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(54) Title: STABILIZED PHARMACEUTICAL COMPOSITIONS OF SAXAGLIPTIN

(57) Abstract: The present invention relates to stable, solid pharmaceutical composition comprising saxagliptin alone or in combination with metformin hydrochloride, wherein saxagliptin is stabilized by incorporating acidic stabilizer(s) and stability enhancing carrier(s). The invention also provides a process for preparation of stable, solid oral pharmaceutical compositions.

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"STABILIZED PHARMACEUTICAL COMPOSITIONS OF SAXAGLIPTIN"

This application claims priority to Indian Patent Applications 2153/CHE/2012 dated May 29, 2012 and 5181/CHE/2012 dated Dec 12, 2012.

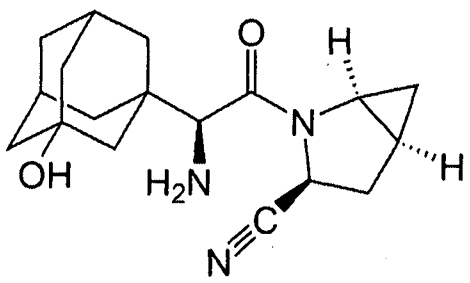
FIELD OF INVENTION

The present invention relates to stable, solid pharmaceutical composition comprising saxagliptin alone or in combination with metformin hydrochloride, wherein saxagliptin is stabilized by incorporating atleast one acidic stabilizer and one or more stability enhancing carrier. Compositions according to the invention are stable and able to prevent the intra-molecular cyclization of highly unstable saxagliptin. The invention also provides a process for preparation of stable, solid oral pharmaceutical compositions.

BACKGROUND OF THE INVENTION AND RELATED PRIOR ART

In general DPP-IV inhibitors are used for the treatment of diabetes, either alone or in combination with other anti-diabetic agents. The first agent of dipeptidyl peptidase IV inhibitors (DPP-IV) class is sitagliptin phosphate (MK-0431) approved in 2006; other approved agents of this class are vildagliptin (LAF-237), saxagliptin (BMS-47718), linagliptin (BI-1356) and alogliptin (SYR-322) approved in 2013. Other DPP-IV inhibitors are P93/01 (Prosidion), Denagliptin (GW823093; GSK), Carmegliptin (RO4876904; Roche), RO0730699 (Roche), TS021 (Taisho), E3024 (Eisai), Melogliptin (GRC 8200; Glenmark) and Dutogliptin (PHX-1149; Phenomix).

Saxagliptin is orally active reversible DPP-IV inhibitor, and is marketed under the trade names Onglyza® and Kombiglyze XR® by Bristol-Myers Squibb for the treatment of type 2 diabetes. Saxagliptin is chemically known as (1S, 3S, 5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo [3.1.0] hexane-3-carbonitrile and having the below structure of formula.



Saxagliptin and its acid addition salts are disclosed in U.S. Pat. No. 6,395,767. In addition, U.S. Pat. No. 7,420,079 discloses saxagliptin and its hydrochloride, trifluoroacetic acid and benzoate salts, as well as saxagliptin monohydrate.

PCT document WO 2008/131149 discloses certain crystal/ polymorphic forms of saxagliptin base as well as saxagliptin acid addition salts like hydrochloride, hydrobromide, hydrogen iodide, nitrate, trifluoroacetic acid, benzoate, fumarate, tartarate and ammonium sulfate.

U.S. patent No. 7,951,400 from Bristol-Myers Squibb Company teaches coated immediate release tablet compositions comprising saxagliptin and polyvinyl alcohol. It states that saxagliptin is very unstable and tends to undergo intra-molecular cyclization in both solid as well as in solution state to form cyclic amidine (mainly cis-cyclic amidine (CA), which is not therapeutically active and therefore, its formation is not desirable. It also states that the rate of intra-molecular cyclization is accelerated when formulations are subject to commonly used processing activities such as wet granulation, roller compaction, or tabletting. In addition, most commonly used excipients, when mixed with this compound, can accelerate the rate of cyclization. The level of cis-cyclic amidine increases when the drug to excipient ratio increases posing more challenges for low strength dosage forms. Given this behaviour of the molecule, manufacture of a conventional tablet dosage form for the DPP4-inhibitor, which is usually the preferred dosage form, is not a routine option. Since a tablet dosage form using traditional manufacturing process is not feasible for saxagliptin, its manufacturing with other therapeutic agents, as a combination tablet will be even more problematic.

The cyclization problem of saxagliptin was solved by coating the cores with two or more coating layers, in which atleast two layers, the an inner seal coat layer and the second saxagliptin layer necessarily consists of a polyvinyl alcohol based polymer, and preferably a third outer protective layer over saxagliptin layer necessarily consists of polyvinyl alcohol based polymer. i.e. saxagliptin is covered/ protected by putting in at least two and preferably three protective layers, each having the polyvinyl alcohol based polymer.

Metformin is chemically known as N,N-Dimethylimidodicarbonimidic diamide and is an antihyperglycemic agent of the biguanide class used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). Metformin hydrochloride has intrinsically poor permeability in the lower portion of the gastrointestinal tract leading to absorption almost exclusively in the upper part of the gastrointestinal tract. Its oral bioavailability is in the range of 40 to 60% and decreases with increase in dosage which suggests some kind of saturable absorption process, or permeability/ transit time limited absorption. It also has a very high water solubility (>300 mg/ml at 25°C). This can lead to difficulty in providing a slow release rate from a formulation and problems in controlling the initial burst of drug from such a formulation. These difficulties are further compounded by the high unit dose, usually 500 mg or more per tablet.

Metformin mono-therapy typically has been used as a first line treatment in diabetic patients. This treatment may be supplemented with other drugs like DPP-IV inhibitor, glitazones or a sulfonylurea to provide an optimal level of glycemic control not attainable using either medication alone.

