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(54) **Title:** PROCESSES FOR THE PREPARATION OF SITAGLIPTIN AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

(57) **Abstract:** The present application relates to improved processes for the preparation of Sitagliptin and pharmaceutically acceptable salts thereof. The present application also relates to the improved crystallization process for the preparation of Sitagliptin Phosphate. The present application also relates to the improved crystallization process for the preparation of Sitagliptin Hydrochloride monohydrate.

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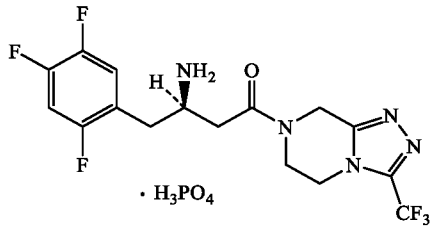
PROCESSES FOR THE PREPARATION OF SITAGLIPTIN AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

FIELD OF THE APPLICATION

The present application relates to improved processes for the preparation of Sitagliptin and its pharmaceutically acceptable salts thereof. The present application also relates to improved process for the preparation of crystalline Sitagliptin Phosphate and crystalline Sitagliptin Hydrochloride monohydrate.

BACKGROUND OF THE APPLICATION

The drug compound having the adopted name "Sitagliptin Phosphate" has chemical names: 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*] pyrazine phosphate (1:1); or (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine phosphate; and is represented by structural Formula I.



Formula I

Sitagliptin is a glucagon-like peptide 1 metabolism modulator, hypoglycemic agent, and dipeptidyl peptidase IV inhibitor, which is believed to exert its action in patients with type 2 diabetes by slowing the inactivation of incretin hormones. A product containing Sitagliptin phosphate in its monohydrate form is marketed in the United States by Merck & Co., Inc. using the brand JANUVIA™. JANUVIA™ is indicated to improve glycemic control in patients with type 2 diabetes mellitus.

Sitagliptin phosphate (1:1) monohydrate, in combination with metformin hydrochloride, is sold by Merck & Co., Inc. using the brand JANUMET™ in the form of tablets for oral administration for combination therapy in the treatment of type 2 diabetes.

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US Patent No. 6,699,871, describes a class of beta-amino tetrahydrotriazolo- [4, 3-α] pyrazines, which are potent inhibitors of DPP-IV and therefore useful for the treatment of Type 2 diabetes. Specifically disclosed in US Patent No. 6,699, 871 is 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a] pyrazine (Sitagliptin). Pharmaceutically acceptable salts of this compound are generically encompassed within the scope of US Patent No. 6,699,871. It also discloses a process for the preparation of Sitagliptin and related compounds. Similar processes are also disclosed in PCT application Nos WO2015114657A2, WO2012099381A2, WO2013013833A1, WO2012035549A2, WO2014086325 A1 and US patent i.e. US 9409912.

PCT application No. WO 2004/085661 A2 discloses a process for the preparation of Sitagliptin in which S-phenyl glycine amide is used as a chiral auxiliary to form an intermediate, which subsequently provides the required enantiomer (Sitagliptin).

PCT application No. WO 2004/087650 A2 discloses another process in which N - protected (3*R*)-3-amino-4- (2,4,5-trifluoro-phenyl)-butyric acid is synthesized enantioselectively and subsequently condensed with a pyrazine intermediate, followed by deprotection to provide Sitagliptin.

US Patent No. 7,326,708, specifically discloses dihydrogenphosphate salt of (2*R*)-4-oxo-4- [3- (trifluoromethyl)-5, 6-dihydro [1,2,4] triazolo [4,3-a] pyrazin-7 (8H)-yl]-1- (2,4,5-trifluorophenyl) butan-2-amine and process for the preparation thereof.

PCT application No. WO 2004/085378 A1 discloses a process for the preparation of Sitagliptin wherein the reduction of the Sitagliptin intermediate is carried out by using rhodium metal and a chiral ferrocenyl diphosphine.

PCT application No. WO 2004/085661 A2 discloses a process for the preparation of Sitagliptin in which (S)-phenylglycine amide is used as a chiral auxiliary to form an intermediate, which subsequently provides the required enantiomer (Sitagliptin). The application discloses the use of Adam's catalyst, *i.e.*, platinum oxide, to promote the diastereoselective hydrogenation of the enamine carbon-carbon double bond in the chiral substrate.

Several pharmaceutically acceptable salts of Sitagliptin are disclosed in WO 2005/72530 A1, WO 2010/00469 A2, WO 2012/25944 A2, WO 2012/147092 A2, WO 2008/00418 A3, WO2010/12781 A2, WO2011/123641 A1, WO2010/078440 A1, WO2012/035549 A2, WO 2015/170340 A2, WO 2016/162877 A1, WO 2015114152 A1, WO 2013186326 A1, IN2015MU2561A, and IN201821011626A.

Specifically PCT application No. WO 2005/72530 A1 discloses various pharmaceutically acceptable salts of Sitagliptin including Sitagliptin hydrochloride. For example, US patent No. 8,183,373 discloses crystalline forms of Sitagliptin hydrochloride designated form III, form IV, and form V. PCT application No. WO 2012/147092 A2 and US patent publication No. 2013/0158265 discloses various pharmaceutically acceptable salts of Sitagliptin including hydrochloride. PCT application No. WO 2008/00418 A3 discloses process for preparation of Sitagliptin hydrochloride in amorphous form. PCT application No. WO 2015/170340 A2 discloses 15 crystalline forms of Sitagliptin hydrochloride as well as their processes.

Although several processes have been reported in the prior art for the preparation of Sitagliptin and its pharmaceutically acceptable salts including phosphate salt; hydrochloride salt, they suffer from one or more drawbacks such as involving the use of hazardous regents like platinum oxide, rhodium catalyst etc., involving the use of costly reagents such as chloro pyrazine, dichloropyrazine etc and involving a number of protection and deprotection steps. Hence, there is still a need for simple, cost effective and industrially viable process for the production of Sitagliptin and its pharmaceutically acceptable salts.

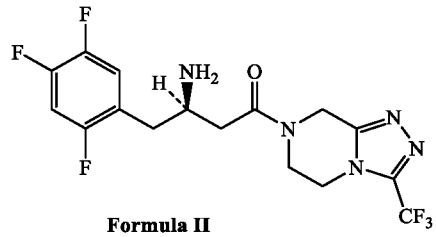
While various processes have been reported in the prior art for the preparation of alternate salts of Sitagliptin including phosphate salt; hydrochloride salt, they suffer from disadvantages such as use of hazardous solvent in scale-up or longer time-cycles, or lesser yield, poor surface properties etc. Hence, there remains a need for simple, cost effective and industrially viable processes with shorter time-cycles for the preparation of pharmaceutically acceptable salts of Sitagliptin like phosphate and hydrochloride having improved surface properties for subsequent pharmaceutical processing.

Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods, and materials are described below. All publications, patent applications, patents, and other references mentioned herein are

incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

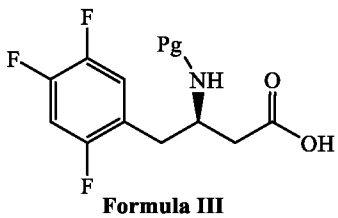
SUMMARY

In a first embodiment, present invention provides a process for the preparation of Sitagliptin of Formula II or a pharmaceutically acceptable salt thereof, comprising:

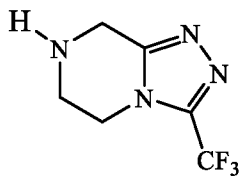


Formula II

(a) reacting, a compound of Formula III with 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine of Formula IV or salt thereof,

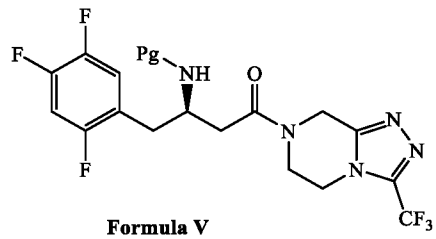


Formula III



Formula IV

in the presence of suitable base under suitable reaction conditions, to give a compound of Formula V, wherein PG is a suitable amino protecting group,



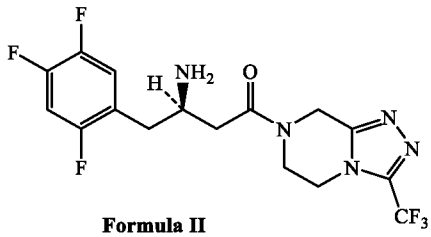
Formula V

(b) deprotecting, the compound of Formula V to afford Sitagliptin of Formula II;

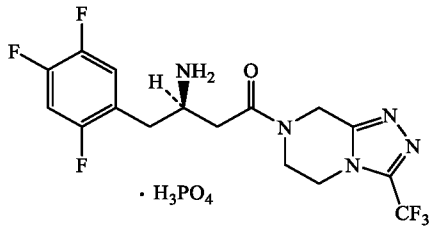
(c) optionally, treating Sitagliptin of Formula II with a source of phosphate ion or a source of chloride ion to obtain Sitagliptin Phosphate of Formula I or Sitagliptin Hydrochloride of Formula I', respectively.

In an aspect of first embodiment, present invention provide a process for the preparation of Sitagliptin or a pharmaceutically acceptable salt thereof without isolating the intermediates formed in step (a) and/or step (b).

In a second embodiment, present invention provides a process for the preparation of a crystalline form of Sitagliptin Phosphate of Formula I, comprising:



Formula II



Formula I

(a) treating Sitagliptin of Formula II with a source of phosphate ion in the presence of suitable solvent or mixture of solvents at about reflux temperature;

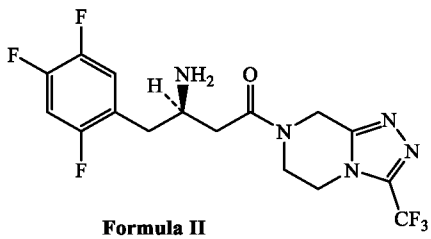
(b) optionally, adding seed crystals of crystalline form of Sitagliptin Phosphate at about reflux temperature;

(c) cooling the reaction mass to about room temperature over a period of about eight hours;

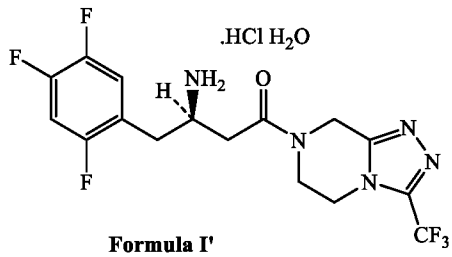
(d) adding suitable anti-solvent; and

(e) isolating Sitagliptin Phosphate of Formula I.

In a third embodiment, present invention provides a process for the preparation of Sitagliptin Hydrochloride monohydrate of Formula I', comprising:



Formula II



Formula I'

(a) treating Sitagliptin of Formula II with a source of chloride ion in the presence of suitable solvent to give Sitagliptin Hydrochloride monohydrate of Formula I';

(b) isolating Sitagliptin Hydrochloride monohydrate of Formula I'.

BRIEF DESCRIPTION OF THE DRAWINGS:

Figure 1 depicts X-ray diffraction pattern of Sitagliptin Phosphate obtained according to the present invention.

Figure 2 depicts X-ray diffraction pattern of Sitagliptin Hydrochloride monohydrate obtained according to the present invention.

DETAILED DESCRIPTION

While the specification concludes with the claims particularly pointing and distinctly claiming the invention, it is believed that the present invention will be better understood from the following description. All percentages and ratios used herein are by weight of the total composition and all measurements made are at 25°C and normal pressure unless otherwise designated. All temperatures are in Degrees Celsius unless specified otherwise. The present invention can comprise (open ended) of the components of the present invention as well as other ingredients or elements described herein.

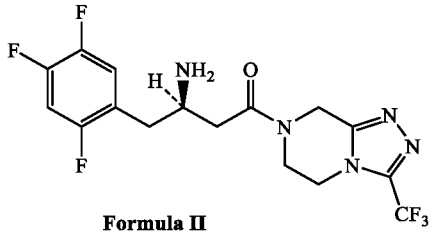
As used herein, "comprising" means the elements recited, or their equivalent in structure or function, plus any other element or elements which are not recited. The terms "having" and "including" are also to be construed as open ended unless the context suggests otherwise.

All ranges recited herein include the endpoints, including those that recite a range "between" two values.

Terms such as "about," "generally," "substantially," and the like are to be construed as modifying a term or value such that it is not an absolute, but does not read on the prior art. Such terms will be defined by the circumstances and the terms that they modify as those terms are understood by those of skill in the art. This includes, at very least, the degree of expected experimental error, technique error and instrument error for a given technique used to measure a value.

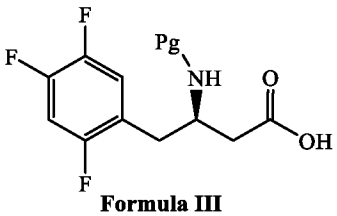
Term such as "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids.

In a first embodiment, present invention provides a process for the preparation of Sitagliptin of Formula II or a pharmaceutically acceptable salt thereof, comprising:

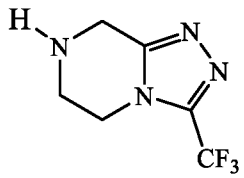


Formula II

(a) reacting, a compound of Formula III with 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine of Formula IV or salt thereof,

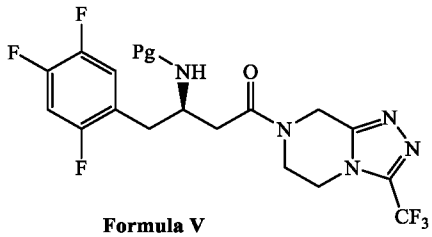


Formula III



Formula IV

in the presence of suitable base under suitable reaction conditions, to give a compound of Formula V, wherein PG is a suitable amino protecting group,



Formula V

(b) deprotecting, the compound of Formula V to afford Sitagliptin of Formula II;

(c) optionally, treating Sitagliptin of Formula II with a source of phosphate ion or a source of chloride ion to obtain Sitagliptin Phosphate of Formula I or Sitagliptin Hydrochloride of Formula I' respectively.

In an aspect of step (a) of first embodiment, suitable amino protecting group can be selected but are not limited to: tert-Butyloxycarbonyl (BOC), Carbobenzyloxy (Cbz) group, p-Methoxybenzyl carbonylgroup, 9-Fluorenylmethyloxycarbonyl (FMOC) group, Benzyl (Bn) group, pMethoxybenzyl (PMB), 3,4-Dimethoxybenzyl (DMPM), p-methoxyphenyl (PMP) group or Tosyl (Ts) group.

