The present invention relates to an improved process for the preparation of Anagliptin, intermediates thereof, or pharmaceutically acceptable thereof. The present invention also directly to another short process for the preparation of Anagliptin. The present invention also specifically provides an improved process for the purification of intermediate of Anagliptin. Further, the present invention relates to a polymorph of Anagliptin or a pharmaceutically acceptable salt thereof and a method for the preparation thereof.
A PROCESS FOR THE PREPARATION OF ANAGLIPTIN AND ITS INTERMEDIATES THEREOF

Field of Invention

The present invention direct to a process for the preparation of Anagliptin or its pharmaceutically acceptable salts and intermediates. The present invention provides an industrially advantageous process for the preparation of Anagliptin. The invention relates to a novel polymorph of Anagliptin or pharmaceutically acceptable salt thereof and its methods of preparation.

Background of the invention

The drug compound having the adopted name "Anagliptin" has chemical name: N-[2-([2-[(2S)-2-Cyanopyrrolidin-1-yl]-2-oxoethyl]amino)-2-methylpropyl]-2-methyl pyrazolo [1,5-a] pyrimidine-6-carboxamide; and has the structural formula I:

![Formula I](image)

The pharmaceutical product Suini® tablets contain Anagliptin as active ingredient. Anagliptin is a DPP-4 (dipeptidyl peptidase-4) inhibitor useful for the treatment of diabetes.

US Patent No. 7,345,180 describes Anagliptin and process for the preparation thereof. The process of US'180 involves reaction of 2-methylpyrazolo [1, 5-a] pyrimidin-6-yl with (S)-l-(2'-Chloroacetyl) pyrrolidine-2-carbonitrile in presence of potassium carbonate and sodium iodide in acetone for a period of 8 hours at room temperature.

Kato Noriyasu et al in Bioorganic and Medicinal Chemistry 19(23), 2011, 7221-7227 reported synthesis of Anagliptin hydrochloride. The process involves selective protection
of 2-amino-2-methylpropylamine with di-tert-butyl dicarbonate and condensation with (S)-l-(2-chloroacetyl) pyrrolidine-2-carbonitrile. After deprotecting of the BOC group, the amino pyrrolidine is condensed with pyrimidine acid in tetrahydrofuran in presence of N, N-carbonyldiimidazole to give Anagliptin which is converted to Anagliptin hydrochloride using hydrochloric acid in 1, 4-dioxan.

Other reported processes in WO 2011/075699, WO 2006/060122, WO 2009/047240, WO 2011/026241, and WO 2011/006074, JP 2010/064982, Freire Felix et. al., in Journal of the American Chemical Society, 131(23), 7970-7972; 2009, Isfort, Christian Schulze et al., in Chemistry - A European Journal, 13(8), 2344-2357; 2007, disclosed the compound Boc-aminopyrrolidine , which is referred as formula VIII in the present application. However, the reported processes suffers one or the other problems like formation of impurities, longer duration of reaction, use of number of solvents, use of bases, etc and made the process expensive.

With respect to reported processes for preparing the compound Boc-aminopyrrolidine Kato Noriyasu et al., in Bioorganic & Medicinal Chemistry, 19(23), 7221-7227; 2011 and US 7,345,180, involves condensation using potassium carbonate in the acetone. However, the prior art process has disadvantages including formation of dimer of pyrrolidine of Formula A more than 10%.

The reported processes also suffer from disadvantages such as use of number of multiple reagents, solvents, low yield and purity of the key intermediate, i.e. Boc-aminopyrrolidine. To make intermediate with lower impurity and removal of carry forward impurities require tedious purification process at final API or its intermediate stages.

The inventors while developing the process of Anagliptin come across the process which involves the reaction of 2-methylpyrazolo[1,5-a] pyrimidine-6-carboxylic acid with 2-methyl-1,2-propane diamine, which reacts further with l-(2-chloroacetyl)-2S-pyrrolidine carbonitrile to get Anagliptin in a very simple steps.
Summary of the Invention

The present invention provides an economically viable industrial eco-friendly process for the preparation of Anagliptin.

In one aspect of the invention is to provide a process, for the preparation of intermediate of Anagliptin, amino pyrrolidine of Formula VI

\[
\text{Formula-VI}
\]

or pharmaceutically acceptable salt thereof,

the process includes the steps of:

1. Protecting of l-amino-2-methyl propanamine with Boc-anhydride in the dichloromethane to provide l-tert-butoxycarbonyl amino-2-methyl-2-propanamine of formula VII;

\[
\text{Formula VII}
\]

2. Condensing of the compound of formula VII with (S)-l-(2-chloroacetyl)pyrrolidine-2-carbonitrile of formula V

\[
\text{Formula V}
\]

in presence of organic base to provide Boc-aminopyrrolidine of formula VIII; and
c) deprotecting Boc-aminopyrrolidine using acid in the alcoholic solvent to provide aminopyrrolidine or pharmaceutically acceptable salt thereof.

In another aspect of the present invention relates to a process for the aminopyrrolidine of Formula VI

![Formula VI](image)

or pharmaceutically acceptable salt thereof,
the process includes the steps of:

a) condensing of 1-tert-butoxycarbonylamino-2-methyl-2-propanamine with (S)-1-(2-chloroacetyl)pyrrolidine-2-carbonitrile of formula V:

![Formula V](image)
in presence of organic base to provide Boc-aminopyrrolidine of formula VIII;
and

![Formula VIII](image)

b) deprotecting Boc-aminopyrrolidine using acid in the alcoholic solvent to provide aminopyrrolidine or pharmaceutically acceptable salt thereof.
In another aspect of the present invention relates to a process for the preparation of Anagliptin or a pharmaceutically acceptable salt thereof, the process includes the steps of:

a) condensing of 1-tert-butoxycarbonylamino-2-methyl-2-propanamine with (S)-1-(2-chloroacetyl)pyrrolidine-2-carbonitrile in presence of organic base to provide Boc-aminopyrrolidine;

b) deprotecting Boc-aminopyrrolidine using acid in alcoholic solvent to provide aminopyrrolidine or pharmaceutically acceptable salt thereof; and

c) conversion of aminopyrrolidine to pure Anagliptin or a pharmaceutically acceptable salt.