U.S. Patent No. 6,475,521 and 6,660,300 discloses biphasic controlled release delivery system for high solubility drugs like metformin. U.S. Patent No. 6,340,475 and 6,488,962 discloses gastric retentive controlled release dosage comprising Metformin. U.S. Patent No. 6,524,618 discloses directly compressible extended release matrix formulation for metformin.

U.S. Patent No. 7,125,873 describes pharmaceutical composition comprising sitagliptin with other anti-diabetic drugs such as biguanide and PPAR agonists. U.S. Patent Application No. 2009/0105265 and 2010/0074950 discloses pharmaceutical compositions comprising combinations of sitagliptin and metformin, methods of preparation and methods of treating Type 2 diabetes using these pharmaceutical compositions. U.S. Patent Application No. 2011/206766 discloses pharmaceutical compositions comprising combinations of DPP-IV inhibitor and anti-diabetic agents.

The present Inventors present an alternative stable, solid oral pharmaceutical compositions of saxagliptin either alone or in combination with metformin hydrochloride, wherein said pharmaceutical compositions prevents the intra-

molecular cyclization of saxagliptin while avoiding polyvinyl alcohol based polymers in multiple layers.

The present invention also provide stable, solid oral pharmaceutical compositions comprising saxagliptin either alone or in combination with metformin hydrochloride, wherein said compositions are stable and able to prevents the intra-molecular cyclization of saxagliptin and also exhibits hardness, friability, disintegration, *in-vitro* dissolution profile and bioequivalence [*in-vivo*] profile similar to that of commercially available Onglyza® and Kombiglyze XR®.

OBJECTS OF THE INVENTION

According to the invention, there is provided a stable, tablet composition comprising a saxagliptin, atleast one acidic stabilizer and one or more stability enhancing carrier.

Another object of the present invention is to provide a stable, immediate release coated tablet composition comprising:

(a) a tablet core;

(b) a seal coat on said tablet core, comprising atleast one stability enhancing carrier;

(c) a drug layer coated on said seal coat, comprising a saxagliptin, atleast one acidic stabilizer and one or more stability enhancing carrier; and

(d) an outer film coating layer coated on said drug layer, comprising atleast one stability enhancing carrier.

Another object of the present invention is to provide a stable, immediate release coated tablet composition comprising:

(a) a tablet core;

(b) a seal coat on said tablet core, comprising hydroxypropyl methylcellulose;

(c) a drug layer coated on said seal coat, comprising a saxagliptin hydrochloride, hydrochloric/ oxalic acid/ citric acid, copovidone and optional excipients; and

(d) an outer film coating layer coated on said drug layer, comprising hydroxypropyl methylcellulose.

Another object of the present invention is to provide a stable, immediate release coated tablet composition comprising:

(a) a tablet core;

(b) a seal coat on said tablet core, comprising hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose;

(c) a drug layer coated on said seal coat, comprising a saxagliptin hydrochloride, hydrochloric acid, copovidone and optional excipients; and

(d) an outer film coating layer coated on said drug layer, comprising hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose.

Another object of the present invention is to provide a stable, immediate release coated tablet composition comprising:

(a) a tablet core comprising metformin hydrochloride, carbopol, hydroxypropyl methylcellulose, stearic acid and optional excipients;

(b) a seal coat on said metformin hydrochloride tablet core, comprising hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose;

(c) a drug layer coated on said seal coat, comprising a saxagliptin hydrochloride, hydrochloric acid, copovidone and optional excipients; and

(d) an outer film coating layer coated on said drug layer, comprising hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose.

Another object of the present invention is to provide a process for the preparation of amorphous saxagliptin hydrochloride comprising the steps of: (a) dissolving saxagliptin hydrochloride, copovidone and hydrochloric acid in methanol; and (b) removing methanol to get amorphous saxagliptin hydrochloride. This amorphous material can be used to make a composition.

Yet another object of the present invention is to provide a stable, tablet compositions comprising saxagliptin hydrochloride either alone or in combination with metformin hydrochloride, wherein said tablet compositions are bioequivalent to the commercially available Onglyza® and Kombiglyze XR® tablets.

SUMMARY OF THE INVENTION

The present invention relates to stable, solid oral pharmaceutical compositions comprising saxagliptin either alone or a combination with metformin hydrochloride, wherein said composition prevents the degradation of saxagliptin during manufacturing as well as during storage.

The stable, solid oral pharmaceutical composition according to the invention relates to immediate release tablets comprising saxagliptin, atleast one acidic stabilizer, one or more stability enhancing carrier(s) and optional excipients, exhibiting *in-vitro* dissolution profiles and bioequivalence (*in-vivo*) similar to commercially available drug products of saxagliptin, and wherein the degradation of saxagliptin is prevented or minimized by employing one or more acidic stabilizer(s) and one or more stability enhancing carrier(s).

In one embodiment the stable, solid oral pharmaceutical composition according to the invention is a tablet, comprising:

(a) an inert tablet core;

(b) a seal coat on the tablet core, comprising hydroxypropyl methylcellulose;

(c) a drug layer coated over the seal coat, comprising a saxagliptin, hydrochloric acid/ oxalic acid/ citric acid, copovidone and optional excipients; and

(d) an outer film coating layer coated on the drug layer, comprising hydroxypropyl methylcellulose.

In one embodiment the stable, solid oral pharmaceutical composition according to the invention is a tablet, comprising:

(a) a tablet core comprising metformin hydrochloride, carbopol, hydroxypropyl methylcellulose, stearic acid and optional excipients;

(b) a seal coat on the tablet core, comprising hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose;

(c) a drug layer coated over the seal coat, comprising a saxagliptin, hydrochloric acid, copovidone and one or more pharmaceutically acceptable excipients; and

(d) an outer film coating layer coated on the drug layer, comprising hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose.