In an aspect of step (a) of first embodiment, suitable solvents can be selected from, but are not limited to, alcohols such as methanol, ethanol, isopropyl alcohol, and n-butanol; organic acids like acetic acid, and propionic acid; ketones such as acetone, methyl isobutyl ketone, methyl ethyl ketone, and n-butanone; halogenated solvents such as dichloromethane, ethylene dichloride, and chloroform; esters such as ethyl acetate, n-propyl acetate, and isopropyl acetate; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, and cyclohexane; ethers such as 1,4-dioxane, and tetrahydrofuran, methyl tertiary butyl ether; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), and dimethylacetamide (DMA) or a mixture thereof.

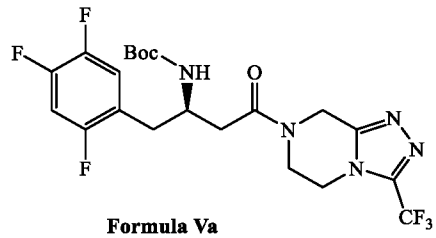
In another aspect of step (a) of first embodiment, suitable base for contacting of Formula III with Formula IV can be selected from, but are not limited to: organic bases like triethyl amine, diisopropyl ethylamine, pyridine, imidazole, N-methyl morpholine, sodium methoxide, diisopropyl amine, 1,1-carbonyl diimidazole and the like, inorganic bases like sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate in aqueous medium or in their solid state form or mixtures thereof.

In another aspect of step (a) of first embodiment, compound of Formula III is activated with suitable acid activating groups like thionyl chloride, pivaloyl chloride, oxalyl chloride, acetic anhydride, alkyl chloroformate, NHS ester followed by reaction with the compound of Formula IV.

Suitable activating agents will be familiar to the person skilled in the art. In a preferred embodiment, compound of Formula III is converted to its acid chloride or mixed anhydride before reacting with the compound of Formula IV.

The term "under suitable reaction conditions" as used herein refers to reaction conditions that support formation of compound of Formula V from compounds of Formula III and Formula IV as described herein.

In a preferred aspect of the first embodiment, the compound of Formula V is tert-butyl (R)-(4-oxo-4-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1-(2,4,5-trifluorophenyl)butan-2-yl)carbamate of Formula Va,



Formula Va

In an aspect of step (b) of first embodiment, the deprotection of amino protecting group of Formula V to afford Sitagliptin base can be conducted in presence of suitable acid. The suitable acid for deprotection can be selected from, but not limited to, hydrochloric acid, trifluoroacetic acid, or suitable mixture thereof and the like.

In an aspect of first embodiment, present invention provide a process for the preparation of Sitagliptin or a pharmaceutically acceptable salt thereof without isolating the intermediates formed in step (a) and/or step (b).

The reaction can be efficiently completed at room temperature or ambient temperature or if required reaction mass can be heated to elevated temperatures or up to about the reflux temperatures, and maintained for about 10 minutes to about 5 hours or longer.

In an aspect of step (c) of first embodiment, Sitagliptin of Formula II is optionally treated with source of a phosphate ion or a source of a chloride ion to give Sitagliptin Phosphate of Formula I or Sitagliptin Hydrochloride monohydrate of Formula I' respectively.

The suitable source of phosphate ion can be selected from, but are not limited to, phosphoric acid, polyphosphoric acid, phosphorous pentoxide, dipotassium hydrogen phosphate, ammonium dihydrogen orthophosphate, sodium dihydrogen orthophosphate, or the like.

The suitable source of chloride ion can be selected from, but are not limited to, hydrogen chloride gas, solvent saturated with hydrogen chloride gas (wherein solvent includes ethers such as isopropyl ether, methyl tertiary butyl ether; alcohols such as methanol, ethanol, isopropanol; water; ketones such as acetone or the like); hydrochloride salt of a suitable amine such as ammonium chloride; sulfur compounds such as thionyl chloride; sulfuryl chloride; carboxylic acid chloride such as acetyl chloride; silyl chloride such as trimethyl silyl chloride; or alkali metal chloride such sodium chloride, potassium chloride in combination with a sulfuric acid or the like or in combination thereof.

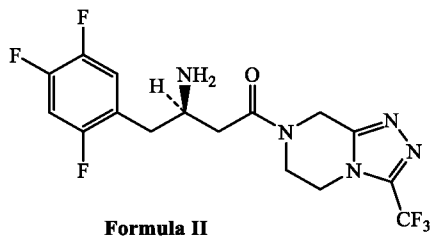
Suitable temperatures for the reaction may be room temperature or ambient temperature, near about 60 °C, near about 80°C, or about the reflux temperature of solvent employed or any

other suitable temperature. Suitable times for the reaction may be from about 30 minutes to about 10 hours, or longer. The phosphate salt of Sitagliptin of Formula I or the chloride salt of Sitagliptin of Formula I' thus obtained may be separated and dried.

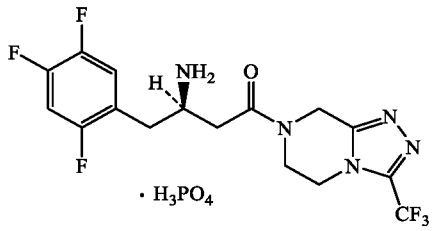
In above step, the crystallization can either be initiated by cooling or by addition of a suitable anti-solvent or by both. An anti-solvent as used herein refers to a solvent in which crystalline Sitagliptin Phosphate or Sitagliptin Hydrochloride monohydrate is less soluble or poorly soluble and can be selected from the aforementioned list of solvents.

Suitable times for crystallization will vary and can be from about 10 minutes to about 1 hour, to about 24 hours, or longer. Suitable temperatures for crystallization include from about -10°C to about 120°C or from about 10°C to about 60°C. Undissolved particles from a mixture comprising Sitagliptin Phosphate or Sitagliptin Hydrochloride monohydrate can be removed suitably by filtration, centrifugation, decantation, or other techniques, such as passing the solution through paper, glass fiber, a particulate bed, or a membrane material.

In a second embodiment, present invention provides a process for the preparation of a crystalline form of Sitagliptin Phosphate of Formula I, comprising:



Formula II



Formula I

(a) treating Sitagliptin of Formula II with a source of phosphate ion in the presence of suitable solvent or mixture of solvents at about reflux temperature;

(b) optionally, adding seed crystals of crystalline form of Sitagliptin Phosphate at about reflux temperature;

(c) cooling the reaction mass to about room temperature over a period of about eight hours;

(d) adding suitable anti-solvent; and

(e) isolating Sitagliptin Phosphate of Formula I.

In an aspect of step (a) of second embodiment, Sitagliptin of Formula II is treated with source of phosphate ion to give Sitagliptin Phosphate of Formula I.

The Sitagliptin in step (a) may be a suspension or a solution. The said mixture may be obtained by providing isolated Sitagliptin free base in a suitable solvent or may be obtained directly

from a reaction in which a Sitagliptin free base is formed. Alternately, Sitagliptin free base can also be generated by neutralization of acid addition salt of Sitagliptin with a suitable base.