In another aspect of the present invention provides a process for the purification of Boc-aminopyrrolidine and its conversion to Anagliptin or pharmaceutically acceptable salt thereof.

A process for the purification of Boc-aminopyrrolidine of formula VIII or a pharmaceutically acceptable salt thereof

\[
\text{Formula VIII}
\]

substantially free from its dimer impurity of Formula A:

\[
\text{Formula A}
\]

the process includes the steps of:

a) treating Boc-aminopyrrolidine in ether solvent;
b) cooling the reaction mixture of step a) to below 15 °C; and
c) recovering the pure Boc-aminopyrrolidine or a pharmaceutically acceptable salt thereof substantially free from its dimer impurity of formula A.

In another aspect of the present invention relates to use of compound of formula VIII free from compound of formula A to make Anagliptin substantially free of impurity A.

The present invention also provides a process for the preparation of Anagliptin or pharmaceutically acceptable salt thereof, having purity 99 % or more, when measured by HPLC. Further, it also provides polymorph to Anagliptin or a pharmaceutically acceptable salt thereof and a method for the preparation thereof.

In another aspect of the present invention is to provide a process for the preparation of Anagliptin:

![Formula I](image)

or pharmaceutically acceptable salt thereof,

The process includes the reaction of amino pyrrolidine of formula VI:

![Formula VI](image)

with pyrazole acid of formula III:

![Formula III](image)
using carbonyldiimidazole in presence of base in chlorinated solvent to provide Anagliptin or a pharmaceutically acceptable salt thereof having purity greater than or equal to 99%.

In another aspect of the present invention provides Anagliptin or a pharmaceutically acceptable salt thereof having purity greater than or equal to 99%.

In another aspect of the present invention provides a novel polymorph of Anagliptin or a pharmaceutically acceptable salt thereof.

In another aspect of the present invention provides a crystalline form of Anagliptin or a pharmaceutically acceptable salt thereof having an X-ray diffraction pattern according to Figure 1, which is expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a copper Kα-radiation source, wherein said X-ray powder diffraction pattern includes two or more peaks selected from the group comprising of peaks with 2 theta angles of 9.99, 16.50, 17.54, 18.75, 19.29, 20.17, and 25.29 ± 0.2.

In another aspect of the present invention provides a process for the preparation of crystalline Anagliptin or a pharmaceutically acceptable salt thereof, which comprises crystallization of a solid from the suspension or solution of Anagliptin or a pharmaceutically acceptable salt thereof in a solvent.

In another aspect of the present invention provides an amorphous form of Anagliptin hydrochloride, which is characterized by an X-ray diffraction pattern shown as Fig. 4.

In another aspect of the present invention provides composition of Anagliptin or a pharmaceutically acceptable salt thereof comprising 90 percent or more of particle have particle size less than or equal to 500 microns or less than or equal to 250 microns or less than or equal to 210 microns.
In another aspect of the invention provides a composition comprises Anagliptin or a pharmaceutically acceptable salt thereof of the present invention and at least one pharmaceutically acceptable carrier or excipient.

**Brief Description of the Drawings**

Figure 1 shows an illustrative example of X-ray powder diffraction pattern of a crystalline form of Anagliptin prepared according to Example 6.

Figure 2 shows an illustrative example of thermogravimetric analysis curve (TGA) thermogram pattern of a crystalline form of Anagliptin prepared according to Example 6.

Figure 3 shows an illustrative example of differential scanning calorimetry (DSC) thermogram pattern of a crystalline form of Anagliptin prepared according to Example 6.

Figure 4 shows an illustrative example of X-ray powder diffraction pattern of an amorphous form of Anagliptin hydrochloride prepared according to Example 7.

**Description of the Invention**

For purposes of the present invention, the following terms are defined below.

In general the term "catalyst" includes metal halides like potassium iodide, sodium bromide, sodium iodide and the like.

The term "suitable organic solvent" includes a mixture of one or more halogenated solvent and ethers, where the preferred solvent is a halogenated solvent.

The term "organic solvent" includes halogenated solvent.
The term "substantially free" as used herein, unless otherwise defined, refers to Anagliptin, an intermediate thereof, or salt thereof that contains dimer pyrrolidine impurity less than 5%, preferably more than about 3%, most preferably less than about 1%.

The intermediates and starting materials of the present invention may be used as free bases or its salts.

The salt or pharmaceutically acceptable salt as used herein, unless otherwise defined, refers to inorganic or organic salt. Inorganic salt may include hydrochloride, hydrobromide and the like; organic salt may include acetate, mesylate, tosylate and the like.

The term "pure" as used herein the HPLC purity of the compound measured by using HPLC technique.

The term "polymorph", unless otherwise defined, includes amorphous, crystalline and solvate of Anagliptin or a pharmaceutically acceptable salt thereof.

The term "pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical product that is generally non-toxic and is not biologically undesirable and includes that which is acceptable for veterinary use and/or human pharmaceutical use.

The salt or pharmaceutically acceptable salt as used herein, unless otherwise defined, refers to inorganic or organic salt. Inorganic salt may include hydrochloride, hydrobromide, and the like; organic salt may include acetate, mesylate, tosylate, trifluoracetate, fumarate, mandalate, lactate, glutamate, ascorbate, citrate and the like.

