

wherein the organic C₄-diacid is selected from maleic acid, malic acid, L-malic acid, D-malic acid, and succinic acid.

PCT Publication No. WO 2012/047871 provides a process for the preparation of crystalline Form K, Form Z, Form D, and amorphous saxagliptin hydrochloride.

Chinese Publication No. CN 102086172 provides a process for the preparation of mesylate, maleate, malate, succinate, and citrate salts of saxagliptin.

Several processes are known in the literature for making saxagliptin, or a salt thereof, for example, PCT Publication Nos. WO 2004/052850, WO 2005/115982, WO 2005/106011 and WO 2005/094323.

In the pharmaceutical industry there is a constant need to identify the critical physicochemical parameters such as novel salts and novel polymorphic forms that affect the drug's performance, stability, etc., which may play a key role in determining a drug's market acceptance and success.

Since saxagliptin or its salts constitute an important therapeutic agent, additional saxagliptin salts are of value to pharmaceutical science. Thus, there is a need for the development of novel saxagliptin salts having improved solubility, stability, bioavailability, storage and handling stability, and less susceptibility to degradation at lower temperatures.

Accordingly, the present inventors have prepared saxagliptin bisulphate, saxagliptin acetate, saxagliptin oxalate, saxagliptin bicarbonate, and saxagliptin carbonate salts. The salts of the present invention are easy to prepare and isolate in solid forms, particularly, in crystalline forms. Further, they can be prepared by an efficient, economical, and reproducible process, which is particularly suited to large scale preparation.

Summary of the Invention

A first aspect of the present invention provides saxagliptin bisulphate.

A second aspect of the present invention provides a crystalline form of saxagliptin bisulphate.

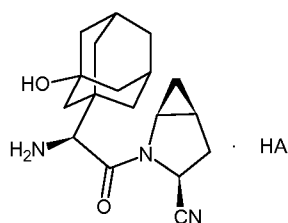
A third aspect of the present invention provides saxagliptin acetate.

A fourth aspect of the present invention provides a crystalline form of saxagliptin acetate.

A fifth aspect of the present invention provides saxagliptin oxalate.

A sixth aspect of the present invention provides a crystalline form of saxagliptin oxalate.

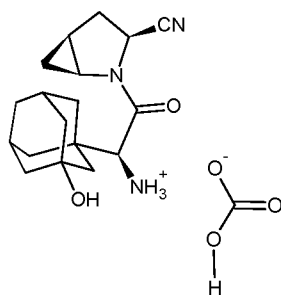
A seventh aspect of the present invention provides a process for the preparation of a compound of Formula I



Formula I

which comprises treating saxagliptin or its salt with HA, wherein HA is selected from sulphuric acid, acetic acid, and oxalic acid.

An eighth aspect of the present invention provides saxagliptin bicarbonate of Formula II.

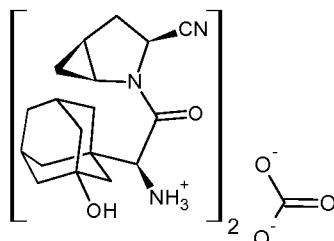


Formula II

A ninth aspect of the present invention provides a crystalline form of saxagliptin bicarbonate.

A tenth aspect of the present invention provides a process for the preparation of saxagliptin bicarbonate, which comprises contacting saxagliptin or its salt with a suitable carbonate source.

An eleventh aspect of the present invention provides saxagliptin carbonate of Formula III.



Formula III

A twelfth aspect of the present invention provides a crystalline form of saxagliptin carbonate.

A thirteenth aspect of the present invention provides a process for the preparation of saxagliptin carbonate, which comprises heating saxagliptin bicarbonate, optionally in the presence of water.

A fourteenth aspect of the present invention provides the use of saxagliptin salts selected from saxagliptin bisulphate, saxagliptin acetate, saxagliptin oxalate, saxagliptin bicarbonate, or saxagliptin carbonate for the preparation of saxagliptin or salts, solvates, or polymorphs thereof.

A fifteenth aspect of the present invention provides a pharmaceutical composition comprising saxagliptin salts selected from saxagliptin bisulphate, saxagliptin acetate, saxagliptin oxalate, saxagliptin bicarbonate, or saxagliptin carbonate, and a pharmaceutically acceptable carrier.

A sixteenth aspect of the present invention provides a method of treating type 2 diabetes mellitus which comprises administering to a patient in need thereof a therapeutically effective amount of saxagliptin salts selected from saxagliptin bisulphate, saxagliptin acetate, saxagliptin oxalate, saxagliptin bicarbonate, or saxagliptin carbonate, and a pharmaceutically acceptable carrier.

