(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 November 2013 (21.11.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/171766 A2

(51) International Patent Classification:
A61K 9/48 (2006.01)

(21) International Application Number:
PCT/IN2013/000311

(22) International Filing Date:
13 May 2013 (13.05.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
IN 1925/CHE/2012 15 May 2012 (15.05.2012) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) **Title**: SAXAGLIPTIN SOLID DISPERSION

(57) **Abstract**: The present invention provides a novel amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier, process for its preparation and pharmaceutical compositions comprising it.

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SAXAGLIPTIN SOLID DISPERSION

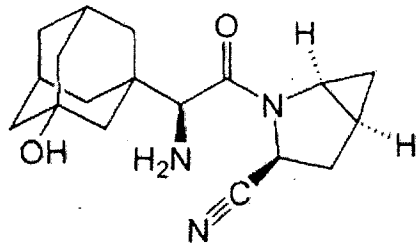
This application claims the benefit of Indian Provisional Patent Application No. 1925/CHE/2012, filed on May 15, 2012, which is incorporated herein by reference.

Filed of the Invention

The present invention provides a novel amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier, process for its preparation and pharmaceutical compositions comprising it.

Background of the Invention

Saxagliptin, chemically (1*S*,3*S*,5*S*)-2-[(2*S*)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile and has the structure formula:



Saxagliptin, previously identified as BMS-477118, is a new oral hypoglycemic (anti-diabetic drug) of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs.

Saxagliptin and its process were disclosed in U.S. Patent No. US 6,395,767.

Polymorphism is defined as "the ability of a substance to exist as two or more crystalline phases that have different arrangement and/or conformations of the molecules in the crystal Lattice. Thus, in the strict sense, polymorphs are different crystalline structures of the same pure substance in which the molecules have different arrangements and/or different configurations of the molecules". Different polymorphs may differ in their physical properties such as melting point, solubility, X-ray diffraction patterns, etc. Although those differences disappear once the compound is dissolved, they can appreciably influence pharmaceutically relevant properties of the solid form, such as handling properties, dissolution rate and stability. Such properties can significantly

influence the processing, shelf life, and commercial acceptance of a polymorph. It is therefore important to investigate all solid forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms of a compound can be distinguished in the laboratory by analytical methods such as X-ray diffraction (XRD), Differential Scanning Calorimetry (DSC) and Infrared spectrometry (IR).

Solvent medium and mode of crystallization play very important role in obtaining one polymorphic Form over the other.

Saxagliptin can exist in different polymorphic Forms, which may differ from each other in terms of stability, physical properties, spectral data and methods of preparation.

U.S. patent no. 7,943,656 disclosed crystalline Form H-1 (MonoHydrate), Form H0.5-2 (hemihydrate) and Form N-3 (Anhydrous) of saxagliptin.

U.S. patent application publication no. 2011/0275687 described amorphous Form and mixture of crystalline Form H-1 and crystalline Form H0.5-2 of saxagliptin.

It was observed that the crystalline Forms and amorphous Form of saxagliptin either not reproducible or not stable.

We have also found a novel amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier. The amorphous solid dispersion of saxagliptin is stable, reproducible and so, the amorphous solid dispersion of saxagliptin is suitable for formulating saxagliptin. Normally amorphous Forms are hygroscopic. Amorphous solid dispersion of saxagliptin is found to be non-hygroscopic.

Thus, an object of the present invention is to provide amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier, process for its preparation and pharmaceutical compositions comprising it.

Summary of the Invention

In one aspect, the present invention provides amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier.

In another aspect, the present invention there is provided a process for the preparation of amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier, which comprises:

a) preparing a solution comprising a mixture of saxagliptin and one or more pharmaceutically acceptable carriers selected from copovidone, ethyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol or soluplus in a solvent; and

b) removing the solvent to obtain amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier.

Yet in another aspect, the present invention provides pharmaceutical compositions comprising a therapeutically effective amount of amorphous solid dispersion of saxagliptin along with a pharmaceutically acceptable carrier, and at least one pharmaceutically acceptable excipient.

