The present invention relates to stable pharmaceutical compositions comprising saxagliptin or a pharmaceutically acceptable salt thereof.
STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING SAXAGLIPTIN

Field of the invention

The present invention relates to stable pharmaceutical compositions comprising DPP4 inhibitor. Particularly, the present invention relates to stable pharmaceutical compositions comprising saxagliptin or a pharmaceutically acceptable salt thereof.

Background of the invention

Saxagliptin is chemically (lS,3S,5S)-2-[(2S)-2-Amino-2-(3-hydroxytricyclo[4.3.1.1^3,7]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile and is disclosed in US 6,395,767. The marketed form of saxagliptin contains saxagliptin hydrochloride which is formed in situ by converting saxagliptin monohydrate to saxagliptin hydrochloride. It is available in the form of tablets with the trade name Onglyza® in United States.

Saxagliptin is used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

US 7,951,400 discloses a coated tablet comprising a tablet core and (a) an inner seal coating layer coated on the tablet core; (b) a second coating layer comprising a medicament coated on the inner seal coating of the tablet core; and (c) optionally an outer protective coating layer coated on the second coating layer of the tablet core.

WO 2012/031 124 A2 discloses a coated tablet comprising (a) a tablet core wherein the tablet core comprises (i) optionally at least one antidiabetic agent or a pharmaceutically acceptable salt thereof, wherein the antidiabetic agent is other than saxagliptin; (b) a first layer that coats the tablet core, wherein the first layer comprises (i) a coating material; and (ii) optionally at least one water soluble antioxidant; (c) a second layer that coats the first layer wherein the second layer comprises (i) a coating material; (ii) at least one water soluble antioxidant; and (iii) an active pharmaceutical ingredient or a pharmaceutically acceptable salt thereof, wherein the active pharmaceutical ingredient is a primary amine or a secondary amine; and (d) a third layer that coats the second layer wherein the third layer comprises (i) a coating material; and (ii) optionally at least one water soluble antioxidant.
The prior art references disclose tablet core coated with an inner seal coating layer, followed by a saxagliptin layer and an outer protective coating layer. The reason for such a design is to entrap the drug between two placebo layers to prevent degradation of saxagliptin. Execution of such a design involves tedious manufacturing process of several coating steps and long processing time. Still, there exists a need to develop a stable pharmaceutical composition comprising saxagliptin by simple manufacturing process with less number of process steps which shows better/comparable stability and bioavailability w.r.t marketed formulation.

The inventors of present invention have developed a composition comprising saxagliptin inside the tablet core optionally coated with a protective coat, which possesses appreciable stability and exhibits the desired in-vitro dissolution of the active agent.

Summary of the invention

The present invention relates to a stable pharmaceutical composition comprising saxagliptin or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipient(s).

An objective of the present invention is to provide process for preparation of pharmaceutical composition comprising saxagliptin or a pharmaceutically acceptable salt thereof.

Another objective of the present invention is to provide method of using the pharmaceutical composition comprising saxagliptin or a pharmaceutically acceptable salt thereof in a subject in need thereof.

The present invention relates to a stable pharmaceutical composition comprising a tablet core comprising saxagliptin or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipient(s).

The present invention further relates to a stable pharmaceutical composition comprising:

a) a tablet core comprising:

(i) an intragranular component comprising saxagliptin or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients(s),
(ii) an extragranular component comprising one or more pharmaceutically acceptable excipient(s), and

b) an outer protective coating layer over the tablet core.

The present invention also relates to a stable pharmaceutical composition comprising saxagliptin, prepared by process comprising the steps of:
(a) dispersing saxagliptin or a pharmaceutically acceptable salt thereof with one or more pharmaceutically acceptable excipients in a suitable solvent,
(b) granulating blend of one or more pharmaceutically acceptable excipients with saxagliptin dispersion of step (a) to form granules,
(c) blending the granules of step (b) with one or more pharmaceutically acceptable excipients,
(d) compressing the blend of step (c) into tablets, and
(e) coating the tablets of step (d) with a protective coating layer.

**Detailed description of the invention**

In an embodiment, the present invention relates to a stable pharmaceutical composition comprising saxagliptin or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

In another embodiment, the present invention relates to process of preparing pharmaceutical composition comprising saxagliptin or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

In another embodiment, the present invention relates to a stable pharmaceutical composition comprising a tablet core comprising saxagliptin or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.