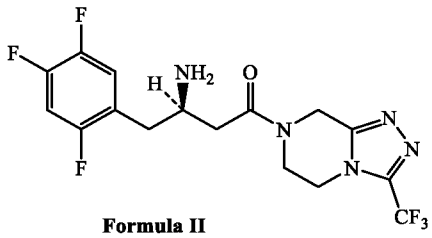
The reaction mixture can be heated to dissolution temperature that can be any temperature as long as the stability of the Sitagliptin or phosphate salt is not compromised and a substantially clear solution is obtained. For example, the dissolution temperature may range from about 20°C to about the reflux temperature of the solvent.

Suitable solvent inert to the reaction can be selected from the list provided above. In a preferred embodiment, suitable solvent is selected from alcohols, esters, ketones, water or mixtures thereof. In a most preferred embodiment, suitable solvent is selected from methanol, ethanol, isopropanol, ethyl acetate, acetone, MIBK, water or mixtures thereof. In a preferred embodiment, suitable anti-solvent is selected from ethers, halogenated hydrocarbon, aromatic hydrocarbon, aliphatic hydrocarbon. In a most preferred embodiment, suitable anti-solvent is selected from tetrahydrofuran, methyl tertiary butyl ether, diisopropyl ether, dichloromethane, toluene, heptane or mixtures thereof. Suitable temperatures for the reaction may be room temperature or ambient temperature, near about 60 °C, near about 80°C, or about the reflux temperature of solvent employed or any other suitable temperature. Suitable times for the reaction may be from about 30 minutes to about 10 hours, or longer. The phosphate salt of Sitagliptin of Formula I thus obtained may be separated and dried.

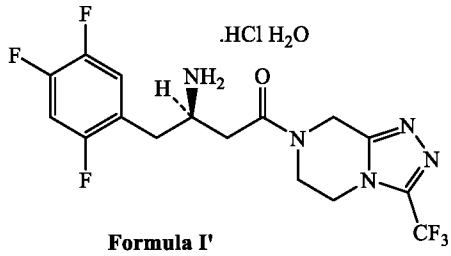
In an aspect of step (b) of second embodiment, optionally, seed crystals of crystalline form of Sitagliptin Phosphate are added into the reaction mixture at the reflux temperature.

In an aspect of step (c) and step (d) of second embodiment, step-wise cooling and addition of a suitable anti-solvent is performed. The reaction mixture can first be cooled from about reflux temperature of solvent to ambient temperature over a period of about 8 hours optionally followed by further cooling to -10°C to 10°C. An anti-solvent as used herein refers to a solvent in which crystalline Sitagliptin Phosphate is less soluble or poorly soluble and can be selected from the aforementioned list of solvents. In a preferred embodiment, MTBE is employed as anti-solvent.

In a third embodiment, present invention provides a process for the preparation of Sitagliptin Hydrochloride monohydrate of Formula I', comprising:



Formula II



Formula I'

(a) treating Sitagliptin of Formula II with source of chloride ion in the presence of suitable solvent to give Sitagliptin hydrochloride monohydrate of Formula I';

(b) isolating the Sitagliptin hydrochloride monohydrate of Formula I'.

In an aspect of step (a) of third embodiment, Sitagliptin of Formula II is treated with source of chloride ion to give Sitagliptin Hydrochloride monohydrate of Formula I'.

The Sitagliptin in step (a) may be a suspension or a solution. The said mixture may be obtained by providing isolated Sitagliptin free base in a suitable solvent or may be obtained directly from a reaction in which a Sitagliptin free base is formed. Alternately, Sitagliptin free base can also be generated by neutralization of acid addition salt of Sitagliptin with a suitable base.

If it is intended to obtain a clear solution in step (a), the reaction mixture can be heated to dissolution temperature that can be any temperature as long as the stability of the Sitagliptin or hydrochloride salt is not compromised and a substantially clear solution is obtained. For example, the dissolution temperature may range from about 20°C to about the reflux temperature of the solvent.

Suitable solvent inert to the reaction can be selected from the list provided above. In a preferred embodiment, suitable solvent is selected from halogenated solvents, hydrocarbon, alcohols, esters, ketones, water or mixtures thereof. In a most preferred embodiment, suitable solvent is selected from methanol, ethanol, isopropanol, tetrahydrofuran, methyl ethyl butyl ether, ethyl acetate, acetone, MIBK, water or mixtures thereof. Suitable temperatures for the reaction may be room temperature or ambient temperature, near about 60 °C, near about 80°C, or about the reflux temperature of solvent employed or any other suitable temperature. Suitable times for the reaction may be from about 30 minutes to about 10 hours, or longer. The hydrochloride salt of Sitagliptin of Formula I' thus obtained may be separated and dried.

In an aspect of step (b) of third embodiment, isolation can be done by step-wise cooling or by addition of a suitable anti-solvent or by both. An anti-solvent as used herein refers to a solvent

in which crystalline Sitagliptin hydrochloride is less soluble or poorly soluble and can be selected from the aforementioned list of solvents.

In above step, isolation can be done by step-wise cooling. For example, the reaction mixture can first be cooled from about reflux temperature of solvent to ambient temperature followed by -10°C to 10°C over a period of about 10 mins to about 1 hour, to about 10 hours or longer.

In above step, the resulting solid may be further dried followed by humidification to afford Sitagliptin hydrochloride monohydrate. Drying may be suitably carried out using conditions mentioned below. Humidification may be suitably carried out by literature reported methods under RH of at least 30% at the temperatures ranging from ambient temperature to about 50°C.

In aforementioned embodiments, suitable times for isolation will vary and can be from about 10 minutes to about 1 hour, to about 24 hours, or longer. Suitable temperatures for crystallization include from about -10°C to about 120°C or from about 10°C to about 60°C. Undissolved particles from a mixture comprising Sitagliptin hydrochloride can be removed suitably by filtration, centrifugation, decantation, or other techniques, such as passing the solution through paper, glass fiber, a particulate bed, or a membrane material.

In aforementioned embodiments, the resulting solid may be optionally further dried. Drying may be suitably carried out using equipment such as a tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like, at atmospheric pressure or under reduced pressure. Drying may be carried out at temperatures less than about 100°C, less than about 60°C, less than about 40°C, or any other suitable temperatures, at atmospheric pressure or under reduced pressure, and in the presence or absence of an inert atmosphere such as nitrogen, argon, neon, or helium. The drying may be carried out for any desired time periods to achieve a desired purity of the product, such as, for example, about 1 to about 15 hours, or longer.

The compounds at any stage of the process of the present invention may be recovered from a suspension/solution using any of techniques such as decantation, filtration by gravity or by suction, centrifugation, slow evaporation, or the like, or any other suitable techniques.

In aforementioned embodiments, once obtained, the crystals of Sitagliptin phosphate & hydrochloride monohydrate may be used as the nucleating agent or "seed" crystals for subsequent crystallizations from solutions.

In another general aspect, the present invention is directed to pharmaceutical compositions comprising Sitagliptin of Formula II or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable excipients.

In another general aspect, Sitagliptin of Formula II or a pharmaceutically acceptable salt thereof obtained from the methods described above has better surface properties for subsequent pharmaceutical processing.

In another general aspect, there is provided crystalline form of Sitagliptin Phosphate having particle size distributions wherein D90 is less than about 300 microns or less than about 250 microns or less than about 200 microns, D50 is less than about 100 microns or less than about 70 microns or less than about 50 micron, D10 is less than about 30 microns or less than about 15 microns or less than about 10 micron.

