellulose	75.56
Pregelatinized starch	5.55
Corn starch	11.11
Copovidone	3.50
Magnesium stearate	1.50

Procedure:

1. Linagliptin and all the excipients, except magnesium stearate, are blended in a blender.
2. The blend obtained in step 1 is lubricated using magnesium stearate.
3. The lubricated blend obtained in step 2 is compressed into tablets.

Example 4:

Ingredients	Percent (%) w/w
Linagliptin	2.78
Silicified microcrystalline cellulose	75.56
Pregelatinized starch	5.55
Corn starch	11.11
Copovidone	3.50
Magnesium stearate	1.50
Purified water	q.s.

Procedure:

1. A granulation fluid is prepared by dispersing copovidone in water.
2. Linagliptin, silicified microcrystalline cellulose, pregelatinized starch, and corn starch are mixed in a mixer to obtain a premix.
3. The premix obtained in step 2 is then granulated with the granulation fluid obtained in step 1.
4. The granules obtained in step 3 are dried and screened.
5. The granules obtained in step 4 are then lubricated with magnesium stearate to obtain lubricated granules.
6. The lubricated granules obtained in step 5 are then compressed into tablets.

Alternatively, part of silicified microcrystalline cellulose and pregelatinized starch can also be added extragranularly.

Example 5:

Ingredients	Percent (%) w/w
Linagliptin	2.78
Dibasic calcium phosphate	19.44
Microcrystalline cellulose	58.33
Low substituted hydroxypropyl cellulose	11.11
Hydroxypropyl cellulose	5.55
Hydrogenated vegetable oil	2.78

Procedure:

1. Linagliptin and all the excipients, except hydrogenated vegetable oil, are blended in a blender.
2. The blend obtained in step 1 is lubricated using hydrogenated vegetable oil.
3. The lubricated blend obtained in step 2 is compressed into tablets.

Example 6:

Ingredients	Percent (%) w/w
Linagliptin	2.78
Dibasic calcium phosphate	19.44
Microcrystalline cellulose	58.33
Low substituted hydroxypropyl cellulose	11.11
Hydroxypropyl cellulose	5.55
Hydrogenated vegetable oil	2.78
Purified water	q.s.

Procedure:

1. A granulation fluid is prepared by dispersing hydroxypropyl cellulose in water.
2. Linagliptin, dibasic calcium phosphate, microcrystalline cellulose, and low substituted hydroxypropyl cellulose are mixed in a mixer to obtain a premix.
3. The premix obtained in step 2 is then granulated with the the granulation fluid obtained in step 1.
4. The granules obtained in step 3 are dried and screened.
5. The granules obtained in step 4 are then lubricated with hydrogenated vegetable oil to obtain lubricated granules.
6. The lubricated granules obtained in step 5 are then compressed into tablets.

Alternatively, part of microcrystalline cellulose can also be added extragranularly.

Example 7:

Ingredients	Percent (%) w/w
Linagliptin	2.78
Microcrystalline cellulose (co-processed with lactose)	80.17
Pregelatinized starch	6.67
Corn starch	5.55
Povidone	3.33
Magnesium stearate	1.50

Procedure:

1. Linagliptin and all the excipients, except magnesium stearate, are blended in a blender.
2. The blend obtained in step 1 is lubricated using magnesium stearate.
3. The lubricated blend obtained in step 2 is compressed into tablets.

Example 8:

Ingredients	Percent (%) w/w
Linagliptin	2.78
Microcrystalline cellulose (co-processed with lactose)	80.17
Pregelatinized starch	6.67
Corn starch	5.55
Povidone	3.33
Magnesium stearate	1.50
Purified water	q.s.

Procedure:

1. A granulation fluid is prepared by dispersing povidone in water.
2. Linagliptin, microcrystalline cellulose (co-processed with lactose), pregelatinized starch, and corn starch are mixed in a mixer to obtain a premix.
3. The premix obtained in step 2 is then granulated with the granulation fluid obtained in step 1.
4. The granules obtained in step 3 are dried and screened.
5. The granules obtained in step 4 are then lubricated with magnesium stearate to obtain lubricated granules.
6. The lubricated granules obtained in step 5 are then compressed into tablets.