In one embodiment the stable, solid oral pharmaceutical composition according to the invention is a tablet, comprising:

(a) a tablet core comprising metformin hydrochloride, carbopol, hydroxypropyl methylcellulose, stearic acid and optional excipients;

(b) a seal coat on the tablet core, comprising hydroxypropyl methylcellulose, stearic acid and copovidone;

(c) a drug layer coated over the seal coat, comprising a saxagliptin, hydrochloric acid, copovidone and optional excipients; and

(d) an outer film coating layer coated on the drug layer, comprising hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose.

In another embodiment the invention provides process for preparing stable, solid oral tablet composition, comprising the steps of:

a) mixing together one or more pharmaceutically acceptable excipients to form a blend;

b) preparing a binder solution comprising one or more binder in a solvent;

c) granulating the material of step a) with said binder solution of step b) to form granules;

d) drying and compressing said granules of step c) to form inert tablet cores;

e) dispersing hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose in water to form dispersion;

f) inert tablet cores of step d) are then coated with said dispersion of step e) to form a seal coating layer on said inert tablet cores;

g) saxagliptin, atleast one acidic stabilizer, one or more stability enhancing carrier(s) and optional excipient(s) are added in a solvent to form a dispersion;

h) inert tablet cores of step f) are then coated with said dispersion of step g) to form saxagliptin layered tablet cores;

i) tablet cores of step h) are then coated with said dispersion of step e) to form outer coating layer on said saxagliptin layer tablet cores.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention is directed to a stable, solid oral pharmaceutical composition containing a DPP-IV inhibitor(s) either alone or in combination with metformin hydrochloride, wherein said compositions are stabilized without employing polyvinyl alcohol based formulations.

According to the invention the DPP-IV inhibitor is selected from the group consisting of Sitagliptin phosphate (MK-0431), Saxagliptin (BMS-47718), Vildagliptin (LAF-237), Linagliptin (BI-1356), Alogliptin (SYR-322), Carmegliptin, Denagliptin, Dutogliptin, E3024, Melogliptin, P93/01, RO0730699 and TS021. The

preferred DPP-IV inhibitor according to the invention is saxagliptin hydrochloride in immediate release form. Solid oral dosage forms according to the invention are tablets, granules, mini-tablets, pellets, capsules and the like.

Particularly preferred solid oral pharmaceutical compositions according to the invention are tablets, which are bioequivalent and exhibit content uniformity, desirable hardness, uniform disintegration and dissolution profile similar to commercially available Onglyza® and Kombiglyze XR® tablets, as well as are stable and able to prevent the intra-molecular cyclization of saxagliptin throughout the shelf life of the product.

The invention provides stable, tablet compositions, comprising saxagliptin in immediate release either alone or in combination with metformin hydrochloride in slow release form, and further containing one or more anti-diabetic agent(s) such as thiazolidinedione or a sulphonylurea derivative.

The solid oral tablet composition according to the invention comprises saxagliptin, atleast one acidic stabilizer, one or more stability enhancing carrier and optional excipients.

The invention provides solid oral tablet composition comprising:

(a) an inert tablet core;

(b) a seal coat on said inert tablet core, comprising one or more stability enhancing carrier;

(c) a drug layer coated on said seal coat, comprising saxagliptin, atleast one acidic stabilizer, one or more stability enhancing carrier and optional excipients; and

(d) an outer film coating layer coated on said drug layer, comprising one or more stability enhancing carrier.

In one preferred embodiment, the invention provides stable, solid oral tablet, comprising:

(a) a inert tablet core;

(b) a seal coat on said tablet core, comprising hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose;

(c) a drug layer coated on said seal coat, comprising a saxagliptin hydrochloride, hydrochloric acid and copovidone; and

(d) an outer film coating layer coated on said drug layer, comprising hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose.

The invention also provides solid oral tablet composition comprising:

(a) an active tablet core comprising metformin hydrochloride, carbopol, hydroxypropyl methylcellulose, stearic acid and optional excipients;

(b) a seal coat on said inert tablet core, comprising one or more stability enhancing carrier;

(c) a drug layer coated on said seal coat, comprising saxagliptin hydrochloride, atleast one acidic stabilizer, one or more stability enhancing carrier and optional excipients; and

(d) an outer film coating layer coated on said drug layer, comprising one or more stability enhancing carrier.

In another preferred embodiment, the invention provides stable, solid oral tablet, comprising:

(a) a tablet core comprising metformin hydrochloride, carbopol, hydroxypropyl methylcellulose, stearic acid and optional excipients;

(b) a seal coat on said tablet core, comprising hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose;

(c) a drug layer coated on said seal coat, comprising a saxagliptin hydrochloride, hydrochloric acid, copovidone and optional excipients; and

(d) an outer film coating layer coated on said drug layer, comprising hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose.

In another embodiment, the invention provides process for preparing stable, solid oral tablet composition, comprising the steps of:

a) mixing together one or more pharmaceutically acceptable excipients to form a blend;

b) preparing a binder solution comprising one or more binder in a solvent;

c) granulating the material of step a) with said binder solution of step b) to form granules;

d) drying and compressing said granules of step c) to form inert tablet cores;

e) dispersing hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose in water to form dispersion;

f) inert tablet cores of step d) are then coated with said dispersion of step e) to form a seal coating layer on said inert tablet cores;

g) saxagliptin hydrochloride, atleast one acidic stabilizer, one or more stability enhancing carrier(s) and optional excipient(s) are added in a solvent to form a dispersion;

h) inert tablet cores of step f) are then coated with said dispersion of step g) to form saxagliptin layered tablet cores;

i) tablet cores of step h) are then coated with said dispersion of step e) to form outer coating layer on said saxagliptin layer tablet cores.