The present invention further relates to a stable pharmaceutical composition comprising:

a) a tablet core comprising:
   (i) an intragranular component comprising saxagliptin or a pharmaceutically acceptable salt thereof, binder and one or more pharmaceutically acceptable excipients, and
(ii) an extragranular component comprising one or more pharmaceutically acceptable excipients.

The present invention further relates to a stable pharmaceutical composition comprising:

a) a tablet core comprising:

(i) an intragranular component comprising saxagliptin or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients,

(ii) an extragranular component comprising one or more pharmaceutically acceptable excipients, and optionally

b) an outer protective coating layer comprising polyvinyl alcohol over the tablet core.

The present invention further relates to a process for preparing a stable pharmaceutical composition comprising:

a) a tablet core comprising:

(i) an intragranular component comprising saxagliptin or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients,

(ii) an extragranular component comprising one or more pharmaceutically acceptable excipients, and optionally

b) an outer protective coating layer comprising polyvinyl alcohol over the tablet core.

The present invention further relates to a stable pharmaceutical composition comprising:

a) a tablet core comprising:

(i) an intragranular component comprising saxagliptin or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients,

(ii) an extragranular component comprising one or more pharmaceutically acceptable excipients, and

b) an outer protective coating layer comprising polyvinyl alcohol over the tablet core.

The present invention further relates to a stable pharmaceutical composition comprising:

a) a tablet core comprising:

(i) an intragranular component comprising saxagliptin or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients,

(ii) an extragranular component comprising one or more pharmaceutically acceptable excipients, and
b) an outer protective coating layer comprising polyvinyl alcohol over the tablet core, wherein the composition does not contain a seal coating layer between the tablet core and the protective coating layer.

The present invention further relates to a stable pharmaceutical composition comprising:

a) a tablet core comprising:

(i) an intragranular component comprising saxagliptin or a pharmaceutically acceptable salt thereof, binder and one or more pharmaceutically acceptable excipients,

(ii) an extragranular component comprising one or more pharmaceutically acceptable excipients, and

b) an outer protective coating layer comprising polyvinyl alcohol over the tablet core.

In an embodiment, the present invention relates to a stable pharmaceutical composition comprising:

a) a tablet core comprising:

(i) an intragranular component comprising saxagliptin or a pharmaceutically acceptable salt thereof, polyvinyl alcohol based composition, and one or more pharmaceutically acceptable excipients,

(ii) an extragranular component comprising one or more pharmaceutically acceptable excipients, and

b) an outer protective coating layer comprising polyvinyl alcohol over the tablet core.

In another embodiment, the present invention further relates to a stable pharmaceutical composition comprising:

a) a tablet core comprising:

(i) an intragranular component comprising saxagliptin or a pharmaceutically acceptable salt thereof; one or more excipients selected from the group comprising polyvinyl alcohol based composition, mannitol, microcrystalline cellulose, and crospovidone; and optionally one or more pharmaceutically acceptable excipients,

(ii) an extragranular component comprising microcrystalline cellulose, crospovidone, magnesium stearate; and optionally one or more pharmaceutically acceptable excipients, and

b) an outer protective coating layer over the tablet core comprising polyvinyl alcohol.
In another preferred embodiment, the present invention further relates to a stable pharmaceutical composition comprising:
a) a tablet core comprising:

(i) an intragranular component comprising saxagliptin or a pharmaceutically acceptable salt thereof; one or more excipients selected from the group comprising hydroxypropyl cellulose, mannitol, microcrystalline cellulose, crospovidone; and optionally one or more pharmaceutically acceptable excipients,
(ii) an extragranular component comprising hydroxypropyl cellulose, ascorbic acid, microcrystalline cellulose, crospovidone, magnesium stearate; and optionally one or more pharmaceutically acceptable excipients, and

b) an outer protective coating layer comprising polyvinyl alcohol over the tablet core.

The present invention also relates to a stable pharmaceutical composition comprising saxagliptin, prepared by process comprising the steps of:
(a) dispersing saxagliptin or a pharmaceutically acceptable salt thereof with one or more pharmaceutically acceptable excipients in a suitable solvent,
(b) granulating blend of one or more pharmaceutically acceptable excipients with saxagliptin dispersion of step (a) to form granules,
(c) blending the granules of step (b) with one or more pharmaceutically acceptable excipients,
(d) compressing the blend of step (c) into tablets, and
(e) coating the tablets of step (d) with a protective coating layer comprising polyvinyl alcohol.