Alternatively, part of microcrystalline cellulose (co-processed with lactose) and pregelatinized starch can also be added extragranularly.

Example 9:

Ingredients	Percent (%) w/w
Linagliptin	0.5-5.0
Silicified microcrystalline cellulose	5.0-90.0
Sodium starch glycolate	1.0-5.0
Magnesium stearate	0.5-3.0

Procedure:

1. Linagliptin and all the excipients, except magnesium stearate, are blended in a blender.
2. The blend obtained in step 1 is lubricated using magnesium stearate.
3. The lubricated blend obtained in step 2 is compressed into tablets.

Example 10:

Ingredients	Percent (%) w/w
Linagliptin	2.78
Dibasic calcium phosphate	22.22
Microcrystalline cellulose	58.84
Sodium starch glycolate	10.00
Hydroxypropyl cellulose	3.89
Colloidal silicon dioxide	0.77
Magnesium stearate	1.50

Procedure:

1. Linagliptin, dibasic calcium phosphate, microcrystalline cellulose, sodium starch glycolate, and hydroxypropyl cellulose were blended together.
2. The blend obtained in step 1 was further mixed with colloidal silicon dioxide.
3. The blend obtained in step 2 was lubricated with magnesium stearate.
4. The lubricated blend obtained in step 3 was compressed into tablets.

***In-vitro* dissolution profile**

The tablets of linagliptin prepared as per the composition of Example 10 were subjected to dissolution studies in 900 ml of 0.1N HCl at 37±0.5°C using USP apparatus I (40 mesh basket) with rotational speed at 50 rpm. Table 1 provides dissolution profile of the tablets in comparison with Tradjenta® tablets.

Table 1

Time (in minutes)	% Drug dissolved	
	Tradjenta®	Example 10 composition
30	100	100
45	99	100

The above data shows that the dissolution profile of the composition prepared as per example 10 is similar to the innovator's Tradjenta® tablets.

Example 11:

Ingredients	Percent (%) w/w
Linagliptin	0.5-5.0
Mannitol	30.0-90.0
Sodium starch glycolate	3.0-30.0
Copovidone	2.0-10.0
Colloidal silicon dioxide	0.5-5.0
Magnesium stearate	0.25-5.0

Procedure:

Linagliptin and all the excipients are blended in a blender and then compressed into tablets.

Example 12:

Ingredients	Percent (%) w/w
Linagliptin	0.5-5.0
Mannitol	30.0-90.0
Low substituted hydroxypropyl cellulose	5.0-25.0
Hydroxypropyl cellulose	2.0-10.0
Magnesium stearate	0.25-5.0
Purified water	q.s.

Procedure:

1. A granulation fluid is prepared by dispersing hydroxypropyl cellulose in water.
2. Linagliptin, mannitol, and low substituted hydroxypropyl cellulose are mixed in a mixer to obtain a premix.
3. The premix obtained in step 2 is then granulated with the granulation fluid prepared in step 1.
4. The granules obtained in step 3 are screened, and then blended with magnesium stearate to obtain lubricated granules.
5. The lubricated granules obtained in step 4 are then compressed into tablets.

Example 13:

Ingredients	Percent (%) w/w
Linagliptin	0.5-5.0
Mannitol	30.0-90.0
Crospovidone	5.0-50.0
Copovidone	2.0-20.0
Magnesium stearate	0.25-5.0
Purified water	q.s.

Procedure:

1. A granulation fluid is prepared by dispersing copovidone in water.
2. Linagliptin, mannitol, and crospovidone are mixed in a mixer to obtain a premix.
3. The premix obtained in step 2 is then granulated with the granulation fluid prepared in step 1.
4. The granules obtained in step 3 are screened, then blended with magnesium stearate to obtain lubricated granules.
5. The lubricated granules obtained in step 4 are then compressed into tablets.