The term "composition" includes, but is not limited to, a powder, a suspension, an emulsion and/or mixtures thereof.
The X-ray diffraction powder patterns of the present invention were obtained using a Bruker or PANalytical export Pro Powder X-ray Diffractometer at Cu Ka radiation, having the wavelength 1.54 Å.

The intermediates and starting materials of the present invention may be used as free bases or its salts.

The intermediates and starting materials of the present invention may be used as free bases.

In one aspect of the present invention is to provide a process for the preparation of intermediate of Anagliptin, amino pyrrolidine of Formula VI,

![Formula VI](image)

or pharmaceutically acceptable salt thereof,

the process includes the steps of:

a) protecting l-amino-2-methyl propanamine with Boc-anhydride in the dichloromethane to provide l-tert-butoxycarbonylamino-2-methyl-2-propanamine of formula VII;

![Formula VII](image)

b) condensing the compound of formula VII with (S)-l-(2-chloroacetyl)pyrrolidine-2-carbonitrile of formula V

![Formula V](image)
Formula V

in presence of organic base to provide Boc-aminopyrrolidine of formula VIII; and

\[
\begin{array}{c}
\text{CN} \\
\text{O} \\
\text{HN} \\
\text{K}
\end{array}
\]

Formula VIII

c) deprotecting Boc-aminopyrrolidine using acid in the alcoholic to provide aminopyrrolidine or pharmaceutically acceptable salt thereof.

The step a) involves a process for the preparation of 1-tert-butoxycarbonylamino-2-methyl-2-propanamine of formula VII.

The present process of making the intermediate Boc-aminopyrrolidine is simple and inexpensive which involves the protection of 1-amino-2-methyl propanamine with Boc-anhydride in the dichloromethane solvent at below 15 °C, particularly at 5-10 °C to get 1-tert-butoxycarbonylamino-2-methyl-2-propanamine. The process of the present invention directly provides pure 1-tert-butoxycarbonylamino-2-methyl-2-propanamine which is free from dimer of diamine impurity of diamine of Formula B without purification step.

Dimer of diamine of formula B:

\[
\begin{array}{c}
\text{O} \\
\text{HN} \\
\text{NH} \\
\text{O}
\end{array}
\]

Formula B

The present invention provides simple process and the reaction completes in shorter period of time, for example, less than 5 hours.
The reaction of step a) involves addition of Boc-anhydride at 5 to 10 °C to the reaction mixture containing 1-amino-2-methyl propanamine i.e diamine in dichloromethane for a period of 10 minutes to 30 minutes or more to avoid exothermic reaction. The reaction may be maintained for 30 minutes to 1 hour or more at below 15 °C and then maintained for 1 to 3 hours at room temperature to avoid the formation of impurities.

After completion of the reaction, the reaction mixture may be treated with water, separated organic layer and then concentrated completely or subjected for isolation of solid.

The 1-tert-butoxycarbonylamino-2-methyl-2-propanamine , the compound of formula VII of the present invention may be used directly for further reaction.

In an embodiment, the present invention provides the 1-tert-butoxycarbonylamino-2-methyl-2-propanamine having less than 1% or less than 0.5% or less than 0.1% of dimer of diamine impurity which is represented by Formula B.

The step b) involves condensation of the 1-tert-butoxycarbonylamino-2-methyl-2-propanamine with (S)-1-(2-chloroacetyl)pyrrolidine-2-carbonitrile in presence of organic base to provide Boc-aminopyrrolidine.

The process of the present invention provides a simple and inexpensive process for preparing Boc-aminopyrrolidine with reduces formation of dimer impurity of pyrrolidine to less than 5%.

The dimer impurity of pyrrolidine of Formula A:
The condensation reaction is performed in presence of organic base such as triethyl amine, diisopropyl amine, pyridine, N-methyl pyrrolidine (NMP) and the like. The reaction may be carried out in the solvent such as chlorinated solvents like dichloromethane, dichloroethane, chloroform and chlorobenzene.

In an embodiment, the condensation reaction is performed in presence of organic base in dichloromethane solvent.

The reaction of condensation may be conducted in presence of metal catalyst, for example, sodium iodide, potassium iodide, lithium iodide and the like. Preferred catalyst for condensation reaction of the present invention is sodium iodide.

The reaction is conducted at the temperature range of between 25°C to 50 °C, or at 35°C to 40 °C. The reaction may be maintained for a period of about 1 to 5 hours to complete the reaction without affecting the formation of impurities.

After completion of the reaction, the reaction mixture may be treated with water and then layers are separated. The resultant organic layer may be concentrated or subjected for solid isolation.

The step c) involves the deprotection of Boc-aminopyrrolidine using acid in alcoholic solvent to provide aminopyrrolidine of Formula VI or pharmaceutically acceptable salt thereof.
The acid used for deprotection includes but are not limited to inorganic acid such as hydrochloric acid, hydrobromic acid, and the like; organic acid such as acetic acid, formic acid and the like.

The alcoholic solvent is selected from the group of methanol, ethanol, isopropyl alcohol, n-butanol and phenol. In an embodiment, the present invention involves use of the acid is hydrochloric acid and the alcohol is isopropyl alcohol.

The reaction may be carried out at elevated temperature in the range of between 35 to 70 °C. The reaction may be maintained at elevated temperature range for a period of about 1 to 5 hours or more. The resultant reaction mixture may be cooled to temperature between the 10 °C to 15 °C and maintained for a period of about 30 minutes or more to increase the precipitation of solid.

The resultant compound aminopyrrolidine of the present invention may have the purity greater than 98 % and dimer impurity less than 3% or less than 1%.