Brief Description of the Drawing

Figure 1 is a powder X-ray diffractogram patterns of amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier.

Powder X-ray diffraction spectrum was measured on a bruker AXS D8 advance powder X-ray diffractometer having a copper-Kα radiation. Approximately 500 mg of sample was gently flattered on a sample holder and scanned from 2 to 50 degrees two-theta, at 0.020 degrees two theta per step and a step time of 1 second. The sample was simply placed on the sample holder. The sample was rotated at 30 rpm at a voltage 40 kV and current 35 mA.

Detailed Description of the Invention

The term "room temperature" refers to temperature at about 25 to 35^0C.

According to one aspect of the present invention, there is provided amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier.

The powdered x-ray diffractogram (PXRD) of amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier is shown in figure 1.

Amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier is found to be stable.

Preferably the pharmaceutically acceptable carriers may be one or more of copovidone, ethyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol or soluplus.

According to another aspect of the present invention, there is provided a process for the preparation of amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier, which comprises:

a) preparing a solution comprising a mixture of saxagliptin and one or more pharmaceutically acceptable carriers selected from copovidone, ethyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol or soluplus in a solvent; and

b) removing the solvent to obtain amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier.

Saxagliptin used in step (a) may preferably be saxagliptin obtained by the known process.

The solvent used in step (a) may preferably be a solvent or a mixture of solvents selected from dimethyl sulfoxide, dimethylacetamide, dimethylformamide, methanol, ethanol, isopropanol, n-butanol and n-pentanol, and more preferably the solvents are dimethyl sulfoxide, dimethylacetamide, dimethylformamide and methanol.

Preferably the pharmaceutically acceptable carriers used in step (a) may be selected from copovidone, soluplus or hydroxypropyl methylcellulose.

The solvent may be removed from the solution in step (b) by known methods, for example, distillation or spray drying.

The distillation of the solvent may be carried out at atmospheric pressure or at reduced pressure. The distillation may preferably be carried out until the solvent is almost completely distilled off.

As used herein, "reduced pressure" refers to a pressure of less than 100 mmHg.

According to another aspect of the present invention, there is provided pharmaceutical compositions comprising a therapeutically effective amount of amorphous solid dispersion of saxagliptin along with a pharmaceutically acceptable carrier, and at least one pharmaceutically acceptable excipient. The amorphous solid dispersion of saxagliptin may preferably be formulated into tablets, capsules, suspensions, dispersions, injectables or other pharmaceutical forms.

Preferably the present invention provides a pharmaceutical composition containing said solid dispersion along with the pharmaceutically acceptable excipients such as diluents, chelating agents, disintegrant, glidant, binders, surfactants, coloring agents and/or luricants.

Specific examples of binders include methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Specific examples of diluents include calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, and the like and mixtures thereof.

Surfactants include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in pharmaceutical dosage forms. These include polyethoxylated fatty acids and its derivatives, for example, polyethylene glycol 400 distearate, polyethylene glycol-20 dioleate, polyethylene glycol 4 – 150 mono dilaurate, and polyethylene glycol – 20 glyceryl stearate; alcohol – oil transesterification products, for example, polyethylene glycol – 6 corn oil; polyglycerized fatty acids, for example, polyglyceryl – 6 pentaoleate; propylene glycol fatty acid esters, for example, propylene glycol monocaprylate; mono and diglycerides, for example, glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and its derivatives, for example, polyethylene glycol – 20 sorbitan monooleate and sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example, polyethylene glycol – 20 cetyl ether and polyethylene glycol – 10 – 100 nonyl phenol; sugar esters, for example, sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as "poloxamer"; ionic surfactants, for example, sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, and palmitoyl carnitine; and the like and mixtures thereof.

Specific examples of disintegrants include low-substituted hydroxypropylcellulose (L-HPC), sodium starch glycollate, carboxymethyl cellulose, calcium carboxymethyl

cellulose, sodium carboxymethyl cellulose, croscarmellose sodium A-type (Ac-di-sol), starch, crystalline cellulose, hydroxypropyl starch, pregelatinized starch, and the like and mixtures thereof.