Alternatively, part of crospovidone can also be added extragranularly.

Example 14:

Ingredients	Percent (%) w/w
Linagliptin	0.5-5.0
Mannitol	10.0-90.0
Pregelatinized starch	5.0-20.0
Corn starch	5.0-40.0
Copovidone	2.0-15.0
Hydrogenated vegetable oil	2.0-7.0
Talc	1.0-10.0
Purified water	q.s.

Procedure:

1. Granulation fluid is prepared by dispersing copovidone in water.
2. Linagliptin, pregelatinized starch, mannitol and corn starch are mixed in a mixer to obtain a premix.
3. The premix obtained in step 2 is then granulated with the granulation fluid prepared in step 1.
4. The granules obtained in step 3 are screened, then lubricated with hydrogenated vegetable oil to obtain lubricated granules.
5. The lubricated granules obtained in step 4 are then compressed into tablets.

Example 15:

Ingredients	Percent (%) w/w
Linagliptin	0.5-5.0
Mannitol	10.0-90.0
Pregelatinized starch	5.0-20.0
Corn starch	5.0-40.0
Copovidone	2.0-15.0
Glyceryl behenate	1.0-5.0
Purified water	q.s.

Procedure:

1. A granulation fluid is prepared by dispersing copovidone in water.
2. Linagliptin, pregelatinized starch, mannitol, and corn starch are mixed in a mixer to obtain a premix.
3. The premix obtained in step 2 is then granulated with the granulation fluid prepared

in step 1.

4. The granules obtained in step 3 are screened, then lubricated with glyceryl behenate to obtain lubricated granules.

5. The lubricated granules obtained in step 4 are then compressed into tablets.

Example 16

Ingredient	Percent (%) w/w
Linagliptin	0.5-5.0
Mannitol	10.0-90.0
Microcrystalline cellulose	10.0-50.0
Pregelatinized starch	5.0-20.0
Corn starch	5.0-30.0
Copovidone	2.0-10.0
Stearic acid	1.0-7.0

Procedure:

Linagliptin and all the excipients are blended in a blender and then compressed into tablets.

Example 17:

Ingredient	Percent (%) w/w
Linagliptin	0.5-5.0
Mannitol	10.0-90.0
Pregelatinized starch	5.0-20.0
Corn starch	5.0-20.0
Copovidone	2.0-10.0
Stearyl fumarate	1.0-7.0
Purified water	q.s.

Procedure:

1. A granulation fluid is prepared by dispersing copovidone in water.

2. Linagliptin, pregelatinized starch, mannitol, and corn starch are mixed in a mixer to obtain a premix.

3. The premix obtained in step 2 is then granulated with the granulation fluid prepared in step 1.

4. The granules obtained in step 3 are screened, then lubricated with stearyl fumarate to obtain lubricated granules.

5. The lubricated granules obtained in step 4 are then compressed into tablets.

Example 18:

Ingredients	Percent (%) w/w
Linagliptin	0.5-5.0
Mannitol	30.0-90.0
Corn starch	5.0-30.0
Copovidone	2.0-10.0
Colloidal silicon dioxide	0.25-5.0
Magnesium stearate	0.25-5.0
Purified water	q.s.

Procedure:

1. Granulation fluid is prepared by dispersing copovidone in water.
2. Linagliptin, mannitol, and corn starch are mixed in a mixer to obtain a premix.
3. The premix obtained in step 2 is then granulated with the granulation fluid prepared in step 1.
4. The granules obtained in step 3 are screened, blended with colloidal silicon dioxide, and then lubricated with magnesium stearate to obtain lubricated granules.
5. The lubricated granules obtained in step 4 are then compressed into tablets.

Example 19:

Ingredients	Percent (%) w/w
Linagliptin	0.5-5.0
Mannitol	10.0-90.0
Microcrystalline cellulose	10.0-90.0
Croscarmellose sodium	0.5-10.0
Copovidone	2.0-10.0
Magnesium stearate	0.25-5.0

Procedure:

Linagliptin and all the excipients are blended in a blender and then compressed into tablets.