In another aspect of the present invention relates to a process for the aminopyrrolidine of Formula VI

![Formula VI](attachment:formula.png)

or pharmaceutically acceptable salt thereof, the process includes the steps of:

a) condensing 1-tert-butoxycarbonylamino-2-methyl-2-propanamine with (S)-l-(2-chloroacetyl)pyrrolidine-2-carbonitrile of formula V:
in presence of organic base to provide Boc-aminopyrrolidine of formula VIII; and

b) deprotecting compound of Boc-aminopyrrolidine using acid in alcoholic solvent to provide aminopyrrolidine or pharmaceutically acceptable salt thereof.

The condensation reaction is performed in presence of organic base such as diisopropyl amine and in solvent such as dichloromethane at a temperature range between 35 to 40 °C. The reaction of condensation is conducted in presence of metal catalyst, for example, sodium iodide.

After completion of the condensation reaction, the reaction mixture may be combined with water and then layers are separated. The resultant organic layer may be concentrated or subjected for solid isolation.

The deprotection of Boc-aminopyrrolidine using acid, for example, hydrochloric acid, the isopropyl alcoholic solvent to provide aminopyrrolidine or pharmaceutically acceptable salt thereof.

The deprotection reaction may be carried out at elevated temperature in the range of between 35 to 70 °C or more. The reaction may be maintained at elevated temperature range for a period of about 1 to 5 hours or more. The resultant reaction mixture may be
cooled to in the temperature in between 10°C to 15°C and maintained for a period of about 30 minutes or more to increase the precipitation of solid.

The resultant aminopyrrolidine of the present invention may have the purity greater than 98 % and dimer impurity less than 3% or less than 1%.

In another aspect of the present invention relates to a process for the preparation of Anagliptin or a pharmaceutically acceptable salt thereof, the process includes the steps of:

a) condensing 1-tert-butoxycarbonylamino-2-methyl-2-propanamine with (S)-l-(2-chloroacetyl)pyrrolidine-2-carbonitrile in presence of organic base to provide Boc-aminopyrrolidine;
b) deprotecting Boc-aminopyrrolidine using acid in alcoholic solvent to provide aminopyrrolidine or pharmaceutically acceptable salt thereof; and
c) conversion of aminopyrrolidine to pure Anagliptin or a pharmaceutically acceptable salt.

The process of the present invention reduces formation of dimer impurity to less than 5%. The condensation reaction is performed in presence of organic base such as such as diisopropyl amine, and in solvent such as dichloromethane.

The deprotection of Boc-aminopyrrolidine using acid such as hydrochloric acid in alcoholic solvent such as isopropyl alcohol to provide aminopyrrolidine pharmaceutically acceptable salt thereof at an elevated temperatures.

The resultant aminopyrrolidine is useful for the preparation of Anagliptin or a pharmaceutically acceptable salt thereof. The process of Anagliptin is schematically presented in the following scheme 1:
The resultant Anagliptin or a pharmaceutically acceptable salt thereof obtained from the present invention is useful for pharmaceutical composition.

In another aspect of the present invention relates to a process for the purification of Boc-aminopyrrolidine or a pharmaceutically acceptable salt thereof substantially free from its dimer impurity of Formula A.
the process includes the steps of:

a) providing suspension or solution of Boc-aminopyrrolidine in ether solvent;
b) cooling the reaction mixture of step a) to below 15 °C; and
c) recovering the pure Boc-aminopyrrolidine or a pharmaceutically acceptable salt thereof substantially free from its dimer impurity of formula A.

The step a) involves providing suspension or solution of Boc-aminopyrrolidine in ether solvent.

A suspension or solution of Boc-aminopyrrolidine in ether solvent may be used directly from the reaction mass from the previous step or isolated Boc-aminopyrrolidine is taken into ether solvent. Ether solvent may comprise methyl tertiary butyl ether, diethyl ether, dimethyl ether, methyl ethyl ether, anisole, tetrahydrofuran or mixtures thereof. The suspension includes syrup of the reaction mass.

The suspension or solution of Boc-aminopyrrolidine may be provided at temperature in the range of 20 °C to the boiling point of the solvent.

The suspension or solution of Boc-aminopyrrolidine may also be provided by dissolving or making the suspension of Boc-aminopyrrolidine in a desired solvent, followed by concentration to a desired extent to produce a suspension or syrup.

The step b) involves cooling the reaction mixture of step a) to below 15 °C to 0°C.

The resultant suspension or solution may be cooled to lower temperature in the range of below 15 °C to 0 °C. The obtained suspension may be maintained at the same temperature for a period of about 30 minutes to 2 hours or more to increase the precipitation of solid with purity greater than or equal to 95%.

The step c) involves recovering the pure Boc-aminopyrrolidine or a pharmaceutically acceptable salt thereof substantially free from its dimer impurity of formula A.
The pure Boc-aminopyrrolidine may be isolated by the techniques known in the art. For example, it may be isolated by using filtration by gravity or by suction, centrifugation, decantation, and the like. For example, the Boc-aminopyrrolidine may be isolated by filtering the cold suspension obtained in (b) at temperature below 15 °C.

After isolation, the solid may optionally be washed with the same solvent from which it is isolated. A wet solid obtained from (c) may be dried in a tray dryer, vacuum oven, air oven, fluidized bed dryer, spin flash dryer, flash dryer, and the like. The drying may be carried out at temperature range in between 30 °C to 85 °C, optionally under reduced pressure. The drying may be carried out for any time periods, such as, for example, for about 1 to about 10 hours, or longer, to give the desired compound Boc-aminopyrrolone or pharmaceutically acceptable salt.