In another general aspect, there is provided crystalline form of Sitagliptin Hydrochloride monohyrate having particle size distributions wherein D90 is less than about 30 microns or less than about 15 microns, D50 is less than about 20 microns or less than about 10 microns, D10 is less than about 10 microns or less than about 05 microns.

The D10, D50, and D90 values are useful ways for indicating a particle size distribution. D90 refers to at least 90 volume percent of the particles having a size smaller than the said value. Likewise, D10 refers to 10 volume percent of the particles having a size smaller than the said value. D50 refers to 50 volume percent of the particles having a size smaller than the said value. Methods for determining D10, D50, and D90 include laser diffraction, such as using equipment from Malvern Instruments Ltd. of Malvern, Worcestershire, United Kingdom.

The compounds of this application are best characterized by the X-ray powder diffraction pattern determined in accordance with procedures that are known in the art. PXRD data reported herein was obtained using CuKα radiation, having the wavelength 1.5406 Å and were obtained using a PANalytical X'Pert PRO instruments. For a discussion of these techniques see J. Haleblain, J. Pharm. Sci. 1975 64:1269-1288, and J. Haleblain and W. McCrone, J. Pharm. Sci. 1969 58:911-929.

Generally, a diffraction angle (2θ) in powder X-ray diffractometry may have an error in the range of $\pm$ 0.2°. Therefore, the aforementioned diffraction angle values should be understood as including values in the range of about $\pm$ 0.2°. Accordingly, the present application includes not only crystals whose peak diffraction angles in powder X-ray diffractometry completely coincide

with each other, but also crystals whose peak diffraction angles coincide with each other with an error of about ± 0.2°. Therefore, in the present specification, the phrase "having a diffraction peak at a diffraction angle (2θ ± 0.2°) of 7.9° " means "having a diffraction peak at a diffraction angle (2θ) of 7.7 ° to 8.1 °". Although the intensities of peaks in the x-ray powder diffraction patterns of different batches of a compound may vary slightly, the peaks and the peak locations are characteristic for a specific polymorphic form. Alternatively, the term "about" means within an acceptable standard error of the mean, when considered by one of ordinary skill in the art. The relative intensities of the PXRD peaks can vary depending on the sample preparation technique, crystal size distribution, various filters used, the sample mounting procedure, and the particular instrument employed. Moreover, instrument variation and other factors can affect the 2-theta values. Therefore, the term "substantially" in the context of PXRD is meant to encompass that peak assignments can vary by plus or minus about 0.2 degree. Moreover, new peaks may be observed or existing peaks may disappear, depending on the type of the machine or the settings (for example, whether a Ni filter is used or not).

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the application in any manner.

Examples

Example 1: tert-butyl (R)-(4-oxo-4-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1-(2,4,5-trifluorophenyl)butan-2-yl)carbamate of Formula Va

5 g of (R)-3-(tert-butoxycarbonylamino)-4-(2,4,5-trifluorophenyl)butanoic acid was added to 50 ml of ethyl acetate and stirred the reaction mixture. Further, 6.30 g of sodium hydrogencarbonate and 25 ml of ethyl acetate was charged into the reaction mixture and cooled. 2.71 g of pivaloyl chloride was dissolved in ethyl acetate and charged into the above reaction mixture and stirred. 4.12 g of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride was added to the reaction mixture and then charged dimethylaminopyridine (DMAP) and stirred. Further, water was charged into the reaction mixture and separated aqueous and organic layer. The aqueous layer was extracted with ethyl acetate and all organic layers was combined and distilled to get the title compound.

Example 2: Preparation of Sitagliptin of Formula II

5 g of (R)-3-(tert-butoxycarbonylamino)-4-(2,4,5-trifluorophenyl)butanoic acid was added to 100 ml of toluene and stirred the reaction mixture. Further, 4.77 g of sodium carbonate was charged into the reaction mixture and cooled. 2.71 g of pivaloyl chloride was dissolved in toluene and charged into the above reaction mixture and stirred. 4.12 g of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride and dimethylaminopyridine (DMAP) was added to the reaction mixture and stirred. Then, conc. HCl added to the reaction mixture and stirred. Further, water was charged into the reaction mixture and separated aqueous and organic layer. The organic layer was extracted with water and all aqueous layer was combined and to it added 3N NaOH. Then, ethyl acetate was added to the reaction mixture and separated the organic layer. The aqueous layer was extracted with ethyl acetate and all organic layers was combined and distilled to get solid material. Then, charged isopropyl alcohol and stirred the resultant reaction mixture. Further, hexane was charged to the reaction mixture and and stirred. The resultant mixture was filtered and washed with hexane to give title compound of 4.4 g.

Example 3: Preparation of Sitagliptin of Formula II

5 g of (R)-3-(tert-butoxycarbonylamino)-4-(2,4,5-trifluorophenyl)butanoic acid was added to 90 ml of toluene and stirred the reaction mixture. Further, 5.11 g of imidazole was charged into the reaction mixture and cooled. 2.71 g of pivaloyl chloride added into the above reaction mixture and stirred. 4.12 g of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride and dimethylaminopyridine (DMAP) was added to the reaction mixture and stirred. Then, conc. HCl added to the reaction mixture and stirred. Further, water was charged into the reaction mixture and separated aqueous and organic layer. The organic layer was extracted with water and all aqueous layer was combined and ethyl acetate was added into it. Then, 3N NaOH was added to the reaction mixture and separated the organic layer. The aqueous layer was extracted with ethyl acetate and all organic layers was combined and distilled to get solid material. Then, charged isopropyl alcohol and stirred the resultant reaction mixture. Further, hexane was charged to the reaction mixture and stirred. The resultant mixture was filtered and washed with hexane to give title compound.

Example 4: Preparation of Sitagliptin of Formula II

10 g of (R)-3-(tert-butoxycarbonylamino)-4-(2,4,5-trifluorophenyl)butanoic acid was added to 250 ml of toluene and stirred the reaction mixture. Further, 9.72 g of triethyl amine (TEA) was charged into the reaction mixture and cooled. 5.43 g of pivaloyl chloride was dissolved in toluene and charged into the above reaction mixture and stirred. 8.23 g of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride and dimethylaminopyridine (DMAP) was added to the reaction mixture and stirred. Then, conc. HCl added to the reaction mixture and stirred. Further, water was charged into the reaction mixture and separated aqueous and organic layer. The organic layer was extracted with water and all aqueous layer was combined and ethyl acetate was added into it. Then, NaOH was added to the reaction mixture and separated the organic layer. The aqueous layer was extracted with ethyl acetate and all organic layers was combined and distilled to get solid material. Then, charged isopropyl alcohol and stirred the resultant reaction mixture. Further, hexane was charged to the reaction mixture and stirred. Then resultant mixture was filtered and washed with hexane to give title compound 8.4g.

Example 5: Preparation of Sitagliptin of Formula II

5 g of (R)-3-(tert-butoxycarbonylamino)-4-(2,4,5-trifluorophenyl)butanoic acid was added to 125 ml of toluene and stirred the reaction mixture. Further, 4.55 g of N-methyl morpholine was charged into the reaction mixture and cooled. 2.71 g of pivaloyl chloride was dissolved in toluene and charged into the above reaction mixture and stirred. 4.12 g of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride and dimethylaminopyridine (DMAP) was added to the reaction mixture and stirred. Then, conc. HCl added to the reaction mixture and stirred to give title compound.