Specific examples of lubricants/glidants include colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and the like and mixtures thereof.

Coloring agents include any FDA approved colors for oral use.

The invention will now be further described by the following examples, which are illustrative rather than limiting.

Examples

Example 1:

Preparation of saxagliptin

Tert-butyl N-[(1S)-2-[(1S,3S,5S)-3-cyano-2-azabicylo[3.1.0]hexan-2yl]-1-[(3S,5R,7S)-3-hydroxyadamantan-1-yl]-2-oxoethyl]carbamate (100 gm) was dissolved in isopropyl alcohol (100 ml) and water (100 ml) and then added hydrochloric acid (5 ml). The reaction mass was stirred for 3 hours at room temperature and the solvent was distilled off under vacuum at below 45^0C to obtain a residual mass. To the residual mass was added methylene chloride (1000 ml) and water (100 ml) and then cooled to 0 to 5^0C. The pH of the reaction mass was adjusted to 9.0 to 10.0 with sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted with methylene chloride. Combined organic layers were dried with sodium sulfate and then concentrated to obtain a residual solid. To the residual solid was added ethyl acetate (170 ml) and then cooled to 10 to 15^0C. Water (170 ml) was added to the reaction mixture slowly for 45 minutes and stirred for 3 hours. The separated solid was filtered and then dried at 30 to 35^0C for 5 hours to obtain 50 gm of saxagliptin.

Example 2:

Preparation of amorphous saxagliptin solid dispersion with copovidone

A mixture of saxagliptin (10 gm) as obtained in example 1 and copovidone (20 gm) was dissolved in methanol (150 ml) at room temperature. The contents were heated to 45 to 50^{0}C and stirred for 1 hour. The solution was filtered through celite bed and the solvent was distilled off under reduced pressure at below 50^{0}C to obtain 29 gm of amorphous saxagliptin solid dispersion with copovidone.

Example 3:

Preparation of amorphous saxagliptin solid dispersion with copovidone

Example 2 was repeated using dimethylformamide solvent instead of methanol solvent to obtain amorphous saxagliptin solid dispersion with copovidone.

Example 4:

Preparation of amorphous saxagliptin solid dispersion with copovidone

Example 2 was repeated using dimethylacetamide solvent instead of methanol solvent to obtain amorphous saxagliptin solid dispersion with copovidone.

Example 5:

Preparation of amorphous saxagliptin solid dispersion with copovidone

Example 2 was repeated using dimethyl sulfoxide solvent instead of methanol solvent to obtain amorphous saxagliptin solid dispersion with copovidone.

Example 6:

Preparation of amorphous saxagliptin solid dispersion with copovidone

Example 2 was repeated using ethanol solvent instead of methanol solvent to obtain amorphous saxagliptin solid dispersion with copovidone.

Example 7:

Preparation of amorphous saxagliptin solid dispersion with hydroxypropyl methylcellulose

A mixture of saxagliptin (20 gm) and hydroxypropyl methylcellulose (20 gm) was dissolved in methanol (300 ml) at room temperature. The contents were heated to 45 to

50^0C and stirred for 1 hour. The solution was filtered through celite bed and the solvent was distilled off under reduced pressure at below 50^0C to obtain 38 gm of amorphous saxagliptin solid dispersion with hydroxypropyl methylcellulose.

Example 8:

Preparation of amorphous saxagliptin solid dispersion with hydroxypropyl methylcellulose

Example 7 was repeated using dimethylformamide solvent instead of methanol solvent to obtain amorphous saxagliptin solid dispersion with hydroxypropyl methylcellulose.

Example 9:

Preparation of amorphous saxagliptin solid dispersion with hydroxypropyl methylcellulose

Example 7 was repeated using dimethylacetamide solvent instead of methanol solvent to obtain amorphous saxagliptin solid dispersion with hydroxypropyl methylcellulose.

Example 10:

Preparation of amorphous saxagliptin solid dispersion with hydroxypropyl methylcellulose

Example 7 was repeated using dimethyl sulfoxide solvent instead of methanol solvent to obtain amorphous saxagliptin solid dispersion with hydroxypropyl methylcellulose.