In another aspect of the present invention relates to a process for the preparation of Anagliptin substantially free of impurity A,

the process includes the steps of:

a) providing suspension or solution of Boc-aminopyrrolidine in ether solvent; and
b) cooling the reaction mixture of step a) to temperature below 15 °C; and
c) recovering the pure Boc-aminopyrrolidine or a pharmaceutically acceptable salt free from its dimer impurity of formula A.
d) conversion of pure Boc-aminopyrrolidine to pure Anagliptin.

The resultant Boc-aminopyrrolone compound of formula VIII is useful for the preparation of aminopyrrolidine of formula VI and Anagliptin, or a pharmaceutically acceptable salt thereof. The process of Anagliptin is schematically presented in the following scheme 2:
The solvent is used in quantities sufficient to make the solution or slurry of the compound under the specific reaction conditions, wherein the solvent quantities may about 3:1 to about 7:1 vis-a-vis reactants quantity.

The resultant Anagliptin or a pharmaceutically acceptable salt thereof obtained from the present invention is useful for pharmaceutical composition.

In another aspect of the present invention is to provide a process for the preparation of Anagliptin:

or pharmaceutically acceptable salt thereof,
the process includes the reaction of amino pyrrolidine of formula VI:
with pyrazole acid of formula III:

using carbonyldiimadazole in presence of base in chlorinated solvent to provide
Anagliptin or a pharmaceutically acceptable salt thereof.

The reaction may be conducted at a temperature range of in between 25°C to 60°C or 25°C to 40°C in the solvent. The reaction may be carried out for a period of about 1 to 5 hours or more.

The chlorinated solvent is selected from dichloromethane, dichloroethane, chloroform, chlorobenzene and the like. Further, the chlorinated solvent may be mixture of solvent with ethers such as dimethyl ether, diethyl ether, dioxane and the like.

In another embodiment, the Anagliptin or a pharmaceutically acceptable salt shown the purity more than 99% when measured by HPLC.

In another aspect of the invention the process for preparation of Anagliptin or a pharmaceutically acceptable salt thereof, the process includes the steps of:

i) reaction between pyrazole acid and carbonyldiimadazole in the solvent; and

ii) addition of a mixture of aminopyrrolidine and base in a solvent to the mixture of step i) to afford Anagliptin or a pharmaceutically acceptable salt thereof.
The mixture of aminopyrrolidine, base and solvent may be prepared at a temperature range in between 15°C to 25°C. The mixture may be stirred for a period of 30 minutes 3 hours or more at a lower temperature. The solvent may be selected from the group of chlorinated solvent, for example, dichloromethane. The base may be selected from inorganic base or organic base. The inorganic base includes but are not limited to sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium hydroxide, potassium bicarbonate and the like; the organic base may be selected from triethyl amine, diisopropyl amine, methyl amine, pyridine, N-methyl pyrrolidine and the like.

The obtained aminopyrrolidine mixture is added to the reaction mixture of pyrazole acid derivative of step (i) at a temperature range is in between of 20°C to 60 °C or at 25°C to about 35 °C. Then the reaction mixture may be stirred for a period of 30 minutes to 2 hours or more for the completion of the reaction.

After completion of the reaction, the reaction mixture may be subjected for isolation of solid by using suitable techniques such as column chromatography and concentration.

In another aspect of the present invention provides Anagliptin or a pharmaceutically acceptable salt thereof having purity greater than or equal to 99%.

The Anagliptin or a pharmaceutically acceptable salt obtained from the present invention has purity greater than or equal to 99.3%. The inventors of the present invention found that the reaction of pyrazole acid derivative and amino pyrrolidine and other conditions like crystallization of solid gives higher purity.

In another aspect of the present invention relates to pharmaceutical composition comprising Anagliptin or a pharmaceutically acceptable salt, which is substantially free from its dimer pyrrolidine impurity, and pharmaceutically acceptable carriers and/or diluents thereof, and if desired, other active ingredients, which may be administered
orally, intravascularly, subcutaneously, intramuscularly or topically for the treatment of type 2 diabetes in a mammal in need thereof.

In another aspect of the present invention provides a polymorph of Anagliptin or a pharmaceutically acceptable salt thereof.

Further, the present invention provides polymorphs of Anagliptin or a pharmaceutically acceptable salt thereof includes crystalline Anagliptin, amorphous Anagliptin, crystalline pharmaceutically acceptable salt of Anagliptin and amorphous pharmaceutically acceptable salt of Anagliptin and solvate thereof.

In another aspect of the present invention provides a crystalline form of Anagliptin or a pharmaceutically acceptable salt thereof having an X-ray diffraction pattern according to Figure 1, which is expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a copper K a-radiation source, wherein said X-ray powder diffraction pattern includes two or more peaks selected from the group comprising of peaks with 2 theta angles of 9.99, 16.50, 17.54, 18.75, 19.29, 20.17, and 25.29 ± 0.2° theta.

The XRPD characteristic peaks of the crystalline form of Anagliptin or a pharmaceutically acceptable salt further defined from the Table 1:

<table>
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<tr>
<th>°2 Theta</th>
<th>d-spacing</th>
<th>Rel. Intensity [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.89</td>
<td>9.93</td>
<td>21.15</td>
</tr>
<tr>
<td>9.99</td>
<td>8.85</td>
<td>43.03</td>
</tr>
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<td>11.22</td>
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<td>15.20</td>
<td>5.82</td>
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<td>5.37</td>
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<td>16.77</td>
<td>5.28</td>
<td>19.32</td>
</tr>
<tr>
<td>17.54</td>
<td>5.05</td>
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<tr>
<td>18.75</td>
<td>4.73</td>
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<td>20.17</td>
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</tr>
<tr>
<td>25.99</td>
<td>3.42</td>
<td>39.91</td>
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</tbody>
</table>
The crystalline form of Anagliptin or a pharmaceutically acceptable salt thereof, which is characterized by thermogravimetric analysis (TGA) represented as Figure 2. The TGA shows that the compound contains less than 0.5% of water/solvent.