In another embodiment, the invention provides process for preparing stable, solid oral tablet composition, comprising the steps of:

a) mixing together metformin hydrochloride, carbopol, hydroxypropyl methylcellulose, and optional excipients to form a blend;

b) preparing a binder solution comprising one or more binder in a solvent;

c) granulating the material of step a) with said binder solution of step b) to form granules;

d) drying and compressing said granules of step c) to form metformin hydrochloride tablet cores;

e) dispersing hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose in water to form dispersion;

f) cores of step d) are then coated with said dispersion of step e) to form a seal coating layer on said metformin hydrochloride tablet cores;

g) saxagliptin hydrochloride, atleast one acidic stabilizer, one or more stability enhancing carrier(s) and optional excipient(s) are added in a solvent to form a dispersion;

h) tablet cores of step f) are then coated with said dispersion of step g) to form saxagliptin layered tablet cores;

i) tablet cores of step h) are then coated with said dispersion of step e) to form outer coating layer on said saxagliptin layer tablet cores.

In yet another embodiment, the tablet cores according to the invention may be prepared by granulating saxagliptin, atleast one acidic stabilizer, one or more stability enhancing carrier and one or more diluent to form active saxagliptin tablet cores and

coating said active tablet cores with one or more coating layers comprising one or more stability enhancing carrier.

Alternatively the tablet composition according to the invention may be in the form of a bilayer tablet, wherein one layer comprises saxagliptin, hydrochloric acid, copovidone and optional excipients and the other layer comprises metformin hydrochloride, carbopol, hydroxypropyl methylcellulose, stearic acid and optional excipients, and coating said bilayer tablet with a coating comprising hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose.

According to the invention the term "saxagliptin" refer to saxagliptin in base form, its polymorphs, hydrates, solvates or pharmaceutically acceptable salts including hydrochloric acid salt, its polymorphs, solvates, and hydrates or saxagliptin in amorphous form including "amorphous solid dispersion of saxagliptin".

The term 'saxagliptin in immediate release' means granules, tablets, cores, pellets, mini-tablets or coating layer, that releases saxagliptin within 30 minutes and comprises saxagliptin hydrochloride, atleast one acidic stabilizer and one or more stability enhancing carrier.

Acidic stabilizers according to the invention are the agents which are used to decrease the pH around the vicinity of saxagliptin and include but not limited to hydrochloric acid, organic acids, cysteine hydrochloride and pharmaceutical excipients having acidic properties.

Organic acid according to the invention refers to edible organic acids such as adipic acid, ascorbic acid, oleic acid, succinic acid, acetic acid, tartaric acid, sorbic acid, fumaric acid, oxalic lactic acid, maleic acid, malonic acid, citric acid, and combination thereof. Hydrochloric acid and oxalic acid are particularly preferred acidic stabilizers. The weight ratio of saxagliptin to acidic stabilizer should be in the ratio of 1:0.05 to about 1:0.10, preferably 1:0.07 to about 1:0.09.

Stability enhancing carrier according to the invention is an excipient(s) that improves the stability of saxagliptin and may be selected from but not limited to mannitol, lactose, polyvinyl acetate, cellulose derivative like hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethyl cellulose and microcrystalline

cellulose, pre-gelatinized starch, sucrose, stearic acid, sorbitol, polyvinylpyrrolidone, polyethylene glycol, copovidone, crospovidone and combination thereof. Copovidone and mixture of hydroxypropyl methylcellulose, microcrystalline cellulose and stearic acid is the most preferred stability enhancing carrier.

Copovidone is the preferred stability enhancing carrier present along with saxagliptin, either in the drug layer or in the active tablet cores. The weight ratio of saxagliptin to copovidone should be in the ratio of 1:3 to about 1:6, which is required for optimum stability of saxagliptin.

A mixture of hydroxypropyl methylcellulose, microcrystalline cellulose and stearic acid is the most preferred stability enhancing carrier mixture for seal coating and outer coating layer. The amount of hydroxypropyl methylcellulose that can be incorporated in said seal coating and outer coating layer is from about 30% to about 60% by weight of the coating layer, the amount of microcrystalline cellulose that can be incorporated is from about 5% to about 10% by weight of the coating layer and the amount of stearic acid that can be incorporated is from about 20% to about 35% by weight of said seal and outer coating layer.

According to the invention the term 'metformin in slow release form' means modified release, extended release, sustained release, pulse release or retard release granules, tablets, pellets, mini-tablets of metformin hydrochloride which releases metformin hydrochloride in slow or extended or sustained or delayed or in controlled/ modified release manner. Metformin hydrochloride in slow release form essentially comprises a mixture of metformin hydrochloride, hydroxypropyl methylcellulose, one or more release retarding agents and optional excipients.

The amount of hydroxypropyl methylcellulose that be incorporated into the slow release metformin cores is in the range of form about 7% to about 14%, preferably 10% to about 12% by weight of metformin core tablet.

The term 'release retarding agent' according to the invention refers to materials capable of retarding/ sustaining/ controlling/ extending/ modifying the release of drug substance and includes one or more waxes, fatty alcohols, fatty acid and esters of fatty acids alone or in combination with carbopol. Preferred release

retarding agent according to the invention contains a mixture of atleast one fatty acid such as stearic acid and Carbopol 971 P.

Carbopol are polymers having high molecular weight crosslinked acrylic acid chains. Depending upon the degree of cross-linking and manufacturing conditions, various grades of carbopol are available like Carbopol 934 P, Carbopol 71 G, Carbopol 971 P, Carbopol 974 P and mixtures thereof. The amount of carbopol that can be present in the slow release metformin cores according to the invention is in the range from about 1% to about 10%, preferably from about 3% to about 7% and more preferably from about 5% to about 6% by weight of metformin core tablet.