"Saxagliptin" according to the present invention, unless otherwise stated, includes, but not limited to, saxagliptin free base, its pharmaceutical acceptable salts, esters, ethers, solvates, hydrates, polymorphs and the like. The amount of saxagliptin used may be in the range of 0.5-30% by weight of the composition, preferably in the range of 0.5-20%.

In another embodiment of the present invention, saxagliptin is converted into saxagliptin acid addition salt insitu in the presence of pharmaceutically acceptable acid.

In another embodiment of the present invention, the stable pharmaceutical composition comprising saxagliptin may be in the form of tablet, or tablets filled in capsule, or a capsule.
In another embodiment of the present invention, the stable pharmaceutical composition comprising saxagliptin may be prepared by any method known in the art such as wet granulation, dry granulation and direct compression, or a combination of such methods.

In another embodiment, the stable pharmaceutical composition comprising saxagliptin of the present invention further comprises one or more other antidiabetic agents including but not limited to acarbose, repaglinide, nateglinide, acetoheamidie, chlorpropamide, glibenclamide (glyburide), gliclazide, glimepiride, glipizide, glyclopyramide, tolazamide, tobutamide, buformin, metformin, phenformin, rosiglitazone, pioglitazone, troglitazone, faraglitazar, englitazone, darglitazone, isaglitazone, reglitazar, rivoglitazone, liraglutide, muraaglitazar, peliglitazar, tesaglitazar, sitagliptin, vildagliptin, linagliptin, dutaglilipin, and aloglipin, canagliflozin, dapagliflozin, remoglitofiozn, seregliiflozin, and the like, or combinations thereof.

"Polyvinyl alcohol based composition" according to the present invention comprises polyvinyl alcohol alone or in combination with one or more excipients such as plasticizer, surfactant, diluent, colorant, glidant, opacifier or the like, or may be a commercially available form under the trade name Opadry® HP, Opadry® II white, Opadry® 200 or Instacoat® and the like, or mixtures thereof.

"Pharmaceutically acceptable salt" according to the present invention includes salt of saxagliptin with organic and/or inorganic acids.

"Pharmaceutically acceptable excipient(s)" are the components added to pharmaceutical formulation to facilitate manufacture, enhance stability, control release, enhance product characteristics, enhance bioavailability, enhance patient acceptability, etc. Pharmaceutically acceptable excipients include, but not limited to one or more of diluents/fillers, binders, disintegrants, antioxidants, lubricants, glidants, compression aids, colors, sweeteners, surfactants, pharmaceutically acceptable acids, film formers, flavors, printing inks, and other excipients known to the art.

Binders hold the ingredients in the composition together. Exemplary binders include, but not limited to, cellulose and its derivatives including, ethyl cellulose, hydroxypropyl cellulose,
hydroxypropyl methylcellulose, methylcellulose and hydroxyethyl cellulose, carboxymethyl cellulose; starch and its derivatives; polyvinylalcohol, polyvinyl alcohol based compositions such as Opadry® HP, Opadry® II white, Opadry® 200 or Instacoat® and the like; hydrocolloids; sugars; polyvinyl pyrrolidone, copovidone, methacrylic acid copolymers, and combinations comprising one or more of the binders. The binder may be used in the range of 1-40% by weight of the dosage form.

Diluents increase the bulk of the composition. Diluents according to the present invention include, but not limited to, sugars such as lactose, sucrose, dextrose; sugar alcohols such as mannitol, sorbitol, xylitol, lactitol; Starlac® (co-processed mixture of Starch and lactose), Microcelac® (co-processed mixture of microcrystalline cellulose and lactose), starch, corn starch, modified starches, pregelatinized starch, dibasic calcium phosphate, tribasic calcium phosphate, powdered cellulose, microcrystalline cellulose, silicified microcrystalline cellulose and the like or combinations thereof. The diluent may be used in the range of 5-95% by weight of the dosage form.

Disintegrants according to the present invention include, but not limited to, water swellable substances, for example, cellulose and its derivatives including low-substituted hydroxypropyl cellulose; cross-linked polyvinylpyrrolidone; cross-linked sodium carboxymethylcellulose, cross-linked calcium carboxymethylcellulose, sodium carboxymethylcellulose, calcium carboxy methylcellulose, microcrystalline cellulose; sodium starch glycolate; ion-exchange resins; starch and modified starches including pregelatinized starch; formalin-casein; alginates, gums, and combinations comprising one or more of the foregoing water swellable substances. The disintegrant may be used in the range of 1-30% by weight of the dosage form.