Example 11:

Preparation of amorphous saxagliptin solid dispersion with hydroxypropyl methylcellulose

Example 7 was repeated using ethanol solvent instead of methanol solvent to obtain amorphous saxagliptin solid dispersion with hydroxypropyl methylcellulose.

Example 12:

Preparation of amorphous saxagliptin solid dispersion with soluplus

A mixture of saxagliptin (10 gm) and soluplus (20 gm) was dissolved in methanol (150 ml) at room temperature. The contents were heated to 45 to 50^{0}C and stirred for 1 hour. The solution was filtered through celite bed and the solvent was distilled off under reduced pressure at below 50^{0}C to obtain 29 gm of amorphous saxagliptin solid dispersion with soluplus.

Example 13:

Preparation of amorphous saxagliptin solid dispersion with soluplus

Example 12 was repeated using dimethylformamide solvent instead of methanol solvent to obtain amorphous saxagliptin solid dispersion with soluplus.

Example 14:

Preparation of amorphous saxagliptin solid dispersion with soluplus

Example 12 was repeated using dimethylacetamide solvent instead of methanol solvent to obtain amorphous saxagliptin solid dispersion with soluplus.

Example 15:

Preparation of amorphous saxagliptin solid dispersion with soluplus

Example 12 was repeated using dimethyl sulfoxide solvent instead of methanol solvent to obtain amorphous saxagliptin solid dispersion with soluplus.

Example 16:

Preparation of amorphous saxagliptin solid dispersion with soluplus

Example 12 was repeated using ethanol solvent instead of methanol solvent to obtain amorphous saxagliptin solid dispersion with soluplus.

Example 17:

Preparation of amorphous saxagliptin solid dispersion with polyethylene glycol

A mixture of saxagliptin (20 gm) and polyethylene glycol (30 gm) was dissolved in methanol (150 ml) at room temperature. The contents were heated to 45 to 50^{0}C and

stirred for 1 hour. The solution was filtered through celite bed and the solvent was distilled off under reduced pressure at below 50^{0}C to obtain 46 gm of amorphous saxagliptin solid dispersion with polyethylene glycol.

Example 18:

Preparation of amorphous saxagliptin solid dispersion with ethyl cellulose

A mixture of saxagliptin (10 gm) and ethyl cellulose (10 gm) was dissolved in methanol (150 ml) at room temperature. The contents were heated to 45 to 50^{0}C and stirred for 1 hour. The solution was filtered through celite bed and the solvent was distilled off under reduced pressure at below 50^{0}C to obtain 18 gm of amorphous saxagliptin solid dispersion with ethyl cellulose.

Example 19:

Preparation of amorphous saxagliptin solid dispersion with copovidone

Tert-butyl N-[(1S)-2-[(1S,3S,5S)-3-cyano-2-azabicylo[3.1.0]hexan-2yl]-1-[(3S,5R,7S)-3-hydroxyadamantan-1-yl]-2-oxoethyl]carbamate (100 gm) was dissolved in isopropyl alcohol (100 ml) and water (100 ml) and then added hydrochloric acid (5 ml). The reaction mass was stirred for 3 hours at room temperature and the solvent was distilled off under vacuum at below 45^{0}C to obtain a residual mass. To the residual mass was added methylene chloride (1000 ml) and water (100 ml) and then cooled to 0 to 5^{0}C. The pH of the reaction mass was adjusted to 9.0 to 10.0 with sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted with methylene chloride. Combined organic layers were dried with sodium sulfate and then concentrated to obtain a residual solid. To the residual solid was added ethyl acetate (170 ml) and then cooled to 10 to 15^{0}C. Water (170 ml) was added to the reaction mixture slowly for 45 minutes and stirred for 3 hours. To the contents were added copovidone (100 gm) and methanol (750 ml) at room temperature. The contents were heated to 45 to 50^{0}C and stirred for 1 hour. The solution was filtered through celite bed and the solvent was distilled off under reduced pressure at below 50^{0}C to obtain 142 gm of amorphous saxagliptin solid dispersion with copovidone.