Fatty acid are selected from the group of consisting of but not limited to stearic acid, hydrogenated palm oil, hydrogenated palm kernel oil, hydrogenated peanut oil, hydrogenated rapeseed oil, hydrogenated rice bran oil, hydrogenated soybean oil, hydrogenated cottonseed oil, hydrogenated sunflower oil, hydrogenated castor oil, decenoic acid, docosanoic acid, palmitic acid, lauric acid, myristic acid, and mixtures thereof. Preferred fatty acid according to the invention is stearic acid is in the range from about 3% to about 10%, preferably from about 4% to about 7% and more preferably from about 5% to about 6% by weight of metformin core tablet.

The slow release metformin core is preferably prepared using wet granulation technique by employing a non-aqueous solvent. Non-aqueous wet granulation solvents or fluids can be selected form but not limited to ethanol, methanol, isopropyl alcohol, and mixtures thereof.

The inert tablet cores according to the invention can be prepared by mixing one or more pharmaceutically acceptable excipients and processing said mixture to form tablets by direct compression technique or by granulation method.

The tablets cores may be active, prepared by processing a mixture of saxagliptin hydrochloride, atleast one acidic stabilizer and one or more stability enhancing carrier and optional excipients to form saxagliptin tablet cores either by a direct compression method or by granulation method.

Alternatively inert seeds/ inert tablet cores coated with a coating layer comprising saxagliptin, atleast acidic stabilizer, one or more stability enhancing

carrier and optional excipients, may be compressed together to form active tablet core(s).

The inert seeds, which are to be layered with the active substance, can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or in mixtures or water soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. The size of the seeds may vary between approximately 0.1 and 2 mm. The seeds layered with active substance are produced either by powder or solution/suspension layering using for instance granulating, spray coating/ layering equipment or other techniques of layering known in the art.

The present invention also related to stable solid oral pharmaceutical composition comprising saxagliptin in amorphous solid dispersion form either alone or in combination with metformin hydrochloride.

According to the invention "amorphous solid dispersion of saxagliptin" refers to solid dispersion comprising saxagliptin, one or more acidic stabilizer(s), at least one polymeric excipient. The polymeric excipient may be water soluble or water insoluble.

The polymeric excipient for "amorphous solid dispersion of saxagliptin" according to the invention may be selected from homopolymers and copolymers of N-vinyl pyrrolidone, like polyvinylpyrrolidone (PVP), copolymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl ethylcellulose, methylcellulose, xanthum gum, polyethylene oxide, polypropylene oxide, polyvinyl acetate, partially hydrolyzed polyvinyl acetate, oligo- and polysaccharides such as carrageenans, galactomannans and xanthan gum and mixtures thereof.

Preferred polymeric excipients for making "amorphous solid dispersion of saxagliptin" according to the invention are povidone, copovidone, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, ethyl cellulose, polyvinyl acetate, polyethylene glycol, sorbitol and mixtures thereof. The most preferred polymeric excipients for making "amorphous solid dispersion of saxagliptin" is selected from plasdone S-630 or PVP K-30.

The "amorphous solid dispersion of saxagliptin" can be prepared by spray drying, melting method, solution-evaporation, melting solvent method (melt evaporation), hot melt extrusion method, lyophilization technique, melt agglomeration process and super critical fluid (Scf) technology with solvent evaporation and spray drying being preferred.

Solvents that can be employed for making "amorphous solid dispersion of saxagliptin" may be selected from but not limited to water, methanol, ethanol, isopropyl alcohol, butanol, acetone, and dichloromethane.

The "amorphous solid dispersion of saxagliptin" according to the invention can be used to prepared stable saxagliptin tablet composition, wherein saxagliptin in said amorphous solid dispersion is stabilized by incorporating atleast one acidic stabilizer and one or more stability enhancing carriers.

In one embodiment the amorphous solid dispersion of saxagliptin hydrochloride is prepared by a process comprising the steps of: a) dissolving saxagliptin hydrochloride, atleast one suitable polymeric excipient and an acidic stabilizer in a solvent; b) adding an anti-solvent; and c) isolating amorphous saxagliptin hydrochloride.

In another embodiment the amorphous solid dispersion of saxagliptin hydrochloride is prepared by a process comprising the steps of: a) dissolving saxagliptin hydrochloride, atleast one suitable polymeric excipient and an acidic stabilizer in a solvent; b) removing said solvent; and c) isolating amorphous saxagliptin hydrochloride.

In one specific embodiment the amorphous solid dispersion of saxagliptin hydrochloride is prepared by a process comprising the steps of: a) dissolving saxagliptin hydrochloride, copovidone and hydrochloric acid in methanol; b) removing said methanol; and c) isolating amorphous saxagliptin hydrochloride. Isolated saxagliptin hydrochloride as made by the above process has an XRD as given in figure 1.

In another embodiment the invention provide a process for the preparation of amorphous solid dispersion of saxagliptin hydrochloride comprising the steps of: a)

dissolving saxagliptin hydrochloride, copovidone and hydrochloric acid in methanol; b) removing methanol to get amorphous saxagliptin hydrochloride and then employing this amorphous saxagliptin hydrochloride to make stable solid oral pharmaceutical composition.

In another specific embodiment, the invention provides process to make stable, solid oral tablet, comprising the steps of:

(a) dispersing hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose in water to form dispersion;

(b) coating the dispersion of step a) on tablet cores to form a seal coat on said tablet cores;

(c) dissolving saxagliptin hydrochloride, copovidone and hydrochloric acid in methanol to form a solution;

(d) coating the seal coated tablet cores of step b) with the solution of step c) in an automatic coating machine to form amorphous saxagliptin hydrochloride layer on said tablet cores;

(e) tablet cores of step (d) are further coating with the dispersion of step a) to form outer coating layer.

The term excipient refer to and include one or more of filler/ diluents, binders, disintegrants, surfactants, lubricants, glidant, coloring agents, sweeteners and flavoring agent.