Antioxidants according to the present invention include, but not limited to, ascorbic acid, sodium ascorbate, butylated hydroxy anisole, butylated hydroxy toluene, propyl gallate, sodium sulfite, sodium metabisulfite, sodium bisulfite, thioglycerol, thioglycollic acid, Vitamin E derivatives, tocopherol, and the like or combinations thereof. The antioxidant may be used in the range of 0.1-10% by weight of the dosage form.

Surfactants are compounds which are capable of improving the wetting of the drug and/or enhancing the dissolution. The surfactants can be selected from hydrophilic surfactants or
lipophilic surfactants or mixtures thereof. The surfactants can be anionic, nonionic, cationic, and zwitterionic surfactants. Surfactants according to the present invention include, but not limited to, polyoxyethylene alkylaryl ethers such as polyoxyethylene lauryl ether, polyoxyethylene cetyl ether, polyoxyethylene stearyl ether; polyethylene glycol fatty acid esters such as PEG monolaurate, PEG dilaurate, Polyethylene glycol 660 12-hydroxyl Stearate Ph. Eur. or Polyoxyl 15 hydroxystearate NF (Solutol HS 15), PEG distearate, PEG dioleate; polyoxyethylene sorbitan fatty acid ester such as polysorbate 40, polysorbate 60, polysorbate 80; sorbitan fatty acid mono esters such as sorbitan monolaurate, sorbitan monooleate, sorbitan sesquioleate, sorbitan trioleate, polyoxyethylene castor oil derivates such as polyoxyl castor oil, polyoxyl hydrogenated castor oil, sodium lauryl sulphate, monooleate, monolaurate, monopalmitate, monostearate, sodium dioctyl sulfosuccinate (DOSS), lecithin, stearyl alcohol, cetostearyl alcohol, cholesterol, polyoxyethylene ricin oil, polyoxyethylene fatty acid glycerides, poloxamer, Cremophore RH 40, and the like or combinations thereof. The surfactant may be used in the range of 0.001-5% by weight of the dosage form.

Lubricants and glidants aids in the processing of powder materials. Exemplary lubricants include, but not limited to, calcium stearate, glycerol behenate, magnesium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, fumaric acid, talc, vegetable oil, zinc stearate, and combinations comprising one or more of the foregoing lubricants. The lubricant may be used in the range of 0.01-5% by weight of the dosage form. Exemplary glidants include, but not limited to, talc, silicon dioxide, silicic acid, corn starch and the like. The glidant may be used in the range of 0.01-5% by weight of the dosage form.

Pharmaceutically acceptable acid according to the present invention includes, but not limited to, inorganic acids or organic acids.

Suitable inorganic acids according to the present invention includes, but not limited to, hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like or combinations thereof.

Suitable organic acids according to the present invention includes, but not limited to, acetic, pamoic, maleic, citric, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic,
esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, oxalic, and the like or combinations thereof.

In another embodiment, the present invention relates to a process for preparing a stable pharmaceutical composition comprising saxagliptin, which comprises the steps of:
(a) dispersing saxagliptin or a pharmaceutically acceptable salt thereof with one or more pharmaceutically acceptable excipients in a suitable solvent,
(b) granulating blend of one or more pharmaceutically acceptable excipients with saxagliptin dispersion of step (a) to form granules,
(c) blending the granules of step (b) with one or more pharmaceutically acceptable excipients,
(d) compressing the blend of step (c) into tablets, and
(e) coating the tablets of step (d) with a protective coating layer comprising polyvinyl alcohol.

In another embodiment, the present invention relates to a process for preparing a stable pharmaceutical composition comprising saxagliptin or a pharmaceutically acceptable salt thereof, which comprises the steps of:
(a) dissolving saxagliptin or a pharmaceutically acceptable salt thereof in hydrochloric acid,
(b) dispersing polyvinylalcohol based composition in saxagliptin solution of step (a) and adjusting the pH,
(c) granulating blend of one or more pharmaceutically acceptable excipients with saxagliptin dispersion of step (b) to form granules,
(d) blending the granules of step (c) with one or more pharmaceutically acceptable excipients,
(e) compressing the blend of step (d) into tablets, and
(f) coating the tablets of step (e) with a protective coating layer comprising polyvinyl alcohol.

In another embodiment, the present invention relates to a process for preparing a stable pharmaceutical composition comprising saxagliptin or a pharmaceutically acceptable salt thereof, which comprises the steps of:
(a) dissolving saxagliptin or a pharmaceutically acceptable salt thereof in hydrochloric acid,
(b) dispersing hydroxypropyl cellulose in saxagliptin solution of step (a) and adjusting the pH,
(c) granulating blend of one or more pharmaceutically acceptable excipients with saxagliptin dispersion of step (b) to form granules,
(d) blending the granules of step (c) with one or more pharmaceutically acceptable excipients,
(e) compressing the blend of step (d) into tablets, and
(f) coating the tablets of step (e) with a protective coating layer comprising polyvinyl alcohol.