Detailed Description of the invention

A first aspect of the present invention provides saxagliptin bisulphate.

A second aspect of the present invention provides a crystalline form of saxagliptin bisulphate. The crystalline form of saxagliptin bisulphate of the present invention may be

characterized by an XRPD pattern substantially the same as depicted in Figure 1, exhibiting interplanar spacing (d) values at about 3.63, 3.39, 3.27, and 3.20 (Å), and further exhibiting interplanar spacing (d) values at about 4.22, 3.89, 3.09, 3.05, 2.98, 2.91, 2.79, and 2.63 (Å). The crystalline form of saxagliptin bisulphate has an XRPD pattern with characteristic peak values (2θ) at about 24.50, 26.26, 27.25, and $27.84 \pm 0.2^\circ$, and additional characteristic peak values (2θ) at about 21.04, 22.82, 28.89, 29.26, 29.98, 30.71, 32.05, and $34.06 \pm 0.2^\circ$. The crystalline form of saxagliptin bisulphate of the present invention may be characterized by FTIR as depicted in Figure 2. The crystalline form of saxagliptin bisulphate of the present invention may be characterized by DSC as depicted in Figure 3, with a characteristic endothermic peak value at about 100.90°C in the DSC thermogram.

A third aspect of the present invention provides saxagliptin acetate.

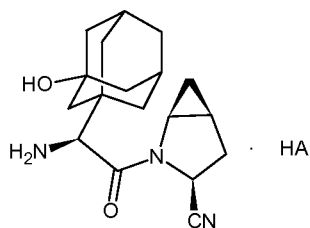
A fourth aspect of the present invention provides a crystalline form of saxagliptin acetate. The crystalline form of saxagliptin acetate of the present invention may be characterized by an XRPD pattern substantially the same as depicted in Figure 4, exhibiting interplanar spacing (d) values at about 11.97, 9.84, 5.98, 4.96, and 4.91 (Å), and further exhibiting interplanar spacing (d) values substantially at about 6.27, 5.16, 4.71, 4.68, 4.50, 4.45, 3.99, and 3.87 (Å). The crystalline form of saxagliptin acetate has an XRPD pattern with characteristic peak values (2θ) at about 7.38, 8.98, 14.79, 17.85, and $18.03 \pm 0.2^\circ$, and additional characteristic peak values (2θ) at about 14.12, 17.17, 18.82, 18.92, 19.70, 19.94, 22.26, and $22.97 \pm 0.2^\circ$. The crystalline form of saxagliptin acetate of the present invention may be characterized by FTIR as depicted in Figure 5. The crystalline form of saxagliptin acetate of the present invention may be characterized by DSC as depicted in Figure 6, with characteristic endothermic peak values at about 68.12, 79.62, 152.38, and 161.14°C in the DSC thermogram.

A fifth aspect of the present invention provides saxagliptin oxalate.

A sixth aspect of the present invention provides a crystalline form of saxagliptin oxalate. The crystalline form of saxagliptin oxalate of the present invention may be characterized by an XRPD pattern substantially the same as depicted in Figure 7, exhibiting interplanar spacing (d) values substantially at about 12.99, 6.28, 4.96, 4.91, and 4.67 (Å), and further exhibiting interplanar spacing (d) values at about 5.99, 5.93, 5.69, 4.59, 4.32, 4.01, and 3.08 (Å). The crystalline form of saxagliptin oxalate has an XRPD

pattern with characteristic peak values (2 θ) at about 6.80, 14.06, 17.88, 18.06, and 18.98 $\pm$ 0.2 $^\circ$, and additional characteristic peak values (2 θ) at about 14.76, 14.93, 15.56, 19.30, 20.54, 22.15, and 28.97 $\pm$ 0.2 $^\circ$. The crystalline form of saxagliptin oxalate of the present invention may be characterized by FTIR as depicted in Figure 8. The crystalline form of saxagliptin oxalate of the present invention may be characterized by DSC as depicted in Figure 9, with a characteristic endothermic peak value at about 61.67 $^\circ$ C, and a characteristic exothermic peak value at about 186.24 $^\circ$ C in the DSC thermogram.

A seventh aspect of the present invention provides a process for the preparation of a compound of Formula I



Formula I

which comprises treating saxagliptin or its salt with HA, wherein HA is selected from sulphuric acid, acetic acid, or oxalic acid.

The saxagliptin or its salt used as the starting material may be prepared by any of the methods known in the art including those described in, for example, U.S. Patent Nos. 6,395,767, and 7,943,656; PCT Publications WO 2004/052850, WO 2005/115982, WO 2005/106011, WO 2005/094323, WO 2010/115974, WO 2012/017028, WO 2012/017029, and WO 2012/047871.