Example 6: tert-butyl (R)-(4-oxo-4-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1-(2,4,5-trifluorophenyl)butan-2-yl)carbamate of Formula Va;

10 g of (R)-3-(tert-butoxycarbonylamino)-4-(2,4,5-trifluorophenyl)butanoic acid was added to 2.78 ml of toluene and stirred the reaction mixture. Further, 16.29 g of Diisopropyl ethyl amine (DIPEA) was charged into the reaction mixture and cooled. 5.43 g of pivaloyl chloride was dissolved in toluene and charged into the above reaction mixture and stirred. 8.23 g of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride and

dimethylaminopyridine (DMAP) was added to the reaction mixture and stirred to give title compound.

Example 7: Preparation of Sitagliptin Phosphate of Formula I

50 g of (R)-3-(tert-butoxycarbonylamino)-4-(2,4,5-trifluorophenyl)butanoic acid was added to 1250 ml of toluene and stirred the reaction mixture. Further, 46 g of imidazole was charged into the reaction mixture and stirred. 28.9g of pivaloyl chloride was dissolved in toluene and charged into the above reaction mixture and stirred. 44.6 g of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride was added to the reaction mixture and stirred. Further, water was charged into the reaction mixture and separated aqueous and organic layer. All organic layer (toluene) was combined and conc. HCl was added into it and reaction mixture was stirred. Further, water was charged into the reaction mixture and separated aqueous and organic layer. All aqueous layer was combined and added dichloromethane into it. Then, NaOH was added and separated the organic and aqueous layer. All organic layer (DCM) was combined and added 85% phosphoric solution in methanol. The resultant mixture was stirred and DCM was distilled out completely. Charged methanol and water to reaction mass and stirred the resultant reaction mass. Further, MTBE was added into it and stirred. Then resultant mixture was filtered and washed with MTBE followed by drying to give title compound.

Example 8: Preparation of Sitagliptin Phosphate of Formula I

37 g of (R)-3-(tert-butoxycarbonylamino)-4-(2,4,5-trifluorophenyl)butanoic acid was added to 880 ml of toluene and stirred the reaction mixture. Further, 34 g of imidazole was charged into the reaction mixture and the reaction mass was heated to 50°C and stirred. 2.14 g of pivaloyl chloride was dissolved in toluene and charged into the above reaction mixture and stirred. 32.9 g of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride was added to the reaction mixture and the reaction mass was stirred for 15 hours. Further, 555 ml of water was charged into the reaction mixture and aqueous and organic layers were separated. All organic layer (toluene) was combined and 43.2 ml of conc. HCl was added into it and reaction mixture was stirred. Further, 185 ml of water was charged into the reaction mixture and separated aqueous and organic layer. All aqueous layer was combined and 184 ml of dichloromethane was added into it. Then, 22.1 g of NaOH was added and separated the organic and aqueous layer. All organic layer

(DCM) was combined and 19.2 g of 85% phosphoric acid solution in methanol was added. The resultant mixture was stirred and DCM was distilled out completely. Charged 148 ml of methanol to reaction mass and the reaction mass was stirred at 60°C. The solvent was evaporated under reduced pressure. Charged 88ml of water and 444 ml of methanol and the reaction mass was stirred at 60°C till clear solution is obtained. Charged seed crystals of Sitagliptin Phosphate into the reaction mass and the reaction mass was stirred for 3 hours at 60°C. The reaction mass was gradually cooled to 30°C, over a period of 4 hours. Charged 1100 ml of MTBE into the reaction mass and the reaction mass was stirred at 30°C for 6 hours. The resultant mixture was then filtered and washed with MTBE followed by drying to give 30.8g of title compound.

Example 9: Preparation of Sitagliptin Phosphate of Formula I

10 g of (R)-3-(tert-butoxycarbonylamino)-4-(2,4,5-trifluorophenyl)butanoic acid was added to 240 ml of toluene and stirred the reaction mixture. Further, 9.2 g of imidazole was charged into the reaction mixture and the reaction mass was heated to 50°C and stirred. 5.7 g of pivaloyl chloride was dissolved in toluene and charged into the above reaction mixture and stirred. 8.9 g of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride was added to the reaction mixture and the reaction mass was stirred for 15 hours. Further, 250 ml of water was charged into the reaction mixture and aqueous and organic layers were separated. All organic layer (toluene) was combined and 15 ml of conc. HCl was added into it and reaction mixture was stirred. Further, 30 ml of water was charged into the reaction mixture and separated aqueous and organic layer. All aqueous layer was combined and 50 ml of dichloromethane was added into it. Then, 8 g of NaOH was added and separated the organic and aqueous layer. All organic layer (DCM) was combined and 5.2 g of 85% phosphoric acid solution in methanol was added. The resultant mixture was stirred and DCM was distilled out completely. Charged 120 ml of methanol to reaction mass and the reaction mass was stirred at 60°C till clear solution is obtained. The reaction mass was gradually cooled to 30°C, over a period of 6 hours. Charged 440 ml of MTBE into the reaction mass and the reaction mass was stirred at 30°C for 6 hours. The resultant mixture was then filtered and washed with MTBE followed by drying to give title compound.

Example 10: Preparation of Sitagliptin hydrochloride monohydrate of Formula I'

50 g of (R)-3-(tert-butoxycarbonylamino)-4-(2,4,5-trifluorophenyl)butanoic acid was added to 1250 ml of toluene and stirred the reaction mixture. Further, 46 g of imidazole was charged into the reaction mixture and stirred and then charged 28.9 g of pivaloyl chloride dissolved in 100ml toluene and stirred followed by addition of 44.6 g of 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride and resultant reaction mixture was stirred. Further, 500 ml water was charged into the reaction mixture and separated aqueous and organic layer followed by addition of conc. HCl to the toluene layer and stirred the reaction mixture. Further, 150ml water was charged into the reaction mixture and separated aqueous and organic layer. 250ml dichloromethane was added to the aqueous layer followed by 205 ml of 4N NaOH solution was added. Then 16.5ml conc. HCl was added to dichloromethane layer. The resultant mixture was stirred and dichloromethane was distilled out partially. Charged 100ml isopropanol to reaction mass and heated at about reflux temperature till clear solution is observed followed by seeding with 0.5g Sitagliptin hydrochloride monohydrate (1%) into the reaction mixture. Further, the resultant reaction mass was gradually cooled to ambient temperature and then to ~ -5°C and was stirred. Then resultant solid was isolated by filtration and washed with 100ml isopropanol followed by drying and humidification to give title compound 56.0g

Example 11: Preparation of Sitagliptin hydrochloride monohydrate of Formula I'

20 g of Sitagliptin free base of Formula II was added to mixture of 200 ml dichloromethane and 60ml isopropanol and stirred the reaction mixture. Further, 7 ml of isopropanolic HCl was charged slowly into the reaction mixture and stirred followed by addition of 240 ml methyl tertiary butyl ether (MTBE) and reaction mixture was stirred overnight. Then resultant mixture was filtered and washed with MTBE followed by drying to give title compound 12.4g.