The crystalline form of Anagliptin or a pharmaceutically acceptable salt thereof, which is characterized by differential scanning calorimetry (DSC) has an endotherm peak at about 118 °C and the same is shown by the Figure 3.

In another aspect of the present invention provides a process for the preparation of crystalline Anagliptin or a pharmaceutically acceptable salt thereof, comprising crystallization of a solid from the suspension or solution of Anagliptin or a pharmaceutically acceptable salt thereof in a solvent.

The starting material used for the preparation of crystalline polymorph of Anagliptin or pharmaceutically acceptable salt thereof may be in form of amorphous, syrup mass or in solution obtained directly from the reaction or in form of solvate.

The solvent used for the crystallization of solid includes and is not limited to alcohol such as methanol, ethanol, isopropyl alcohol, n-butanol and the like; esters such as ethyl acetate, isopropyl acetate and the like; chlorinated solvent such as dichloromethane, dichloroethylene, chloroform, chlorobenzene and the like; ether such as tetrahydrofuran, diethyl ether, methyl tertiary butyl ether, dioxane and the like; ketone such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; hydrocarbon such as n-hexane, cyclohexane, heptane, toluene and the like; water or in combination thereof.

The techniques for crystallization include recrystallization, anti-solvent technique, sudden cooling, and the like. In an embodiment, the present invention produces crystalline Anagliptin or a pharmaceutically acceptable salt thereof from the recrystallization technique.
In another aspect of the present invention provides a process for the preparation of crystalline Anagliptin or a pharmaceutically acceptable salt thereof, the process includes the steps of:

a) providing solution of Anagliptin or a pharmaceutically acceptable salt in an ester solvent;

b) cooling the solution of step a);

c) recovering the crystal solid from the step b).

The solution may be provided by the dissolution of compound in an ester or may be directly obtained from the reaction. The dissolution may be carried out at a temperature range in between 30°C to 90°C or 50°C to 85°C. The solution may be treated with carbon and may be filtered through hyflo to provide clear solution.

The resultant solution is cooled to a temperature range in between of 0°C to 15°C and stirred for a period of about 30 minutes to 1 hour or more to influence the yield of the solid and crystallinity.

The resultant solid of step b) may be separated / recovered by using suitable techniques such as filtration by gravity or by suction, centrifugation, decantation, and the like. After separation, the solid may optionally be washed with suitable solvent such as isopropyl acetate.

The wet solid may optionally be further dried. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer and the like. The drying may be carried out at temperatures range 35°C to 60°C or 40°C to 45°C. The drying can be carried out for any time periods necessary for obtaining a desired weight consistent, such as from about 1 to about 8 hours, or longer.

In another aspect of the present invention provides an amorphous form of Anagliptin or a pharmaceutically acceptable salt thereof. In an embodiment, the present invention
provides an amorphous form of Anagliptin hydrochloride, which is characterized by an X-ray diffraction pattern shown as Figure 4.

In another aspect of the present invention provides composition of Anagliptin or a pharmaceutically acceptable salt thereof comprising 90 percent or more of particle have particle size less than or equal to 500 microns or less than or equal to 250 microns or less than or equal to 210 microns.

The determined particle size D90 less than or equal to 500 microns shows high solubility, good powder flowability and uniform particle distribution which are advantages characteristic for stable formulation.

In another aspect of the present invention provides composition of Anagliptin or a pharmaceutically acceptable salt thereof comprising 50 percent (D50) or more of particles have particle size less than 200 or less than 100 microns.

In another aspect of the present invention provides composition of Anagliptin or a pharmaceutically acceptable salt thereof comprising 10 percent (D10) or more of particles have particle size less than 100 or less than 50 microns or less than 25 microns.

In another aspect of the present invention to provides a pharmaceutical composition comprises Anagliptin or a pharmaceutically acceptable salt thereof of the present invention and at least one pharmaceutically acceptable excipient or carrier.

The polymorphs of the present invention can be formulated as solid compositions for oral administration in the form of capsules, tablets, pills, powders or granules. In these compositions, the active product according to the invention is mixed with one or more pharmaceutically acceptable excipients. The drug substance can be formulated as liquid compositions for oral administration including for example solutions, suspensions, syrups, elixirs and emulsions, containing inert diluents, solvents or vehicles such as water, sorbitol, glycerine, propylene glycol or liquid paraffin, may be used.
The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous, sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilization may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilizing agents in the composition, by irradiation or by heating. They may be prepared in the form of sterile compositions, which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

Pharmaceutically acceptable excipients that are of use in the present invention include but are not limited to diluents such as starch, pregelatinized starch, lactose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar and the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, pregelatinized starch and the like; disintegrants such as starch, sodium starch glycolate, pregelatinized starch, crospovidone, croscarmellose sodium, colloidal silicon dioxide and the like; lubricants such as stearic acid, magnesium stearate, zinc stearate and the like; glidants such as colloidal silicon dioxide and the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants, complex forming agents such as various grades of cyclodextrins, resins; release rate controlling agents such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, ethyl cellulose, methyl cellulose, various grades of methyl methacrylates, waxes and the like. Other pharmaceutically acceptable excipients that are of use include but not limited to film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants and the like.

The present invention may further be illustrated by the following examples which may be provided merely to be exemplary of the invention and do not limit the scope of the
invention. Certain modifications and equivalents may be apparent to those skilled in the art and may be intended within the scope of the present invention.