The saxagliptin or its salt prepared by any of the methods known in the art may be isolated or directly treated with HA.

The saxagliptin or its salt prepared by any of the methods known in the art may be optionally purified prior to treatment with HA to remove foreign particulate matter. Alternatively, it may be treated with activated charcoal to remove coloring and other related impurities in a suitable solvent. The solution of saxagliptin or its salt may be optionally concentrated to reduce the amount of solvent. The saxagliptin salt may optionally be converted to saxagliptin base before treatment with HA.

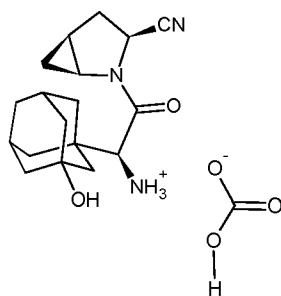
Treating saxagliptin or its salt with HA may include adding, dissolving, slurring, stirring, or a combination thereof. Saxagliptin or its salt may be treated with HA directly, or in the presence of a suitable solvent at a suitable temperature.

The term “solvent” includes any solvent, or a solvent mixture, including for example, water, esters, alkanols, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents, or mixtures thereof.

Examples of esters include ethyl acetate, *n*-propyl acetate, isopropyl acetate, and *n*-butyl acetate. Examples of alkanols include those primary, secondary, and tertiary alcohols having from one to six carbon atoms. Examples of suitable alkanols include methanol, ethanol, *n*-propanol, isopropanol, and butanol. Examples of halogenated hydrocarbons include dichloromethane, chloroform, and 1,2-dichloroethane. Examples of ketones include acetone and methyl ethyl ketone. Examples of ethers include diethyl ether and tetrahydrofuran. Examples of polar aprotic solvents include *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulphoxide, acetonitrile, and *N*-methylpyrrolidone.

Saxagliptin or its salt is treated with HA at a temperature of from about -10°C to about 10°C, preferably, from about -5°C to about 5°C. The formation of the saxagliptin salt may be accelerated by stirring the reaction mixture for about 10 minutes to about 4 hours at a temperature of from about -5°C to about 40°C, preferably from about 0°C to about 25°C. After completion of the reaction, the saxagliptin salt of Formula I may be isolated by filtration, decantation, solvent precipitation, trituration, evaporation, distillation, or combinations thereof.

An eighth aspect of the present invention provides a saxagliptin bicarbonate of Formula II.



Formula II

A ninth aspect of the present invention provides a crystalline form of saxagliptin bicarbonate. The crystalline form of saxagliptin bicarbonate of the present invention may be characterized by an XRPD pattern substantially the same as depicted in Figure 10, exhibiting interplanar spacing (d) values at about 3.70, 2.99, and 2.86 (Å), and further exhibiting interplanar spacing (d) values at about 7.45, 3.17, 3.12, 2.64, 2.39, and 2.30 (Å). The crystalline form of saxagliptin bicarbonate has an XRPD pattern with characteristic peak values (2θ) at about 24.05, 29.84, and $31.18 \pm 0.2^\circ$, and additional characteristic peak values (2θ) at about 11.86, 28.13, 28.60, 33.88, 37.55, and $39.01 \pm 0.2^\circ$. The crystalline form of saxagliptin bicarbonate of the present invention may be characterized by FTIR as depicted in Figure 11. The crystalline form of saxagliptin bicarbonate of the present invention may be characterized by DSC as depicted in Figure 12, with a characteristic endothermic peak value at about 76.94°C in the DSC thermogram.

A tenth aspect of the present invention provides a process for the preparation of saxagliptin bicarbonate, which comprises contacting saxagliptin or its salt with a suitable carbonate source.

The saxagliptin or its salt prepared by any of the methods known in the art may be isolated or directly treated with a suitable carbonate source.

The saxagliptin or its salt prepared by any of the methods known in the art, before treatment with a suitable carbonate source, may be optionally purified to remove foreign particulate matter or treated with activated charcoal to remove coloring and other related impurities in a suitable solvent. The solution of saxagliptin or its salt may be optionally concentrated to reduce the amount of solvent. The saxagliptin salt may optionally be converted to saxagliptin base before treatment with a suitable carbonate source, optionally in the presence of a base.

The term “carbonate source” includes carbon dioxide gas, dry ice, and carbonic acid prepared in situ by dissolving carbon dioxide gas in water.