Example 12: Preparation of Sitagliptin hydrochloride monohydrate of Formula I'

20 g of Sitagliptin free base of Formula II was added to 120 ml of isopropanol and stirred the reaction mixture and heated the reaction mixture at about 50°C followed by lot wise addition of 6.7 g isopropanolic HCl and 100 ml isopropanol and then maintained at the same temperature followed by seeding with 0.2 g Sitagliptin hydrochloride monohydrate. Then the resultant mixture

was stirred overnight followed by filtration and washing with 20ml isopropanol followed by drying to give title compound 10.3g.

Example 13: Preparation of Sitagliptin hydrochloride monohydrate of Formula I'

To the 102 g dichloromethane layer (containing 10 g Sitagliptin free base of Formula II as obtained from example 8), 0.6ml water was added and reaction mixture was stirred followed by lot wise addition of 6.7g isopropanolic HCl and 100 ml isopropanol and then maintained at the same temperature. Then the resultant mixture was stirred overnight followed by filtration and drying to give title compound 9.9g.

Example 14: Preparation of Sitagliptin hydrochloride monohydrate of Formula I'

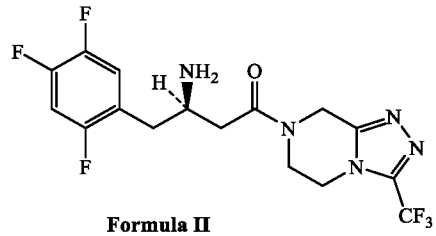
To the 225 g toluene layer (containing 10g tert-butyl (R)-(4-oxo-4-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1-(2,4,5-trifluorophenyl)butan-2-yl)carbamate [BoC Sitagliptin] as obtained from example 8), 35 ml isopropanolic HCl was added slowly. The reaction mixture was stirred for about 5-7h followed by complete distillation of the resultant reaction mass and then 150ml isopropanol was charged and mixture was stirred at ambient temperature followed by seeding with Sitagliptin hydrochloride monohydrate and then heating at about 50°C. The resultant mixture was stirred overnight at the same temperature followed by cooling to ambient temperature & maintenance for about 2 hours. Then the resultant solid was isolated by filtration and drying to give title compound 10.9 g.

Example 15: Preparation of Sitagliptin hydrochloride monohydrate of Formula I'

30 g of Sitagliptin free base of Formula II was added to 300 ml of dichloromethane and heated to about 35°C followed by addition of 10 g of conc. HCl. Then the resultant mixture was distilled completely followed by chasing with 120 ml isopropanol and then addition of mixture of 390 ml isopropanol and 180 of ml water. The resultant mixture was heated at about 75°C followed by filtration and then cooling to ambient temperature. To this mixture, 300 ml of MTBE was added and stirred overnight followed by filtration and drying to give the title compound 28 g.

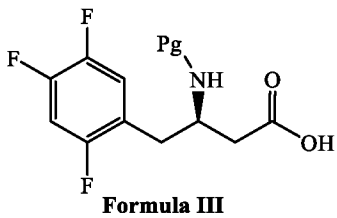
We Claim:

1) A process for the preparation of Sitagliptin of Formula II or a pharmaceutically acceptable salt thereof, comprising:

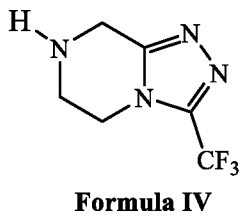


Formula II

(a) reacting a compound of Formula III with 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine of Formula IV or salt thereof,

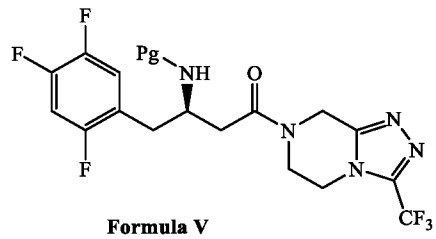


Formula III



Formula IV

in the presence of suitable base under suitable reaction conditions, to give a compound of Formula V, wherein PG is a suitable amino protecting group,



Formula V

(b) deprotecting, the compound of Formula V to afford Sitagliptin of Formula II;

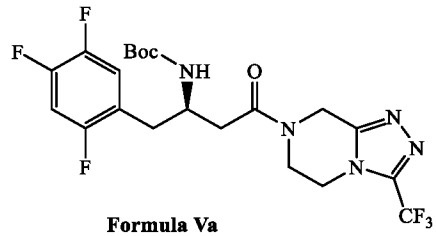
(c) optionally, treating Sitagliptin of Formula II with a source of phosphate ion or a source of chloride ion to obtain Sitagliptin Phosphate of Formula I or Sitagliptin Hydrochloride of Formula I' respectively.

2) The process according to claim 1, wherein the suitable amino protecting group is selected from the group consisting of tert-Butyloxycarbonyl (BOC), Carbobenzyloxy (Cbz) group, p-Methoxybenzyl carbonylgroup, 9-Fluorenylmethyloxycarbonyl (FMOC) group, Benzyl (Bn)

group, p-Methoxybenzyl (PMB), 3,4-Dimethoxybenzyl (DMPM), p-methoxyphenyl (PMP) group or Tosyl (Ts) group and like.

3) The process according to claim 1, wherein the base in step a) is selected from the group consisting of triethyl amine, diisopropyl ethylamine, pyridine, imidazole, N-methyl morpholine, diisopropyl amine or 1,1-carbonyl diimidazole, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate and like.

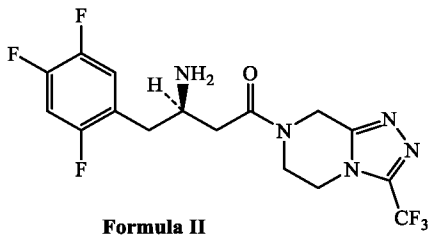
4) The process according to claim 1, wherein the compound of Formula V is tert-butyl (R)-(4-oxo-4-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1-(2,4,5-trifluorophenyl)butan-2-yl)carbamate of Formula Va,



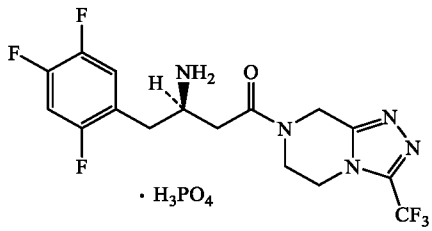
Formula Va

5) The process according to claim 1, wherein Sitagliptin of Formula II or a pharmaceutically acceptable salt thereof is prepared without isolating the intermediates formed in step (a) and/or step (b).

6) A process for the preparation of a crystalline form of Sitagliptin Phosphate of Formula I, comprising:



Formula II



Formula I

(a) treating Sitagliptin of Formula II with a source of phosphate ion in the presence of suitable solvent or mixture of solvents at about reflux temperature;

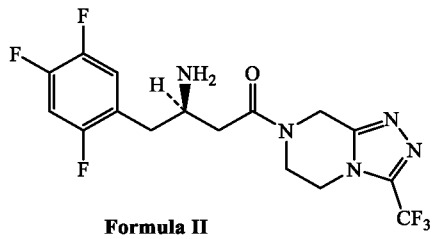
(b) optionally, adding seed crystals of crystalline form of Sitagliptin Phosphate at about reflux temperature;

(c) cooling the reaction mass to about room temperature over a period of about eight hours;

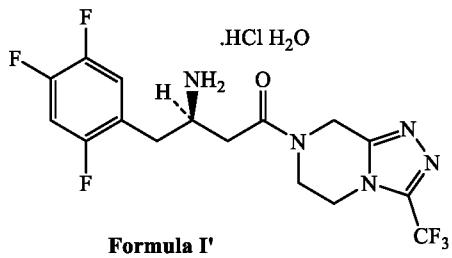
(d) adding suitable anti-solvent; and

(e) isolating Sitagliptin Phosphate of Formula I.