Diluents can be selected from but not limited to mannitol, sorbitol, dibasic calcium phosphate dihydrate, microcrystalline cellulose, powdered cellulose, calcium carbonate and mixtures thereof. A preferred diluent is microcrystalline cellulose commercially available is various grades such as Avicel PH 101, Avicel PH 102, Avicel, PH 103, Avicel PH 105, and Avicel PH 200, manufactured by the FMC Corporation.

Binding agents can be selected from but not limited to hydroxypropylcellulose (HPC), hydroxyethyl cellulose, starch 1500, polyvinylpyrrolidone (povidone), co-povidone and mixtures thereof. A preferred binding agent is polyvinylpyrrolidone. Said binders may be present in an amount from about 1% to

about 10% by weight, preferably from about 2% to about 5% by weight of the composition.

Disintegrants can be selected form but not limited to modified starches, modified cellulose polymers, or polycarboxylic acids, such as croscarmellose sodium, sodium starch glycollate, polacrillin potassium, carboxymethylcellulose calcium (CMC Calcium) and mixtures thereof. In one embodiment, the disintegrant is croscarmellose sodium. Croscarmellose sodium NF Type A is commercially available under the trade name "Ac-di-sol."

The composition according to the invention may contain one or more lubricants or glidants. Examples of lubricants include magnesium stearate, calcium stearate, sodium stearyl fumarate, hydrogenated castor oil, and mixtures thereof. Preferred lubricants are magnesium stearate, sodium stearyl fumarate or a mixture thereof. Examples of glidants include colloidal silicon dioxide, calcium phosphate tribasic, magnesium silicate, talc and mixtures thereof.

In preparing solid oral pharmaceutical compositions of the invention, solvent that can be employed for making film coating suspensions/ dispersions for seal coat, the drug layer and outer coating layer may be selected from water, ethanol, methanol, acetone and isopropyl alcohol.

The film coating layer comprising stability enhancing carrier may optionally include one or more plasticizers such as triacetin, diethyl phthalate, tributyl sebacate and 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 one or more colorants.

In an effort to solve the stability problem of this highly unstable saxagliptin, wherein saxagliptin undergoes intra-molecular cyclization, the inventors have surprisingly found that saxagliptin stability is improved by decreasing the pH in and around the vicinity of saxagliptin, which is achieved by incorporating one or more acidic stabilizers along with saxagliptin and stability enhancing carrier(s).

The unit dosage strength of saxagliptin for incorporation into the solid oral dosage forms of the present invention is an amount from about 1 mg to about 100 mg

of the active agent, preferred dosage strength is an amount from about 2.5 - 10 mg e.g. 2.5 mg, 5 mg and 10 mg.

The dosage strength of metformin hydrochloride that can be incorporated into the solid oral dosage forms of the present invention is 250, 500, 625, 750, 850, and 1000 mg and represents the dosage strengths approved for marketing to treat Type 2 diabetes.

The following examples further exemplify the invention and are not intended to limit the scope of the invention.

Example 1-6

Ingredients	% w/w					
	Ex. 1	**Ex. 2**	**Ex. 3**	**Ex. 4**	**Ex. 5**	**Ex. 6**
Metformin HCl	59.39	59.95	61.17	59.26	60.02	59.42
Carbopol	5.34	5.40	5.51	5.33	5.40	5.35
Povidone	2.97	3.00	4.65	4.50	2.40	4.52
Povidone	1.54	1.56	-	-	2.16	-
Hypromellose	11.88	11.99	12.23	11.85	12.00	11.88
Stearic acid	5.94	6.00	9.18	8.89	3.00	8.91
Stearic acid	2.97	3.00	-	-	6.00	-
Isopropyl alcohol	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Colloidal silicon dioxide	0.48	0.48	0.49	0.47	0.48	0.48
Magnesium Stearate	1.54	1.56	1.59	1.54	1.56	1.54
Seal coating						
Hypromellose	1.31	-	-	-	-	-
Microcrystalline cellulose	0.24	-	-	-	-	-
Stearic acid	0.83	-	-	-	-	-
Copovidone	-	0.24	-	-	-	0.24
Sucrose	-	-	-	0.89	-	-
Mannitol	-	-	-	0.65	-	-
Talc	-	-	-	0.44	-	-
Pregelatinised starch	-	-	-	-	1.80	-
polyethylene glycol	-	-	-	-	0.24	-
Saxagliptin coating						
Saxagliptin hydrochloride	0.30	0.30	0.31	0.30	0.30	0.30
Copovidone	1.51	-	1.56	-	-	-
Colloidal silicon dioxide	0.83	-	0.85	-	-	-
Crospovidone	-	0.30	-	-	0.30	-
Oxalic acid	-	0.60	-	0.59	0.60	0.59
Pregelatinised starch	-	-	-	2.43	-	2.44
polyethylene glycol	-	-	-	0.36	-	0.36
Hydrochloric Acid	0.02	-	0.03		-	-
Outer protective coating						
Hypromellose	1.53	-	1.35	-	-	1.78
Microcrystalline cellulose	0.28	-	0.24	-	-	-
Stearic acid	0.97	-	0.86	-	-	-
Copovidone	-	0.72	-	0.71	0.72	-
polyethylene glycol	-	-	-	-	-	0.18
Titanium dioxide	0.11	-	-	-	-	0.12
Iron Oxide Red	0.01	-	-	-	-	-

Example 7-9:

Ingredients	% w/w		
	Ex. 7	Ex. 8	Ex. 9 (without acidic excipient)
Microcrystalline cellulose	45.15	38.22	38.27
Anhydrous Lactose	26.56	39.73	39.78
Crospovidone	3.79	-	-
Croscarmellose sodium	-	2.32	2.32
Magnesium Stearate	0.38	0.81	0.81
Seal Coating			
Hypromellose	1.48	2.04	2.04
Microcrystalline cellulose	0.11	0.37	0.37
Stearic acid	0.68	1.30	1.30
Purified Water	q. s.	q. s.	q. s.
Saxagliptin Coating			
Saxagliptin hydrochloride	2.11	2.32	2.32
Copovidone	10.75	6.49	6.49
Colloidal silicon dioxide	5.88	3.03	3.04
Hydrochloric Acid	0.17	0.14	---
Outer Protective coating			
Hypromellose	1.53	2.01	2.01
Microcrystalline cellulose	0.28	0.35	0.35
Stearic acid	0.97	1.10	1.10
Titanium dioxide	0.15	0.16	0.16
Iron oxide Red	0.02	-	-

Ex. 10:

Ingredients	% w/w
Saxagliptin hydrochloride	6.02
Lactose anhydrous	75.39
Hydrochloric acid	0.04
Citric acid anhydrous	8.43
Copovidone	3.61
Crospovidone	1.93
magnesium stearate	0.96
Outer protective coating	
Hydroxypropyl methyl cellulose	1.99
Microcrystalline cellulose	0.36
Stearic acid	1.27

Procedure:

A. Core Tablets

1. Lactose anhydrous, Citric acid anhydrous and Copovidone were mixed together;
2. Saxagliptin and hydrochloric acid were added in methanol to form a binder solution;
3. The material of step no. 1 was granulated with the binder solution of step;
4. The granules of step no. 3 were dried and mill;
5. The granules of step no. 4 were mixed with crospovidone and lubricated with magnesium stearate.
6. Lubricated blend of step no. 5 was compressed into tablets using suitable tooling.

B. Outer protective coating

7. Hydroxypropyl methyl cellulose, stearic acid and microcrystalline cellulose were dispersed in sufficient amount of water to form dispersion.
8. The tablets of step no. 6 were coated with the dispersion of step no 7 to form a coating.

Ex. 11: Preparation of amorphous Saxagliptin hydrochloride

Saxagliptin hydrochloride (30%), Plasdone S-630 (68.5%) and hydrochloric acid (1.5%) were dissolved in methanol (200 ml). The clear solution was filtered to remove any un-dissolved particulate. Methanol was removed from the clear solution and solid powder was obtained. This solid was identified as amorphous saxagliptin hydrochloride as given in Figure 1.

Comparative dissolution study:

The dissolution test was carried out using USP I apparatus at 100 RPM, 1000 ml of phosphate buffer pH 6.8 at 37 ± 0.5 °C and the results re provided in Table I given below:

Table I:

Time	Kombiglyze® XR tablet 5/1000 mg	Ex. 1	Ex. 7
% saxagliptin released			
10 min	96	94	35
15 min	97	98	63
20 min	97	99	85
30 min	98	100	91
% Metformin hydrochloride released			
1 hr	23	28	--
2 hr	39	41	--
3 hr	50	50	
4 hr	59	58	--
6 hr	72	69	--
8 hr	82	79	--
10 hr	89	86	--
12 hr	93	90	--

Stability Studies:

A 12 weeks stability study of the tablets (Ex. 1, Ex. 2 and Ex. 7) prepared according to the invention and a test composition (Ex. 9) as well as Kombiglyze® XR tablet (5 mg saxagliptin hydrochloride and 1000 mg metformin hydrochloride) were carried out in sealed HDPE containers. The sealed HDPE containers were stored in accelerated stability conditions at 40 ± 2°C and 75 ± 5% relative humidity (RH). Table II provides the amount of impurities at the initial stage and after completion of 12 weeks.

Table II:

Composition tested	Total Impurity [Initial]	Total Impurity [After 12 Weeks]
Kombiglyze® XR tablet 5/1000 mg	1.775	--
Ex. 1	0.537	0.646
Ex. 2	0.526	0.818
Ex. 7	0.091	0.141
Ex. 9	3.027	--

Powder X-ray Diffraction (PXRD):

The X-ray diffraction patterns of amorphous saxagliptin hydrochloride were measured on Bruker D8 ADVANCE powder X-ray diffractometer equipped with Goniometer of θ/θ configuration and LynxEye detector. The instrument was operated at 40kV and 40mA. The experiments were conducted over the 2θ range of 3.0°-45.0°, 0.030° with 0.01° step size and 170 seconds step time.

Brief description of the figures:

FIG. 1 is a representative X-ray diffraction pattern of amorphous saxagliptin hydrochloride.

We Claim:

1. A stable, solid oral tablet composition comprising
(a) a tablet core;
(b) a seal coating layer coated on said tablet core;
(c) a drug coating layer comprising saxagliptin hydrochloride, at least one acidic stabilizer and atleast one stability enhancing carrier coated on said seal coating; and
(d) an outer film coating layer coated on said drug layer.

2. The tablet composition according to claim 1, wherein said acidic stabilizer is selected from hydrochloric acid, organic acid, cysteine hydrochloride or combinations thereof.

3. The tablet composition according to claim 1, wherein said stability enhancing carrier is selected from mannitol, polyvinyl acetate, pre-gelatinized starch, sucrose, sorbitol, microcrystalline cellulose, polyvinylpyrrolidone, copovidone, crospovidone, cellulose derivatives, stearic acid and mixtures thereof.

4. The tablet composition according to claim 1, comprising
(a) an inert tablet core;
(b) a seal coating layer coated on said tablet core comprising hydroxypropyl methylcellulose, microcrystalline cellulose and stearic acid;
(c) a drug coating layer comprising saxagliptin hydrochloride, hydrochloric acid and copovidone coated on said seal coating; and
(d) an outer film coating layer coated on said saxagliptin layer comprising hydroxypropyl methylcellulose, microcrystalline cellulose and stearic acid.