The term “base” includes hydroxides, carbonates, and bicarbonates of alkali and alkaline earth metals; ammonia; alkyl amines; hydrazine; and the like. Examples of hydroxides, carbonates, and bicarbonates of alkali and alkaline earth metals may include lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium

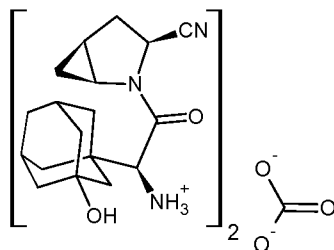
carbonate, sodium bicarbonate, or potassium bicarbonate. Examples of alkyl amines may include diethyl amine, triethyl amine, or methyl diethyl amine.

Treating saxagliptin or its salt with a suitable carbonate source may include adding, dissolving, slurrying, stirring, or combinations thereof. Saxagliptin or its salt may be treated with a suitable carbonate source directly or in the presence of a suitable solvent at a suitable temperature.

The term “solvent” includes any solvent, or a solvent mixture, including for example, water, alkanols, esters, ketones, polar aprotic solvents, or mixtures thereof. Examples of alkanols include primary, secondary and tertiary alcohols having from one to six carbon atoms. Examples of suitable alkanols include methanol, ethanol, *n*-propanol, isopropanol, and butanol. Examples of esters include ethyl acetate, *n*-propyl acetate, isopropyl acetate, and *n*-butyl acetate. Examples of ketones include acetone and methyl ethyl ketone. Examples of polar aprotic solvents include *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulphoxide, acetonitrile, and *N*-methylpyrrolidone.

In a specific embodiment of this aspect, saxagliptin is treated with dry ice at a temperature of from about 20°C to about 30°C, in ethanol while stirring for about 30 minutes to about 1 hour, preferably, from about 35 minutes to about 45 minutes. Ethanol is removed by distillation under vacuum, followed by the addition of ethyl acetate while stirring. Saxagliptin bicarbonate of Formula II may be isolated by filtration, decantation, solvent precipitation, trituration, evaporation, distillation, or combinations thereof.

An eleventh aspect of the present invention provides saxagliptin carbonate of Formula III.



Formula III

A twelfth aspect of the present invention provides a crystalline form of saxagliptin carbonate. The crystalline form of saxagliptin carbonate of the present invention may be characterized by FTIR as depicted in Figure 13. The crystalline form of saxagliptin

carbonate of the present invention may be characterized by DSC as depicted in Figure 14. The crystalline form of saxagliptin carbonate has a characteristic endothermic peak value at about 113.45°C in the DSC thermogram.

A thirteenth aspect of the present invention provides a process for the preparation of saxagliptin carbonate, which comprises heating saxagliptin bicarbonate, optionally in the presence of water.

In a specific embodiment of this aspect, saxagliptin bicarbonate is dissolved in water and stirred at a temperature of from about 50°C to about 100°C, preferably, from about 65°C to about 70°C, for about 3 hours to about 6 hours, preferably, for about 4 hours to about 5 hours. Water is then removed by distillation under vacuum. The residue obtained is stirred with ethyl acetate and then removed by distillation under vacuum to obtain the solid. The solid may be washed with ethyl acetate, and is then isolated by filtration, decantation, solvent precipitation, trituration, evaporation, distillation, or combinations thereof to obtain the saxagliptin carbonate.

A fourteenth aspect of the present invention provides the use of saxagliptin salts selected from saxagliptin bisulphate, saxagliptin acetate, saxagliptin oxalate, saxagliptin bicarbonate, or saxagliptin carbonate for the preparation of saxagliptin or salts, solvates, or polymorphs thereof.

Saxagliptin salts may be used for the preparation of saxagliptin by contacting with a base or heating, optionally in the presence of water. The base may be selected from the group comprising of hydroxides, carbonates, and bicarbonates of alkali and alkaline earth metals; ammonia; alkyl amines; hydrazine; and the like. Examples of hydroxides, carbonates, and bicarbonates of alkali and alkaline earth metals include lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, or potassium bicarbonate. Examples of alkyl amines may include diethyl amine, triethyl amine, or methyl diethyl amine. Saxagliptin thus obtained may be converted to salts, solvates, or polymorphs thereof.

A fifteenth aspect of the present invention provides a pharmaceutical composition comprising saxagliptin salts selected from saxagliptin bisulphate, saxagliptin acetate, saxagliptin oxalate, saxagliptin bicarbonate, or saxagliptin carbonate, and a pharmaceutically acceptable carrier.

A sixteenth aspect of the present invention provides a method of treating type 2 diabetes mellitus which comprises administering to a patient in need thereof a therapeutically effective amount of saxagliptin salts selected from saxagliptin bisulphate, saxagliptin acetate, saxagliptin oxalate, saxagliptin bicarbonate, or saxagliptin carbonate, and a pharmaceutically acceptable carrier.

Brief Description of the Figures

Figure 1 and Figure 1a depict the X-Ray Powder Diffractogram (XRPD) of saxagliptin bisulphate and the associated values, respectively, prepared as per Example 1.