Example 20:

Ingredients	Percent (%) w/w
Linagliptin	0.5-5.0
Copovidone	2.0-10.0
Mannitol	10.0-90.0
Microcrystalline cellulose	10.0-90.0
Crospovidone	5.0-50.0
Hydrogenated vegetable oil	2.0-7.0
Talc	1.0-10.0
Purified water	q.s.

Procedure:

1. A granulation fluid is prepared by dispersing copovidone in water.
2. Linagliptin, mannitol, microcrystalline cellulose, and crospovidone are mixed in a mixer to obtain a premix.
3. The premix obtained in step 2 is then granulated with the granulation fluid prepared in step 1.
4. The granules obtained in step 3 are screened, blended with talc, and then lubricated with hydrogenated vegetable oil to obtain lubricated granules.
5. The lubricated granules obtained in step 4 are then compressed into tablets.

Example 21:

Ingredients	Percent (%) w/w
Linagliptin	2.77
Mannitol	44.27
Corn starch	4.43
Hydroxypropyl cellulose	14.94
Crospovidone	1.38
Microcrystalline cellulose	11.07
Mannitol	20.14
Magnesium stearate	1.00
Purified water	q.s.
Total Tablet Weight (mg)	**180.70**

Procedure:

1. Linagliptin, the first part of mannitol, corn starch, and hydroxypropyl cellulose were blended together.
2. The blend obtained in step 1 was granulated using water to obtain a wet mass.
3. The wet mass obtained in step 2 was dried and milled to obtain granules.

4. The granules obtained in step 3 were blended with crospovidone, microcrystalline cellulose, and the second part of mannitol.
5. The granules obtained in step 4 were lubricated with magnesium stearate.
6. The lubricated granules obtained in step 5 were then compressed into tablets.

Example 22:

Ingredients	Percent (%) w/w
Linagliptin	2.77
Mannitol	44.27
Corn starch	4.43
Hydroxypropyl cellulose	14.94
Sodium starch glycolate	1.38
Microcrystalline cellulose	11.07
Mannitol	20.14
Magnesium stearate	1.00
Purified water	q.s.
Total Tablet Weight (mg)	180.70

Procedure:

1. Linagliptin, the first part of mannitol, corn starch, and hydroxypropyl cellulose were blended together.
2. The blend obtained in step 1 was granulated using water to obtain a wet mass.
3. The wet mass obtained in step 2 was dried and milled to obtain granules.
4. The granules obtained in step 3 were blended with sodium starch glycolate, microcrystalline cellulose, and the second part of mannitol.
5. The granules obtained in step 4 were lubricated with magnesium stearate.
6. The lubricated granules obtained in step 5 were then compressed into tablets.

Example 23:

Ingredients	Percent (%) w/w
Linagliptin	2.77
Mannitol	44.27
Corn starch	4.43
Hydroxypropyl cellulose	14.94
Sodium starch glycolate	1.38
Microcrystalline cellulose	10.07
Mannitol	20.14
Hydrogenated vegetable oil	1.99
Purified water	q.s.
Total Tablet Weight (mg)	**180.70**

Procedure:

1. Linagliptin, the first part of mannitol, corn starch, and hydroxypropyl cellulose were blended together.
2. The blend obtained in step 1 was granulated using water to obtain a wet mass.
3. The wet mass obtained in step 2 was dried and milled to obtain granules.
4. The granules obtained in step 3 were blended with sodium starch glycolate, microcrystalline cellulose, and the second part of mannitol.
5. The granules obtained in step 4 were lubricated with hydrogenated vegetable oil.
6. The lubricated granules obtained in step 5 were then compressed into tablets.