In another embodiment of the present invention, suitable solvents include but are not limited to
diluted solutions of hydrochloric acid, isopropyl alcohol, water, acetone, ethanol, methylene chloride, DMF and the like or mixtures thereof.

The composition according to the present invention may be uncoated or optionally coated
with functional coating, film coating, moisture barrier coating or a protective coating composition. The coating composition mainly comprises of film forming polymers and one or more of plasticizers, opacifier, surfactant, anti tacking agents, coloring agent and the like.

The coating layer polymer may be hydroxypropyl methylcellulose, polyvinyl alcohol (PVA),
ethyl cellulose, methacrylic polymers or hydroxypropyl cellulose, preferably PVA. The coating layer may also optionally include a plasticizer such as triacetin, propylene glycol, diethyl phthalate, tributyl sebacate or polyethylene glycol (PEG), preferably PEG; and an anti-adherent or glidant such as talc, fumed silica or magnesium stearate, opacifying agent such as titanium dioxide. The coating layer may also include iron oxide based colorants. The coating material is commercially available under the trade name Opadry® HP, Opadry® II white, Opadry® 200 or Instacoat®, and the like, or mixtures thereof.

The coating according to the present invention is applied by solubilising or suspending the excipients in solvents such as isopropyl alcohol, water, acetone, ethanol, methylene chloride, hydrochloric acid and the like, or mixtures thereof.

In another embodiment, the composition according to the present invention comprises saxagliptin in the range of 0.5 to 50 mg.

In another embodiment, the composition comprising saxagliptin according to the present invention can be used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.
In another embodiment, the composition comprising saxagliptin can be packed in any suitable packaging material known in the art such as, but not limited to, HDPE bottles and blister pack made from material comprising one or more of PVC, PVDC, PVC/PVDC and aluminium, or bulk packs made of aluminium.

In another embodiment, the HDPE bottles containing saxagliptin composition further contains one or more of a moisture absorber, an oxygen absorber, or a polyester head fill.

In another embodiment, the moisture absorber may be selected from activated carbon, silicas, silica gel, zeolites, molecular sieves, hydrogels, calcium oxide, calcium sulfate, calcium chloride and diatomaceous earth.

In another embodiment, the HDPE bottles comprise saxagliptin composition along with silica gel and a polyester head fill.

In another embodiment, the HDPE bottles comprise saxagliptin composition along with silica gel, activated carbon and a polyester head fill.

In another embodiment, the composition comprising saxagliptin according to the present invention was found to be stable after storage at 40°C/75% RH for atleast three months.

In another embodiment, the composition comprising saxagliptin according to the present invention has a moisture content in the range of 1-10%.

In another embodiment, the active ingredient saxagliptin or its salt may be in the amorphous form, or crystalline form, or a mixture of such forms.

The following examples further exemplify the invention and are not intended to limit the scope of the invention. It is obvious to those skilled in the art to find out the composition for other dosage forms and substitute the equivalent excipients as described in this specification or with the one known to the industry.
**Example 1**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Qty (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxagliptin monohydrate</td>
<td>2.50</td>
</tr>
<tr>
<td>Opadry® II*</td>
<td>5.00</td>
</tr>
<tr>
<td>Mannitol</td>
<td>99.00</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>77.87</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>15.00</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>18.00</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>4.00</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.13</td>
</tr>
<tr>
<td>0.1N hydrochloric acid</td>
<td>q.s.</td>
</tr>
</tbody>
</table>

**Film Coating**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Qty (mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opadry® II*</td>
<td>6.75</td>
</tr>
<tr>
<td>0.1N hydrochloric acid</td>
<td>q.s.</td>
</tr>
</tbody>
</table>

*Opadry II contains polyvinyl alcohol (partially hydrolyzed); titanium dioxide; polyethylene glycol/Macrogol 3350 and talc.