Figure 2 depicts the Fourier-Transform Infra-red (FTIR) spectrum of saxagliptin bisulphate prepared as per Example 1.

Figure 3 depicts the Differential Scanning Calorimetry (DSC) of saxagliptin bisulphate prepared as per Example 1.

Figure 4 and Figure 4a depict the XRPD of saxagliptin acetate and the associated values, respectively, prepared as per Example 2.

Figure 5 depicts the FTIR spectrum of saxagliptin acetate prepared as per Example 2.

Figure 6 depicts the DSC of saxagliptin acetate prepared as per Example 2.

Figure 7 and Figure 7a depict the XRPD of saxagliptin oxalate and the associated values, respectively, prepared as per Example 4.

Figure 8 depicts the FTIR spectrum of saxagliptin oxalate prepared as per Example 4.

Figure 9 depicts the DSC of saxagliptin oxalate prepared as per Example 4.

Figure 10 and Figure 10a depict the XRPD of saxagliptin bicarbonate and the associated values, respectively, prepared as per Example 5.

Figure 11 depicts the FTIR spectrum of saxagliptin bicarbonate prepared as per Example 5.

Figure 12 depicts the DSC of saxagliptin bicarbonate prepared as per Example 5.

Figure 13 depicts the FTIR spectrum of saxagliptin carbonate prepared as per Example 6.

Figure 14 depicts the DSC of saxagliptin carbonate prepared as per Example 6.

The XRPD of the samples were determined by using Instrument: PANalytical; Mode: Expert PRO; Detector: Xcelerator; ScanRange: 3-40; Step size: 0.02; Range: 3-40 degree 2 theta; CuK α radiation at 45kV.

FTIR of the samples was determined by using Instrument: Perkin Elmer; SCAN: 16 scans, Resolution: 4.0 cm⁻¹; potassium bromide pellet method.

DSC of the samples was determined by using Instrument: Perkin Elmer, Diamond DSC. Data collection parameters: Scanning rate: 10°C/min; Temperature: 30°C - 300°C.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art, and are intended to be included within the scope of the present invention.

EXAMPLES

Example 1: Preparation of Saxagliptin bisulphate

A mixture of saxagliptin (1.5 g) and ethyl acetate (30 mL) was stirred and cooled to -5°C, followed by drop-wise addition of sulphuric acid solution (0.466 g) in ethyl acetate (15 mL) at -5°C to 0°C for 5 minutes. The temperature of the reaction mixture was raised to 15°C with continuous stirring for 15 minutes, followed by the addition of methanol (4.5 mL), and then stirred for 30 minutes at 15°C to 20°C. The solvent was distilled off from the reaction mixture completely under vacuum at 35°C. Ethyl acetate (45 mL) was charged, and stirred at 20°C to 22°C for 14 hours to obtain the solid. The solid was filtered under vacuum in nitrogen environment, washed with *n*-hexane (20 mL), and dried under vacuum at 35°C to 40°C for about 7 hours to obtain the title compound.

Yield: 1.5 g

Example 2: Preparation of Saxagliptin acetate

A mixture of saxagliptin (1.13 g) and isopropanol (10 mL) was stirred, and cooled to 5°C, followed by the addition of acetic acid (0.22 g) at 5°C to 10°C, and then stirred for 1 hour while gradually raising the temperature to about 20°C to 25°C. The reaction mixture was cooled to 0°C to 5°C, and then stirred for 4 hours, maintaining the same temperature, to obtain a white solid. The solid was filtered through a sintered funnel under

vacuum in a nitrogen environment, washed with isopropanol (10 mL), and dried under vacuum at 40°C to 45°C for 12 hours to 14 hours to obtain the title compound.

Yield: 400 mg

Example 3: Preparation of Saxagliptin acetate from Saxagliptin trifluoroacetate

A mixture of saxagliptin trifluoroacetate (1.5 g) and dichloromethane (30 mL) was charged in a round bottomed flask, stirred, and cooled to 0°C. 8% Aqueous sodium bicarbonate solution (9 mL) was added drop-wise to the reaction mixture over 5 minutes at 0°C to 2°C. The mixture was stirred, and the temperature was raised to 18°C. Sodium chloride (4.5 g) was added, and stirred at 17°C to 19°C for 25 minutes, and filtered through a cotton plug. The filtrate obtained was allowed to settle for 10 minutes. The aqueous layer was extracted thrice with dichloromethane (10 mL). All the organic layers were combined. Sodium sulphate was added, and filtered through a cotton plug. The filtrate was cooled to 15°C in 5 minutes. Dichloromethane-acetic acid solution (2 mL of dichloromethane in 0.2 mL of acetic acid) was added to the filtrate at 15°C. The solvent was distilled off to the maximum extent under reduced pressure at 15°C, and then ethyl acetate (15 mL) was added, and stirred at 15°C for 30 minutes. The solid obtained was filtered under vacuum, washed with chilled ethyl acetate (5 mL), and kept under vacuum suction for 5 minutes. The material obtained was dried under vacuum at 20°C to 25°C for 14 hours to 16 hours to obtain the title compound.