EXAMPLES

Example 1: A process for preparing Boc-aminopyrrolidine

To the mixture of 1-amino-2-methyl propanamine (500 gm) in dichloromethane (2.5 L) at 5-10 °C was added Boc-anhydride solution slowly (310 gm in 0.5 L dichloromethane). The reaction mixture was maintained at the same temperature for 1 hour. After 1 hour, reaction mixture was brought to 25-30 °C and maintained for 3 hours. To the reaction mixture, water (1.5 L) was added and continued stirring. After 30 minutes, separated organic layer and distilled the solvent to get 1-tert-butoxycarbonylamino-2-methyl-2-propanamine residue in dichloromethane.

To the above residue, dichloromethane (3.5 L), (S)-l-(2-chloroacetyl)pyrrolidine-2-carbonitrile (chloro pyrrolidine) (400 gm), sodium iodide (334 gm), and diisopropyl amine (226 gm) were added. The reaction mixture was heated to 35-40 °C and maintained for 5 hours. The reaction mixture was cooled to 25-30 °C and water (2.5 L) was added and stirred the solution for 30 minutes. The organic layer was separated and distill-off the solvent to get the title compound (850 gm).

HPLC purity: >90 %
Dimer impurity: 2.5%

Example-2: A process for preparing amino pyrrolidine

To the mixture of Boc-aminopyrrolidine (100 gm) in isopropyl alcohol (1000 ml), aqueous hydrochloric acid (80.4 gm) were added. The reaction mixture was heated to 60-65 °C and maintained for 5 hours. The mixture was cooled to 40-45 °C and then added isopropyl alcohol (200 ml). The mixture was further cooled to 5-10 °C and maintained
for 2 hours. The solid was filtered and washed with chilled isopropyl alcohol to get pure amino pyrrolidine dihydrochloride (72.1 gm).

**HPLC purity**: 98%

**Dimer impurity**: 1%

**Example 3**: A process for preparing Boc-aminopyrrolidine

To the mixture of 1-amino-2-methyl propanamine (500 gm) in dichloromethane (2.5 L) at 5-10 °C was added Boc-anhydride solution slowly (310 gm in 0.5 L dichloromethane). The reaction mixture was maintained at the same temperature for 1 hour. After 1 hour, reaction mixture was brought to 25-30 °C and maintained for 3 hours. To the reaction mixture, water (1.5 L) was added and continued stirring. After 30 minutes, separated organic layer and distilled the solvent to get 1-tert-butoxycarbonylamino-2-methyl-2-propanamine residue in dichloromethane.

To the above residue, dichloromethane (3.5 L), (S)-l-(2-chloroacetyl)pyrrolidine-2-carbonitrile (chloro pyrrolidine) (400 gm), sodium iodide (334 gm), and diisopropyl amine (226 gm) were added. The reaction mixture was heated to 35-40 °C and maintained for 5 hours. The reaction mixture was cooled to 25-30 °C and water (2.5 L) was added and stirred the solution for 30 minutes. The organic layer was separated and distill-off the solvent till syrupy mass was observed.

**Dimer impurity**: 2.5%

**Example-4**: A process purification of Boc-aminopyrrolidine of Formula VIII

Methyl tertiary butyl ether (2.5 L) was added to the Boc-aminopyrrolidine and cooled the reaction mixture to 5-10 °C. The reaction mixture was maintained for 2 hours at 5-10 °C, filtered the solid and washed with chilled methyl tertiary butyl ether (500 ml) to get pure Boc-aminopyrrolidine (620 gm).

**HPLC purity**: 98.5%

**Dimer impurity**: 0.62%
Example-5: A process for preparing amino pyrrolidine

To the mixture of Boc-aminopyrrolidine (100 gm) obtained from the example-2 in isopropyl alcohol (1000 ml), aqueous hydrochloric acid (80.4 gm) were added. The reaction mixture was heated to 60-65 °C and maintained for 5 hours. The mixture was cooled to 40-45 °C and then added isopropyl alcohol (200 ml). The mixture was further cooled to 5-10 °C and maintained for 2 hours. The solid was filtered and washed with chilled isopropyl alcohol to get pure amino pyrrolidine dihydrochloride (72.1 gm).

**HPLC purity**: 99.1%,

**Dimmer impurity**: 0.08%.

Example 6: A process for preparing Anagliptin and its crystalline form

To the mixture of pyrazole acid (40 gm) in dichloromethane (1200 ml) carbonyldiimidazole (43.9 gm) was added and stirred for 4 hours at 25-35 °C. In another RBF added amino pyrrolidine (67.1 gm) and dichloromethane (400 ml) and cooled the reaction mass to 10-15°C and then triethyl amine (114.2 gm) was added. This reaction mass was added to above pyrazole acid mass and maintained the reaction at 25-35 °C for 2 hours. After completion of the reaction, the reaction mixture was washed with water (2x640 ml). Then the organic layer was distilled to get syrupy mass. The product was dissolved in isopropyl acetate (200ml) at 50-85 °C and then cooled to room temperature followed by cooled to 10-15 °C. The resultant solid was filtered and dried to get Anagliptin (53.2 gm) as white color crystalline powder.

**HPLC purity**: 99.38%

**XRD**: Crystalline form represented as Figure 1

**TGA**: represented as Figure 2

**DSC**: 118.5 °C represented as Figure 3

**M.P**: 118.2 to 118.6 °C

**Particle size distribution**: $d_{(0.9)}$: 205.291 microns; $d_{(0.5)}$: 95.024 microns; $d_{(0.1)}$: 21.658 microns.
Example-7: Preparation Anagliptin Hydrochloride

To the solution of Anagliptin (5.0 gm) in dioxane (15 ml) isopropyl alcohol hydrochloride (2.0 gm) was added. To this suspension diethyl ether (50 ml) was added and stirred for 1 hour at 25-30 °C. Filtered the solid and washed with diethyl ether, and dried to get Anagliptin hydrochloride (4.0 gm).