5. The tablet composition according to claim 1, comprising
(a) an active tablet core comprising metformin hydrochloride, hydroxypropyl methylcellulose, carbopol, stearic acid and optional excipients;
(b) a seal coating layer coated on said tablet core comprising hydroxypropyl methylcellulose, microcrystalline cellulose and stearic acid;
(c) a drug coating layer comprising saxagliptin hydrochloride, hydrochloric acid and copovidone coated on said seal coating; and

(d) an outer film coating layer coated on said saxagliptin layer comprising hydroxypropyl methylcellulose, microcrystalline cellulose and stearic acid.

6. The tablet composition according to claim 5, wherein said active tablet core is prepared by wet granulation technique employing non-aqueous granulating fluid.

7. The tablet composition according to claim 6, wherein said non-aqueous fluid is selected from ethanol, methanol, isopropyl alcohol and mixture thereof.

8. The tablet composition according to claim 1, wherein said saxagliptin hydrochloride is in amorphous form.

9. A process to make stable, solid oral tablet composition, comprising the steps of:

(a) dispersing hydroxypropyl methylcellulose, stearic acid and microcrystalline cellulose in water to form a dispersion;

(b) coating said dispersion of step a) on a tablet core to form a seal coat;

(c) dissolving saxagliptin hydrochloride, copovidone and hydrochloric acid in methanol to form a solution;

(d) coating said seal coated tablet core of step b) with the solution of step c) to form an amorphous saxagliptin hydrochloride layer on said tablet core;

(e) coating said dispersion of step a) on tablet core of step (d) to form outer film coating layer.

10. A process for the preparation of amorphous saxagliptin hydrochloride comprising the steps of:

(a) dissolving saxagliptin hydrochloride, copovidone and hydrochloric acid in methanol; and

(b) removing said methanol form the solution of step (a) u to get an amorphous saxagliptin hydrochloride.

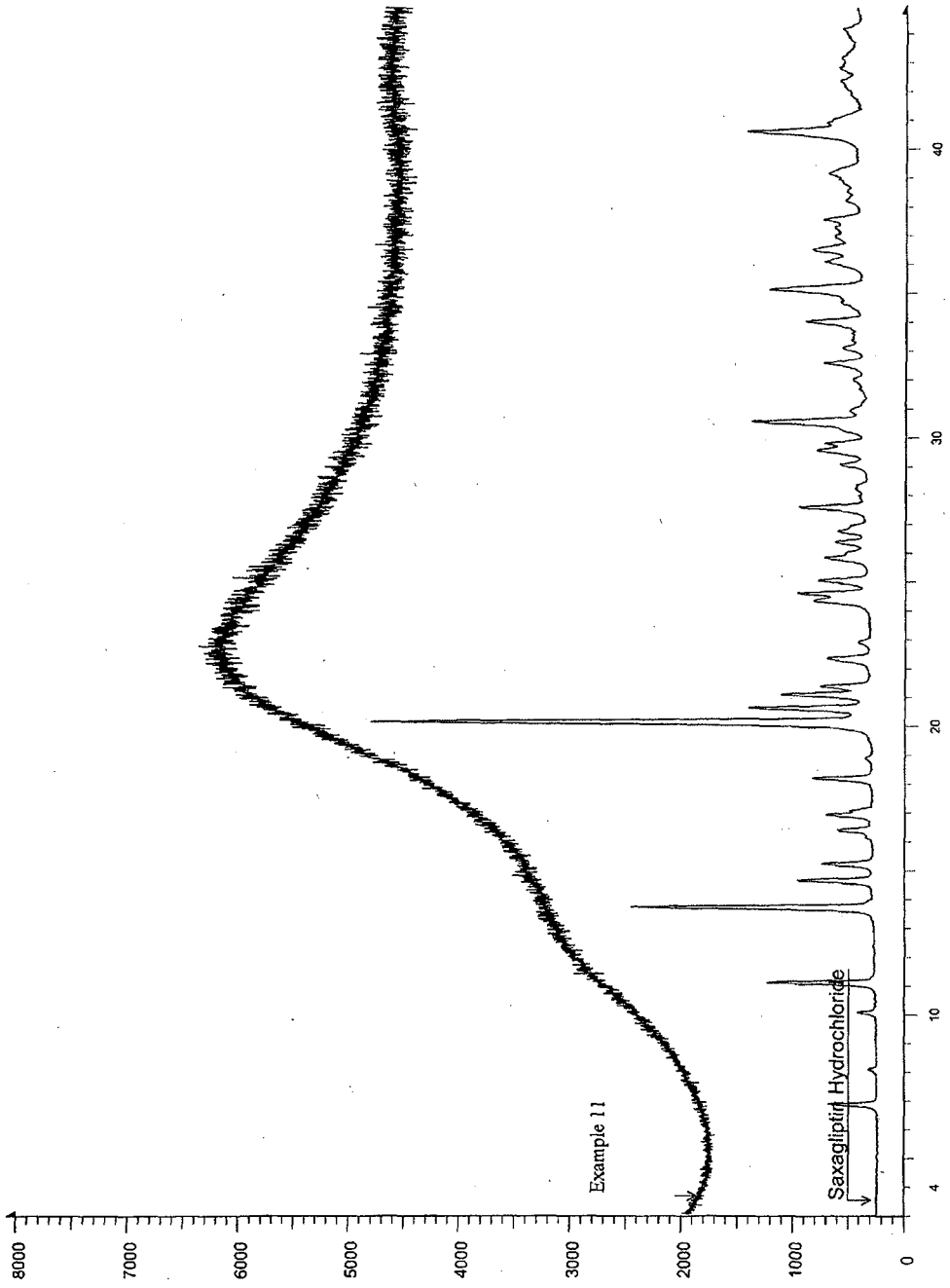

8000
7000
6000
5000
4000
3000
2000
1000
0
4
10
20
30
40
2-Theta - Scale
Example 11
Saxagliptin Hydrochloride

Figure 1