Yield: 840 mg

Example 4: Preparation of Saxagliptin oxalate

A mixture of saxagliptin (1.0 g) and dichloromethane (15 mL) was stirred and cooled to 0°C, followed by the addition of oxalic acid (0.358 g) and isopropanol (3 mL) at 0°C. The reaction mixture was stirred for 2 hours at 0°C to 5°C, and further stirred for another 2 hours at 8°C to 10°C to obtain the white solid. The solid was filtered under vacuum, washed with dichloromethane (5 mL), and dried under vacuum at 33°C to 37°C for 8 hours to obtain the title compound.

Yield: 200 mg

Example 5: Preparation of Saxagliptin bicarbonate

Saxagliptin hydrochloride (5 g) was dissolved in water (50 mL) at 22°C, stirred, and cooled to 1°C in 15 minutes, followed by drop-wise addition of 10% aqueous

potassium carbonate solution (20 mL) at 0°C to 5°C over 10 minutes to adjust the pH to 8.3. The reaction mixture was stirred for 10 minutes at 5°C and the pH was checked and adjusted to 8.3. The water in the reaction mixture was distilled off under vacuum at 25°C in 2 hours, followed by the addition of ethanol (60 mL). The inorganic substances in the reaction mixture were filtered under vacuum. The inorganic substances were washed with ethanol (15 mL) and filtered to obtain filtrate. The obtained filtrates were distilled off under vacuum at 25°C in 1 hour to obtain an oily mass.

The oily mass of saxagliptin free base (6.2 g) was dissolved in ethanol (15 mL) at 25°C, and stirred for 10 minutes. Dry ice (50 g) was added slowly under stirring in 35 minutes. Ethanol was distilled off under vacuum completely at 25°C in 30 minutes to obtain a sticky mass. Ethyl acetate (60 mL) was added to the sticky mass, and stirred at 25°C for 30 minutes to obtain a solid. The solid obtained was filtered, washed with ethyl acetate (10 mL), and then dried under vacuum for 14 hours at 25°C to obtain the title compound.

Yield: 2.52 g

Example 6: Preparation of Saxagliptin carbonate

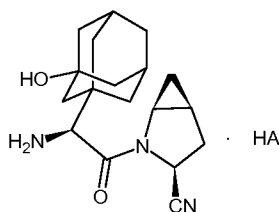
Saxagliptin bicarbonate (300 mg) obtained as per Example 5 was dissolved in water (30 mL) and stirred for 4 hours at 65°C to 70°C. The water in the reaction mixture was recovered at 65°C to 70°C under vacuum to obtain a residue. To the residue, ethyl acetate (20 mL) was added, stirred for 10 minutes at 55°C, and the solvent was recovered under vacuum at 50°C to 55°C to obtain a solid mass. To the solid mass, ethyl acetate (10 mL) was added, and stirred for 15 minutes. The solid obtained was filtered, then dried under vacuum at 65°C for 14 hours to obtain the title compound.