7) The process according to claim 6, wherein the suitable solvents are selected from a group consisting of alcohols, esters, ketones, water or mixtures thereof.
8) The process according to claim 7, wherein the suitable solvents are selected from, methanol, ethanol, isopropanol, ethyl acetate, acetone, MIBK, water or mixtures thereof.
9) The process according to claim 6, wherein the suitable anti-solvent are selected from a group consisting of ether, halogenated hydrocarbon, aromatic hydrocarbon, aliphatic hydrocarbon.
10) The process according to claim 6, wherein suitable anti-solvent is selected from tetrahydrofuran, methyl tertiary butyl ether, diisopropyl ether, dichloromethane, toluene, heptane or mixtures thereof.
11) A process for the preparation of Sitagliptin Hydrochloride monohydrate of Formula I', comprising:



Formula II



Formula I'

(a) treating Sitagliptin base of Formula II with source of chloride ion in the presence of suitable solvent to give Sitagliptin hydrochloride monohydrate of Formula I';
(b) isolating the Sitagliptin hydrochloride monohydrate of Formula I'.

12) The process according to claim 9, wherein the suitable solvents are selected from a group consisting of dichloromethane, toluene, methanol, ethanol, isopropanol, water, tetrahydrofuran, methyl tertiary butyl ether or mixtures thereof.
13) A pharmaceutical composition comprising Sitagliptin of Formula II or a pharmaceutically acceptable salt thereof, prepared according to process of claim 1.

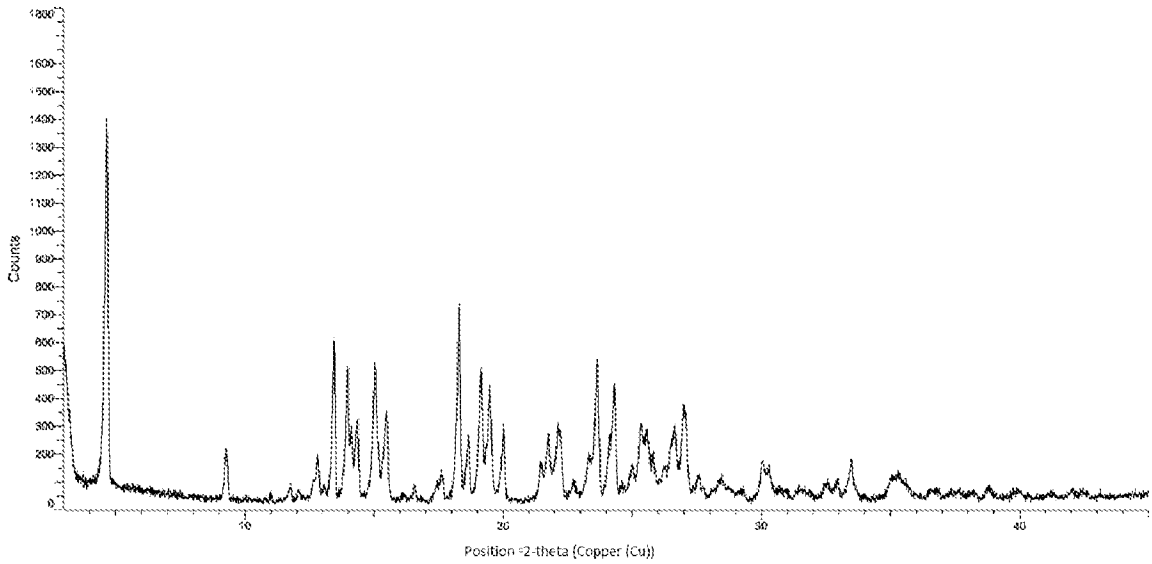


Figure 1

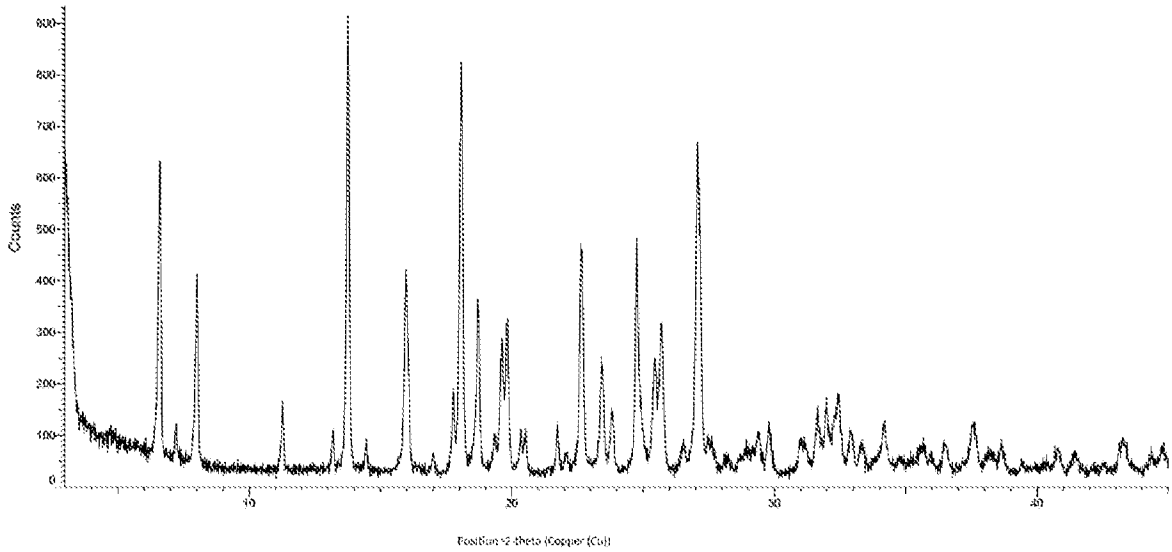


Figure 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2019/060013

A. CLASSIFICATION OF SUBJECT MATTER
C07C229/34,A61K31/495 Version=2020.01

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C, A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US2009192326 A1 (PERLMAN NURIT[IL]) 30 July 2009 (30-07-2009) examples 8-9	1-5
Y	Liu F Et Al: 'The asymmetric synthesis of Sitagliptin, a selective dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes', JOURNAL OF CHEMICAL RESEARCH 2010, April, 23-232, doi: 10.3184/030823410X12709912414009 whole document	6-10
Y	WO2011060213 A2 (REDDYS LAB LTD DR[IN]) 19 May 2011 (19-05-2011) Page-15, lines 20-30	6-10
X	WO2005072530 A1 (MERCK & CO INC[US]) 11 August 2005 (11-08-2005) example 1; page 2	11-13

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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

Date of the actual completion of the international search	Date of mailing of the international search report
20-03-2020	20-03-2020
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Parameswar Sau Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2019/060013

Citation	Pub.Date	Family	Pub.Date
WO 2005072530 A1	11-08-2005	US 2008227786 A1	18-09-2008
		EP 1708571 A4	08-07-2009