Example 24:

Ingredients	Percent (%) w/w
Linagliptin	2.70
Mannitol	77.83
Pregelatinized starch	9.71
Copovidone	5.39
Magnesium stearate	1.46
Purified water	q.s.
Opadry®	2.91
Total Tablet Weight (mg)	**185.40**

Procedure:

1. Linagliptin, mannitol, and pregelatinized starch were blended together.
2. Copovidone was added to water to prepare a granulation fluid.
3. The blend obtained in step 1 was granulated using the granulation fluid obtained in step 2 to obtain a wet mass.
4. The wet mass obtained in step 3 was dried and milled to obtain granules.
5. The granules obtained in step 4 were lubricated with magnesium stearate.
6. The lubricated granules obtained in step 5 were then compressed into tablets.
7. The tablets of step 6 were coated with an Opadry® coating formulation.

Example 25:

Ingredients	Percent (%) w/w
Linagliptin	2.78
Mannitol	49.06
Corn starch	4.44
Copovidone	10.00
Sodium starch glycolate	1.39
Microcrystalline cellulose	11.11
Mannitol	20.22
Sodium stearyl fumarate	1.00
Purified water	q.s.
Total Tablet Weight (mg)	**180.00**

Procedure:

1. Linagliptin, the first part of mannitol, and corn starch were blended together.
2. Copovidone was added to water to prepare a granulation fluid.
3. The blend obtained in step 1 was granulated using the granulation fluid obtained in step 2 to obtain a wet mass.
4. The wet mass obtained in step 3 was dried and milled to obtain granules.
5. The granules obtained in step 4 were blended with sodium starch glycolate, microcrystalline cellulose, and the second part of mannitol.
6. The granules obtained in step 5 were lubricated using sodium stearyl fumarate.
7. The lubricated granules obtained in step 6 were then compressed into tablets.

Example 26:

Ingredients	Percent (%) w/w
Linagliptin	2.78
Mannitol	49.06
Corn starch	4.44
Copovidone	10.00
Sodium starch glycolate	1.39
Microcrystalline cellulose	11.11
Mannitol	20.22
Glyceryl behenate	1.00
Purified water	q.s.
Total Tablet Weight(mg)	**180.00**

Procedure:

1. Linagliptin, the first part of mannitol, and corn starch were blended together.
2. Copovidone was added to water to prepare a granulation fluid.
3. The blend obtained in step 1 was granulated using the granulation fluid obtained in

step 2 to obtain a wet mass.

4. The wet mass obtained in step 3 was dried and milled to obtain granules.
5. The granules obtained in step 4 were then blended with sodium starch glycolate, microcrystalline cellulose, and the second part of mannitol.
6. The granules obtained in step 5 were lubricated using glyceryl behenate.
7. The lubricated granules obtained in step 6 were then compressed into tablets.

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

We Claim:

1. A pharmaceutical composition comprising linagliptin and one or more pharmaceutically acceptable excipients, wherein said composition is free of mannitol.

2. The pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable excipients are selected from one or more of diluents, binders, disintegrants, lubricants, or mixtures thereof.

3. The pharmaceutical composition according to claim 2, wherein the diluent is selected from one or more of microcrystalline cellulose, microcrystalline cellulose co-processed with lactose, microcrystalline cellulose co-processed with silicon dioxide, or mixtures thereof.

4. The pharmaceutical composition according to claim 1, wherein the composition further comprises one or more additional antidiabetic agents.

5. The pharmaceutical composition according to claim 4, wherein one or more additional antidiabetic agents is selected from biguanides, thiazolidinediones, sulfonylureas, insulin, or mixtures thereof.

6. The pharmaceutical composition according to claim 1 prepared by the process comprising the steps of:

(i) blending linagliptin and one or more pharmaceutically acceptable excipients; and

(ii) directly compressing the blend into tablets.

7. The pharmaceutical composition according to claim 1 prepared by the process comprising the steps of:

(i) blending linagliptin and one or more pharmaceutically acceptable excipients;

(ii) preparing a granulation fluid by dispersing a binder in a solvent;

(iii) granulating the blend obtained in step (i) with the granulation fluid obtained in step (ii) to obtain granules; and

(iv) lubricating the granules obtained in step (iii), and then compressing into tablets.