Yield: 150 mg

CLAIMS

1. Saxagliptin bisulphate.
2. The saxagliptin bisulphate of claim 1, in crystalline form.
3. The saxagliptin bisulphate of claim 2, wherein the crystalline form is characterized by an XRPD pattern substantially the same as depicted in Figure 1.
4. The saxagliptin bisulphate of claim 2, characterized by an XRPD pattern having interplanar spacing (d) values at 3.63, 3.39, 3.27, and 3.20 (Å).
5. The saxagliptin bisulphate of claim 4, further characterized by interplanar spacing (d) values at 4.22, 3.89, 3.09, 3.05, 2.98, 2.91, 2.79, and 2.63 (Å).
6. The saxagliptin bisulphate of claim 2, characterized by an XRPD pattern having characteristic peak values (2θ) at 24.50, 26.26, 27.25, and $27.84 \pm 0.2^\circ$.
7. The saxagliptin bisulphate of claim 6, further characterized by characteristic peak values (2θ) at 21.04, 22.82, 28.89, 29.26, 29.98, 30.71, 32.05, and $34.06 \pm 0.2^\circ$.
8. The saxagliptin bisulphate of claim 2, characterized by FTIR as depicted in Figure 2.
9. The saxagliptin bisulphate of claim 2, characterized by DSC as depicted in Figure 3.
10. The saxagliptin bisulphate of claim 2, characterized by an endothermic peak value at about 100.90°C in the DSC thermogram.
11. Saxagliptin acetate.
12. The saxagliptin acetate of claim 11, in crystalline form.
13. The saxagliptin acetate of claim 12, characterized by an XRPD pattern substantially the same as depicted in Figure 4.
14. The saxagliptin acetate of claim 12, characterized by an XRPD pattern having interplanar spacing (d) values at 11.97, 9.84, 5.98, 4.96, and 4.91 (Å).
15. The saxagliptin acetate of claim 14, further characterized by interplanar spacing (d) values at 6.27, 5.16, 4.71, 4.68, 4.50, 4.45, 3.99, and 3.87 (Å).
16. The saxagliptin acetate of claim 12, characterized by an XRPD pattern having characteristic peak values (2θ) at 7.38, 8.98, 14.79, 17.85, and $18.03 \pm 0.2^\circ$.
17. The saxagliptin acetate of claim 16, further characterized by characteristic peak values (2θ) at 14.12, 17.17, 18.82, 18.92, 19.70, 19.94, 22.26, and $22.97 \pm 0.2^\circ$.
18. The saxagliptin acetate of claim 12, characterized by FTIR as depicted in Figure 5.
19. The saxagliptin acetate of claim 12, characterized by DSC as depicted in Figure 6.

20. The saxagliptin acetate of claim 12, characterized by endothermic peak values at about 68.12, 79.62, 152.38, and 161.14°C in the DSC thermogram.
21. Saxagliptin oxalate.
22. The saxagliptin oxalate of claim 21, in crystalline form.
23. The saxagliptin oxalate of claim 22, characterized by an XRPD pattern substantially the same as depicted in Figure 7.
24. The saxagliptin oxalate of claim 22, characterized by an XRPD pattern having interplanar spacing (d) values at 12.99, 6.28, 4.96, 4.91, and 4.67 (Å).
25. The saxagliptin oxalate of claim 24, further characterized by interplanar spacing (d) values at 5.99, 5.93, 5.69, 4.59, 4.32, 4.01, and 3.08 (Å).
26. The saxagliptin oxalate of claim 22, characterized by an XRPD pattern having characteristic peak values (2θ) at 6.80, 14.06, 17.88, 18.06, and 18.98 ± 0.2°.
27. The saxagliptin oxalate of claim 26, further characterized by characteristic peak values (2θ) at 14.76, 14.93, 15.56, 19.30, 20.54, 22.15, and 28.97 ± 0.2°.
28. The saxagliptin oxalate of claim 22, characterized by FTIR as depicted in Figure 8.
29. The saxagliptin oxalate of claim 22, characterized by DSC as depicted in Figure 9.
30. The saxagliptin oxalate of claim 22, characterized by an endothermic peak value at about 61.67°C and an exothermic peak value at about 186.24°C in the DSC thermogram.
31. A process for the preparation of a compound of Formula I

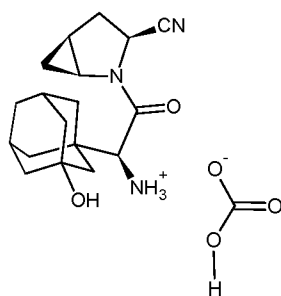


Formula I

which comprises treating saxagliptin or its salt with HA, wherein HA is selected from sulphuric acid, acetic acid, or oxalic acid.

32. The process according to claim 31, wherein the saxagliptin or its salt is treated with HA directly, or in the presence of a solvent.
33. The process according to claim 32, wherein the solvent is selected from water, esters, alkanols, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents, or mixtures thereof.

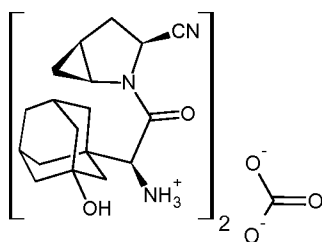
34. The process according to claim 33, wherein the ester is selected from ethyl acetate, *n*-propyl acetate, isopropyl acetate, and *n*-butyl acetate.
35. The process according to claim 33, wherein the alkanol is selected from methanol, ethanol, *n*-propanol, isopropanol, and butanol.
36. The process according to claim 33, wherein the halogenated hydrocarbon is selected from dichloromethane, chloroform, and 1,2-dichloroethane.
37. The process according to claim 33, wherein the ketone is selected from acetone and methyl ethyl ketone.
38. The process according to claim 33, wherein the ether is selected from diethyl ether and tetrahydrofuran.
39. The process according to claim 33, wherein the polar aprotic solvent is selected from *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulphoxide, acetonitrile, and *N*-methylpyrrolidone.
40. The process according to claim 32, wherein the reaction is carried out at a temperature of -10°C to 10°C.
41. The process according to claim 40, wherein the reaction is carried out at a temperature of -5°C to 5°C.
42. Saxagliptin bicarbonate of Formula II.