Example 20:

Preparation of amorphous saxagliptin solid dispersion with hydroxypropyl methylcellulose

Tert-butyl N-[(1S)-2-[(1S,3S,5S)-3-cyano-2-azabicylo[3.1.0]hexan-2yl]-1-[(3S,5R,7S)-3-hydroxyadamantan-1-yl]-2-oxoethyl]carbamate (100 gm) was dissolved in isopropyl alcohol (100 ml) and water (100 ml) and then added hydrochloric acid (5 ml). The reaction mass was stirred for 3 hours at room temperature and the solvent was distilled off under vacuum at below 45^0C to obtain a residual mass. To the residual mass was added methylene chloride (1000 ml) and water (100 ml) and then cooled to 0 to 5^0C. The pH of the reaction mass was adjusted to 9.0 to 10.0 with sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted with methylene chloride. Combined organic layers were dried with sodium sulfate and then concentrated to obtain a residual solid. To the residual solid was added ethyl acetate (170 ml) and then cooled to 10 to 15^0C. Water (170 ml) was added to the reaction mixture slowly for 45 minutes and stirred for 3 hours. To the contents were added hydroxypropyl methylcellulose (50 gm) and methanol (700 ml) at room temperature. The contents were heated to 45 to 50^0C and stirred for 1 hour. The solution was filtered through celite bed and the solvent was distilled off under reduced pressure at below 50^0C to obtain 94 gm of amorphous saxagliptin solid dispersion with hydroxypropyl methylcellulose.

Example 21:

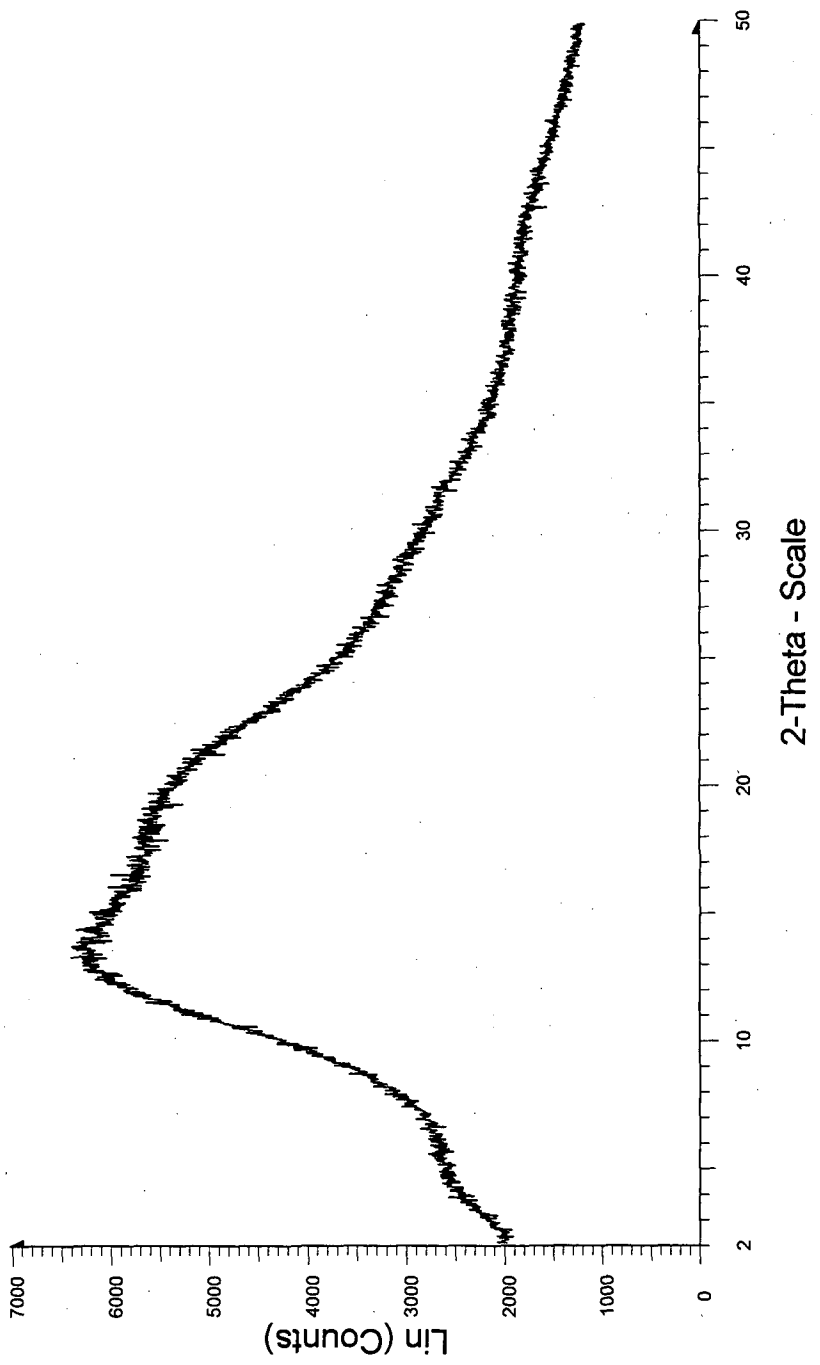
Preparation of amorphous saxagliptin solid dispersion with soluplus