XRD: Amorphous and is represented as Figure 4

Moisture content: 6.46% w/w

HPLC purity: 99.10%
We Claim:

1. A process for the preparation of a compound amino pyrrolidine of Formula VI:

```
HN
O
N

    NC

NH2
```

Formula VI

or pharmaceutically acceptable salt thereof, the process comprising;

a) protecting l-amino-2-methyl propanamine with Boc-anhydride in the dichloromethane solvent to obtain l-tert-butoxycarbonylamino-2-methyl-2-propanamine of formula VII;

```
O

    O

H2N

NH
```

Formula VII

b) reacting the compound of formula VII with (S)-l-(2-chloroacetyl)pyrrolidine-2-carbonitrile of formula V

```
Cl

    O

N

    NC
```

Formula V

in presence of organic base to provide Boc-aminopyrrolidine of formula VIII;

```
O

    O

N

    NC

H
```

Formula VIII

c) deprotecting Boc-aminopyrrolidine using acid in alcoholic solvents to obtain aminopyrrolidine and optionally converting to pharmaceutically acceptable salt thereof.
2. The process of claim 1, wherein the protection of step a) is performed at the temperature in the range of 5-10 °C.

3. The process of claim 1, wherein the compound 1-tert-butoxycarbonylamino-2-methyl-2-propanamine having less than 1% of a compound of formula B of dimer of diamine impurity.

   ![Formula B](image)

4. The process of claim 1, wherein the condensation of step b) is performed in the dichloromethane solvent.

5. The process of claim 1, wherein the organic base is diisopropylamine.

6. The process of claim 1, wherein the acid is hydrochloric acid and alcoholic is isopropyl alcohol.

7. A compound 1-tert-butoxycarbonylamino-2-methyl-2-propanamine having purity greater than or equal to 98% and containing dimer impurity of Formula B less than or equal to 1% when determined by HPLC

   ![Formula B](image)

8. The process of claim 1, wherein the compound aminopyrrolidine is further converted to Anagliptin or a pharmaceutically acceptable salt thereof.

9. A process for the preparation of compound aminopyrrolidine of Formula VI
or pharmaceutically acceptable salt thereof, the process comprising:

a) condensing of 1-tert-butoxycarbonylamino-2-methyl-2-propanamine with (S)-1-(2-chloroacetyl)pyrrolidine-2-carbonitrile of formula V:

\[
\text{Formula V}
\]

in presence of organic base to obtain Boc-aminopyrrolidine of formula VIII; and

\[
\text{Formula VIII}
\]

b) deprotecting Boc-aminopyrrolidine using acid in the alcoholic solvent to obtain aminopyrrolidine or pharmaceutically acceptable salt thereof.

10. The process of claim 9, wherein the organic base is diisopropylamine.

11. A process for the purification of Boc-aminopyrrolidine of formula VIII or a pharmaceutically acceptable salt thereof

\[
\text{Formula VIII}
\]

substantially free from its dimer impurity of Formula A
the process comprising:

a) providing suspension or solution of Boc-aminopyrrolidine in ether solvent;

b) cooling the reaction mixture of step a) to below 15 °C; and

c) recovering the pure Boc-aminopyrrolidine or a pharmaceutically acceptable salt thereof substantially free from its dimer impurity of formula A.

12. The process of claim 11, wherein the ether solvent is methyl tertiary butyl ether, diethyl ether, dimethyl ether, methyl ethyl ether, anisole, tetrahydrofuran or a mixture thereof.

13. The process of claim 11, wherein the temperature is in the range of 5 to 10 °C.

14. A compound Boc-aminopyrrolidine having greater than or equal to 99% of HPLC purity and less than or equal to 1% of dimer impurity of formula A.
15. The process of claim 11, wherein the Boc-aminopyrrolidine is further converted to Anagliptin.

16. A process for the preparation of Anagliptin:

\[
\text{Formula I}
\]

or pharmaceutically acceptable salt thereof, the process comprising: reaction of amino pyrrolidine of formula VI:

\[
\text{Formula VI}
\]

with pyrazole acid of formula III:

\[
\text{Formula III}
\]

using carbonyldiimidazole in presence of base in chlorinated solvent to provide Anagliptin or a pharmaceutically acceptable salt thereof

17. The process of claim 16, wherein the chlorinated solvent is dichloromethane.

18. The process of claim 16, wherein the reaction is carried out at the temperature range of between 25 to about 40 °C.

19. The process of claim 16, wherein the base is triethylamine.
20. The process of claim 16, wherein the purity of Anagliptin or a pharmaceutically acceptable salt thereof is greater than or equal to 99.3%.

21. A crystalline form of Anagliptin or a pharmaceutically acceptable salt thereof, which is characterized by characteristic peaks of X-ray powder diffraction pattern comprising two or more peaks of 9.99, 16.50, 17.54, 18.75, 19.29, 20.17, and 25.29 ± 0.2° theta.

22. The compound of claim 21, wherein crystalline form of Anagliptin or a pharmaceutically acceptable salt thereof, having particle size distribution crystalline form of Anagliptin, wherein D90 is less 500 microns, D50 is less 200 microns and D10 is less 100 microns.

23. The compound of claim 21, further characterized in that it has an endotherm peak at about 118 °C as determined by differential scanning calorimetry represented as Figure 3.

24. The compound of claim 21, further characterized in that it has Thermogravimetric analysis represented in Figure 2.

25. A process for the preparation of crystalline Anagliptin or a pharmaceutically acceptable salt thereof, comprising crystallization Anagliptin or a pharmaceutically acceptable salt thereof in a solvent, which is ester solvent.

26. The process of claim 25, wherein the solvent is isopropyl acetate.

27. An amorphous form of Anagliptin or a pharmaceutically acceptable salt thereof represented as Figure 4.
Fig. 4