Formula II

43. The saxagliptin bicarbonate of claim 42, in crystalline form.
44. The saxagliptin bicarbonate of claim 43, characterized by an XRPD pattern substantially the same as depicted in Figure 10.
45. The saxagliptin bicarbonate of claim 43, characterized by an XRPD pattern having interplanar spacing (*d*) values at 3.70, 2.99, and 2.86 (Å).
46. The saxagliptin bicarbonate of claim 45, further characterized by interplanar spacing (*d*) values at 7.45, 3.17, 3.12, 2.64, 2.39, and 2.30 (Å).

47. The saxagliptin bicarbonate of claim 43, characterized by an XRPD pattern having characteristic peak values (2θ) at 24.05, 29.84, and $31.18 \pm 0.2^\circ$.
48. The saxagliptin bicarbonate of claim 47, further characterized by characteristic peak values (2θ) at 11.86, 28.13, 28.60, 33.88, 37.55, and $39.01 \pm 0.2^\circ$.
49. The saxagliptin bicarbonate of claim 43, wherein the crystalline form is characterized by FTIR as depicted in Figure 11.
50. The saxagliptin bicarbonate of claim 43, characterized by DSC as depicted in Figure 12.
51. The saxagliptin bicarbonate of claim 43, characterized by an endothermic peak value at about 76.94°C in the DSC thermogram.
52. A process for the preparation of saxagliptin bicarbonate, which comprises contacting saxagliptin or its salt with a suitable carbonate source.
53. The process according to claim 52, wherein the carbonate source is selected from carbon dioxide gas, dry ice, or carbonic acid prepared in situ by dissolving carbon dioxide gas in water.
54. The process according to claim 52, wherein the saxagliptin or its salt is treated with a suitable carbonate source directly or in the presence of a solvent.
55. The process according to claim 54, wherein the solvent is selected from water, alkanols, esters, ketones, polar aprotic solvents, or mixtures thereof.
56. The process according to claim 55, wherein the alkanol is selected from methanol, ethanol, *n*-propanol, isopropanol, and butanol.
57. The process according to claim 55, wherein the ester is selected from ethyl acetate, *n*-propyl acetate, isopropyl acetate, and *n*-butyl acetate.
58. The process according to claim 55, wherein the ketone is selected from acetone and methyl ethyl ketone.
59. The process according to claim 55, wherein the polar aprotic solvent is selected from *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulphoxide, acetonitrile, and *N*-methylpyrrolidone.
60. Saxagliptin carbonate of Formula III.

**Formula III**

61. The saxagliptin carbonate of claim 60, in crystalline form.
62. The saxagliptin carbonate of claim 61, characterized by FTIR as depicted in Figure 13.
63. The saxagliptin carbonate of claim 61, characterized by DSC as depicted in Figure 14.
64. The saxagliptin carbonate of claim 61, characterized by an endothermic peak value at about 113.45°C in the DSC thermogram.
65. A process for the preparation of saxagliptin carbonate, which comprises heating saxagliptin bicarbonate in the presence of water.
66. The process according to claim 65, wherein the reaction is carried out at a temperature of 50°C to 100°C.
67. The process according to claim 66, wherein the reaction is carried out at a temperature of 65°C to 70°C.
68. A process for the preparation of saxagliptin or salts, solvates, or polymorphs thereof, which includes the use of saxagliptin salts selected from the group consisting of saxagliptin bisulphate, saxagliptin acetate, saxagliptin oxalate, saxagliptin bicarbonate, or saxagliptin carbonate.
69. The process according to claim 68, wherein the process includes contacting saxagliptin salts with a base or heating in the presence of water.
70. The process according to claim 69, wherein the base is selected from hydroxides, carbonates, and bicarbonates of alkali and alkaline earth metals; ammonia; alkyl amines; and hydrazine.
71. A pharmaceutical composition comprising saxagliptin salts selected from saxagliptin bisulphate, saxagliptin acetate, saxagliptin oxalate, saxagliptin bicarbonate, or saxagliptin carbonate, and a pharmaceutically acceptable carrier.
72. A method of treating type 2 diabetes mellitus which comprises administering to a patient in need thereof a therapeutically effective amount of saxagliptin salts selected from

saxagliptin bisulphate, saxagliptin acetate, saxagliptin oxalate, saxagliptin bicarbonate, or saxagliptin carbonate, and a pharmaceutically acceptable carrier.