Tert-butyl N-[(1S)-2-[(1S,3S,5S)-3-cyano-2-azabicylo[3.1.0]hexan-2yl]-1-[(3S,5R,7S)-3-hydroxyadamantan-1-yl]-2-oxoethyl]carbamate (100 gm) was dissolved in isopropyl alcohol (100 ml) and water (100 ml) and then added hydrochloric acid (5 ml). The reaction mass was stirred for 3 hours at room temperature and the solvent was distilled off under vacuum at below 45^0C to obtain a residual mass. To the residual mass was added methylene chloride (1000 ml) and water (100 ml) and then cooled to 0 to 5^0C. The pH of the reaction mass was adjusted to 9.0 to 10.0 with sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted with methylene chloride. Combined organic layers were dried with sodium sulfate and then concentrated

to obtain a residual solid. To the residual solid was added ethyl acetate (170 ml) and then cooled to 10 to 15^{0}C. Water (170 ml) was added to the reaction mixture slowly for 45 minutes and stirred for 3 hours. To the contents were added soluplus (100 gm) and methanol (750 ml) at room temperature. The contents were heated to 45 to 50^{0}C and stirred for 1 hour. The solution was filtered through celite bed and the solvent was distilled off under reduced pressure at below 50^{0}C to obtain 140 gm of amorphous saxagliptin solid dispersion with soluplus.

We claim:

1. An amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier.
2. The amorphous solid dispersion of claim 1, wherein the pharmaceutically acceptable carrier comprises one or more of copovidone, ethyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol or soluplus.
3. The amorphous solid dispersion of claim 1, having a powder X-ray diffractogram as shown in figure 1.
4. A process for the preparation of amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier of claim 1, which comprises:
    a. preparing a solution comprising a mixture of saxagliptin and one or more pharmaceutically acceptable carriers selected from copovidone, ethyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol or soluplus in a solvent; and
    b. removing the solvent to obtain amorphous solid dispersion of saxagliptin in combination with a pharmaceutically acceptable carrier.
5. The process as claimed in claim 4, wherein the solvent used in step (a) is a solvent or a mixture of solvents selected from dimethyl sulfoxide, dimethylacetamide, dimethylformamide, methanol, ethanol, isopropanol, n-butanol and n-pentanol.
6. The process as claimed in claim 5, wherein the solvents are dimethyl sulfoxide, dimethylacetamide, dimethylformamide and methanol.
7. The process as claimed in claim 4, wherein the pharmaceutically acceptable carriers used in step (a) is selected from copovidone, soluplus or hydroxypropyl methylcellulose.
8. Pharmaceutical compositions comprising a therapeutically effective amount of amorphous solid dispersion of saxagliptin along with a pharmaceutically acceptable carrier, and at least one pharmaceutically acceptable excipient.
9. The pharmaceutical composition as claimed in claim 8, wherein the amorphous solid dispersion of saxagliptin is formulated into tablets, capsules, suspensions, dispersions or injectables.


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