The processing steps involved in manufacturing stable composition comprising saxagliptin are given below:

i) Saxagliptin was dissolved in 0.1 N hydrochloric acid and the pH was adjusted to 2.00 ± 0.03.

ii) Opadry II was dispersed in the saxagliptin solution of step (i) and the pH of the dispersion was adjusted to 2.00 ± 0.03 by adding concentrated hydrochloric acid.

iii) Mannitol and part of microcrystalline cellulose and part of crospovidone were blended.

iv) The blend of step (iii) was granulated using saxagliptin dispersion of step (i) and the granules were dried and milled.

v) The granules of step (iv) were blended with hydroxypropyl cellulose, ascorbic acid and remaining parts of microcrystalline cellulose and crospovidone.

vi) The blend of step (v) was lubricated with magnesium stearate and compressed to form tablets.
vii) The prepared tablets of step (vi) were coated with the Opadry II film coating solution to obtain film-coated tablets.

**Examples 2 - 5**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Example 2</th>
<th>Example 3</th>
<th>Example 4</th>
<th>Example 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxagliptin monohydrate</td>
<td>5.00</td>
<td>2.50</td>
<td>2.50</td>
<td>2.50</td>
</tr>
<tr>
<td>Opadry® II*</td>
<td>-</td>
<td>5.00</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Polyvinyl alcohol</td>
<td>-</td>
<td>-</td>
<td>5.00</td>
<td>5.00</td>
</tr>
<tr>
<td>Mannitol</td>
<td>115.00</td>
<td>99.00</td>
<td>99.00</td>
<td>99.00</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>88.12</td>
<td>81.87</td>
<td>77.87</td>
<td>81.87</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose</td>
<td>13.00</td>
<td>18.00</td>
<td>18.00</td>
<td>18.00</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>8.75</td>
<td>15.00</td>
<td>15.00</td>
<td>15.00</td>
</tr>
<tr>
<td>Ascorbic Acid</td>
<td>4.00</td>
<td>-</td>
<td>4.00</td>
<td>-</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1.13</td>
<td>1.13</td>
<td>1.13</td>
<td>1.13</td>
</tr>
<tr>
<td>0.1N hydrochloric acid</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Film Coating</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opadry® 200 pink*</td>
<td>6.75</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Opadry® II*</td>
<td>-</td>
<td>6.75</td>
<td>6.75</td>
<td>6.75</td>
</tr>
<tr>
<td>0.1N hydrochloric acid</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Opadry® 200 pink contains polyvinyl alcohol, titanium dioxide, talc, glycercil monostearate, sodium lauryl sulphate, iron oxide red, FD&C Yellow#6/Sunset Yellow FCF aluminium lake and iron oxide yellow.

*Opadry II contains polyvinyl alcohol (partially hydrolyzed); titanium dioxide; polyethylene glycol/Macrogol 3350 and talc.

The compositions given in examples 2-5 were prepared using similar procedure described in Example 1.
Table 1 given below shows the comparative dissolution profile of saxagliptin tablets according to the present invention (Examples 1 and 2) and Onglyza® Tablets carried out in 900 ml of 0.1N HCL using Apparatus USP II (Paddle) with sinker, at 50 rpm speed.

Table 1

<table>
<thead>
<tr>
<th>Time in min</th>
<th>% Drug released</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Example 1</td>
</tr>
<tr>
<td>10</td>
<td>69</td>
</tr>
<tr>
<td>15</td>
<td>86</td>
</tr>
<tr>
<td>20</td>
<td>88</td>
</tr>
<tr>
<td>30</td>
<td>89</td>
</tr>
<tr>
<td>45</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 2 given below shows the Impurity profile of saxagliptin tablets prepared according to the present invention (Examples 1 and 2) after storing at 40°C/75% RH for 3 months in HDPE bottles.

Table 2

<table>
<thead>
<tr>
<th>Impurities</th>
<th>Limits (% w/w)</th>
<th>Example 1</th>
<th></th>
<th>Example 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>1 Month</td>
<td>3 Months</td>
<td>Initial</td>
<td>1 Month</td>
</tr>
<tr>
<td>Amide</td>
<td>1.0%</td>
<td>0.02</td>
<td>0.05</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Amidine-1</td>
<td>1.5%</td>
<td>0.07</td>
<td>0.16</td>
<td>0.18</td>
<td>0.02</td>
</tr>
<tr>
<td>Amidine-2</td>
<td>1.5%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>0.01</td>
</tr>
<tr>
<td>Diketo piperazine</td>
<td>1.0%</td>
<td>0.05</td>
<td>0.1</td>
<td>0.09</td>
<td>Not detected</td>
</tr>
<tr>
<td>C2-Epimer</td>
<td>1.0%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>C3-Epimer</td>
<td>1.0%</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Not detected</td>
</tr>
<tr>
<td>Maximum unknown</td>
<td>0.5%</td>
<td>0.13</td>
<td>0.12</td>
<td>0.07</td>
<td>0.17</td>
</tr>
<tr>
<td>Total</td>
<td>3%</td>
<td>0.56</td>
<td>0.58</td>
<td>0.56</td>
<td>0.15</td>
</tr>
</tbody>
</table>
Claims:

1. A stable pharmaceutical composition comprising:
   a) a tablet core comprising:
      (i) an intragranular component comprising saxagliptin or a pharmaceutically
          acceptable salt thereof, and one or more pharmaceutically acceptable excipients,
      (ii) an extragranular component comprising one or more pharmaceutically acceptable
          excipients, and optionally
   b) an outer protective coating layer comprising polyvinyl alcohol over the tablet core.

2. The stable pharmaceutical composition according to claim 1, wherein an outer protective
   coating layer comprising polyvinyl alcohol is present over the tablet core.

3. The stable pharmaceutical composition according to claim 1 or 2, wherein the saxagliptin
   or a pharmaceutically acceptable salt thereof is present in an amount of about 0.5-30% by
   weight of the composition.

4. The stable pharmaceutical composition according to any of the preceding claims 1-3,
   wherein the composition further comprises one or more other antidiabetic agents.

5. The stable pharmaceutical composition according to claim 4, wherein one or more other
   antidiabetic agent is selected from the group comprising acarbose, repaglinide, nateglinide,
   acetohexamide, chlorpropamide, glibenclamide, gliclazide, glimepiride, glipizide,
   glyclopyramide, tolazamide, tolbutamide, buformin, metformin, phenformin, rosiglitazone,
   pioglitazone, troglitazone, faraglitazar, englitazone, darglitazone, isaglitazone, reglitazar,
   rivoglutazone, liraglutide, muraglitazar, peliglitazar, tesaglitazar, sitagliptin, vildagliptin,
   linagliptin, dutogliptin, and alogliptin, canagliflozin, dapagliflozin, remogliflozin,
   sergliflozin, and combination thereof.

6. The stable pharmaceutical composition according to any of the preceding claims 1-5,
   wherein one or more pharmaceutically acceptable excipients are selected from a group
   comprising diluents, binders, disintegrants, antioxidants, lubricants, glidants, acids and
   surfactants.
7. The stable pharmaceutical composition according to claim 6, wherein the diluent is selected from a group comprising lactose, sucrose, dextrose, mannitol, sorbitol, xylitol, lactitol, starch, corn starch, modified starches, pregelatinized starch, dibasic calcium phosphate, tribasic calcium phosphate, powdered cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, and combination thereof.

8. The stable pharmaceutical composition according to claim 6, wherein the disintegrant is selected from a group comprising low-substituted hydroxypropyl cellulose, cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethylcellulose, cross-linked calcium carboxymethylcellulose, sodium carboxymethylcellulose, microcrystalline cellulose, sodium starch glycolate, ion-exchange resins, starch, pregelatinized starch, formalin-casein, alginates, gums, and combination thereof.

9. The stable pharmaceutical composition according to claim 6, wherein the binder is selected from a group comprising ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, starch and its derivatives, polyvinyl alcohol, polyvinyl alcohol based compositions, hydrocolloids, sugars, polyvinyl pyrrolidone, copovidone, methacrylic acid copolymers, and combination thereof.

10. The stable pharmaceutical composition according to claim 6, wherein the acid is selected from a group comprising hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid, acetic acid, pamoic acid, maleic acid, citric acid, hydroxymaleic acid, phenylacetic acid, glutamic acid, benzoic acid, salicylic acid, mesylic acid, esylic acid, besylic acid, sulfanilic acid, 2-acetoxybenzoic acid, fumaric acid, toluenesulfonic acid, oxalic acid, and combination thereof.

11. The stable pharmaceutical composition according to claim 6, wherein the antioxidant is selected from a group comprising ascorbic acid, sodium ascorbate, butylated hydroxy anisole, butylated hydroxy toluene, propyl gallate, sodium sulfite, sodium metabisulfite, sodium bisulfite, thioglycerol, thioglycollic acid, Vitamin E derivatives, tocopherol, and combinations thereof.

12. A process for preparing a stable pharmaceutical composition comprising:
a) a tablet core comprising:
   (i) an intragranular component comprising saxagliptin or a pharmaceutically
       acceptable salt thereof, and one or more pharmaceutically acceptable
       excipients,
   (ii) an extragranular component comprising one or more pharmaceutically acceptable
       excipients, and optionally
b) an outer protective coating layer comprising polyvinyl alcohol over the tablet core.