8. A method for treating diabetes by administering a pharmaceutical composition comprising linagliptin and one or more pharmaceutically acceptable excipients, wherein said composition is free of mannitol.

9. The method for treating diabetes by administering the pharmaceutical composition according to claim 4.

10. The method for treating diabetes according to claim 9, wherein said method comprises sequential or simultaneous administration of one or more additional antidiabetic agent.

11. The method for treating diabetes according to claim 10, wherein the one or more additional antidiabetic agents is selected from one or more of biguanides, thiazolidinediones, sulfonylureas, insulin, or mixtures thereof.

12. A pharmaceutical composition comprising:

(i) linagliptin;

(ii) one or more diluent;

(iii) one or more binder;

(iv) one or more disintegrant; and

(v) one or more lubricant,

wherein the composition is characterized by one or more of the binder being other than copovidone, the disintegrant being other than corn starch and the lubricant being other than magnesium stearate.

13. The pharmaceutical composition according to claim 12, wherein the binder is other than copovidone.

14. The pharmaceutical composition according to claim 12, wherein the disintegrant is other than corn starch.

15. The pharmaceutical composition according to claim 12, wherein the lubricant is other than magnesium stearate.

16. The pharmaceutical composition of claim 12, wherein the binder is other than copovidone, the disintegrant is other than corn starch and the lubricant is other than magnesium stearate.

17. The pharmaceutical composition according claim 12 wherein the composition is prepared by a direct compression process comprising the steps of:

(i) blending linagliptin and all the excipients, except the lubricant;

(ii) lubricating the blend using the lubricant; and

(iii) directly compressing the blend into tablets.

18. The pharmaceutical composition according to any claim 12 wherein the composition is prepared by a wet granulation process comprising the steps of:

(i) preparing a granulation fluid by dispersing a binder in a solvent;

(ii) premixing linagliptin, one or more diluent, and one or more disintegrant to obtain a premix;

(iii) granulating the premix obtained in step (ii) with the granulation fluid obtained in step (i) to form a wet mass;

(iv) drying the wet mass obtained in step (iii) and then milling to obtain granules;

(v) lubricating the granules obtained in step (iv) and finally compressing into tablets; and

(vi) optionally coating the tablet obtained in step (v).

19. A method for treating diabetes by administering to a patient in need thereof a pharmaceutical composition comprising:

(i) linagliptin;

(ii) one or more diluent;

(iii) one or more binder;

(iv) one or more disintegrant; and

(v) one or more lubricant, wherein the binder is other than copovidone, the disintegrant is other than corn starch and the lubricant is other than magnesium stearate.

20. A pharmaceutical composition comprising:

(i) linagliptin;

(ii) one or more diluent;

(iii) one or more binder;

(iv) one or more disintegrant; and

(v) one or more lubricant,

wherein the composition is characterized by being free of mannitol, the binder being other than copovidone, the disintegrant being other than corn starch and the lubricant being other than magnesium stearate.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/060424

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/031124 A2 (SQUIBB BRISTOL MYERS CO [US]; ASTRAZENECA UK LTD [GB]; NARANG AJIT [US]) 8 March 2012 (2012-03-08) claims; examples -----	1-20
X	WO 2012/120040 A1 (BOEHRINGER INGELHEIM INT [DE]; ITO MASANORI [JP]; EGUSA KENJI [JP]; ME) 13 September 2012 (2012-09-13) page 2 page 8, line 6 - line 29 claims -----	1-20
X,P	WO 2013/131967 A1 (BOEHRINGER INGELHEIM INT [DE]) 12 September 2013 (2013-09-12) page 18, line 14 - line 26 page 4, line 10 - line 22 page 6, line 4 - line 15 page 9, line 1 - line 30 ----- -/--	1-5,8-11

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
18 March 2014	31/03/2014

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/060424

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2012/107398 A1 (SCHNEIDER PETER [DE] ET AL) 3 May 2012 (2012-05-03) the whole document	1-20

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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