13. A stable pharmaceutical composition comprising saxagliptin, prepared by process
    comprising the steps of:
    (a) dispersing saxagliptin or a pharmaceutically acceptable salt thereof with one or more
        pharmaceutically acceptable excipients in a suitable solvent,
    (b) granulating blend of one or more pharmaceutically acceptable excipients with saxagliptin
        dispersion of step (a) to form granules,
    (c) blending the granules of step (b) with one or more pharmaceutically acceptable excipients,
    (d) compressing the blend of step (c) into tablets, and
    (e) coating the tablets of step (d) with a protective coating layer comprising polyvinyl alcohol.

14. A process for preparing a stable pharmaceutical composition comprising saxagliptin or a
    pharmaceutically acceptable salt thereof, which comprises the steps of:
    (a) dissolving saxagliptin or a pharmaceutically acceptable salt thereof in hydrochloric acid,
    (b) dispersing polyvinylalcohol based composition in saxagliptin solution of step (a) and
        adjusting the pH,
    (c) granulating blend of one or more pharmaceutically acceptable excipients with saxagliptin
        dispersion of step (b) to form granules,
    (d) blending the granules of step (c) with one or more pharmaceutically acceptable excipients,
    (e) compressing the blend of step (d) into tablets, and
    (f) coating the tablets of step (e) with a protective coating layer comprising polyvinyl alcohol.

15. A process for preparing a stable pharmaceutical composition comprising saxagliptin or a
    pharmaceutically acceptable salt thereof, which comprises the steps of:
    (a) dissolving saxagliptin or a pharmaceutically acceptable salt thereof in hydrochloric acid,
(b) dispersing hydroxypropyl cellulose in saxagliptin solution of step (a) and adjusting the pH.

(c) granulating blend of one or more pharmaceutically acceptable excipients with saxagliptin dispersion of step (b) to form granules,

(d) blending the granules of step (c) with one or more pharmaceutically acceptable excipients,

(e) compressing the blend of step (d) into tablets, and

(f) coating the tablets of step (e) with a protective coating layer comprising polyvinyl alcohol.

16. A method of using the composition of claim 1 comprising saxagliptin or a pharmaceutically acceptable salt thereof in a subject in need thereof.

17. A method of using the composition of claim 1 comprising saxagliptin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K9/20

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 2012/031124 A2 (SQUIBB BRISTOL MYERS CO [US]; ASTRazeneca UK LTD [GB]; NARANG AJIT [US] 8 March 2012 (2012-03-08) cited in the application on claims; examples</td>
<td>1-17</td>
</tr>
<tr>
<td>X.P</td>
<td>WO 2013/105526 AI (TEVA PHARMA [IL]; TEVA PHARMA [US]; SOLOMONOVICH ROEY [IL]; ARI ELI DAF) 18 July 2013 (2013-07-18) the whole document</td>
<td>1-3, 6-10, 12, 13, 16, 17</td>
</tr>
</tbody>
</table>

**Further documents are listed in the continuation of Box C.**

**See patent family annex.**

* Special categories of cited documents:

- **"A"** document defining the general state of the art which is not considered to be of particular relevance
- **"E"** earlier application or patent but published on or after the international filing date
- **"L"** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **"O"** document referring to an oral disclosure, use, exhibition or other means
- **"P"** document published prior to the international filing date but later than the priority date claimed
- **"T"** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- **"X"** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- **"Y"** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- **"A"** document member of the same patent family

**Date of the actual completion of the international search**

13 December 2013

**Date of mailing of the international search report**

03/01/2014

**Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016**

Authorized officer

Ceyte, Mathi Ide
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X, P</td>
<td>EP 2 578 208 AI (SANOVE L I LAC SANAYI VE TICARET A S [TR]) 10 April 2013 (2013-04-10) examples 19,20</td>
<td>1-3,6-9, 12, 16, 17</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2005249467 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR P10510419 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2568391 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1988891 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 102885208 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1753406 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2288288 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL 179454 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 4901727 B2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2008501025 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20070027560 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20120064141 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MY 147639 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 551591 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PE 04252006 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RU 2372894 C2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TW 1354569 B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TW 201204414 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2005266080 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2011200672 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2005117841 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 200609541 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2012031124 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2011295837 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 103370064 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2611442 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2013538814 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2013224296 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2012031124 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2013106526 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2013189358 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2013106526 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2578208 AI</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 [patent family annex] (April 2005)