Abstract: The present invention provides amorphous form of Selexipag and process for the preparation thereof. The present invention also provides amorphous co-precipitate of Selexipag with a pharmaceutically acceptable excipient, process for the manufacture of such pharmaceutical composition.

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AMORPHOUS SELEXIPAG AND PROCESS FOR PREPARATION THEREOF

This application claims the priority from provisional Indian patent application number 2086/MUM/2015 which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to amorphous form of Selexipag (I) and the process for preparation thereof.

![Image of Selexipag (I)]

The present invention also relates to amorphous co-precipitates of Selexipag with pharmaceutically acceptable excipients and the process for the preparation thereof.

BACKGROUND OF THE INVENTION

2-{4-[N-(5,6-diphenylpyrazin-2-yl)-N-isopropyl-amino]butyloxy}-N-(methyl sulfonyl) acetamide (herein "Selexipag") also known as Uptravi®, has a CAS number of 475086-01-2, a molecular formula of C_{26}H_{32}N_{4}O_{4}S and the molecular weight is 496.6 g/mol.

Selexipag, originally discovered and synthesized by Nippon Shinyaku, is a potent, orally available, selective IP prostacyclin receptor agonist.
Selexipag selectively targets the prostacyclin receptor (also called IP-receptor). The IP receptor is one of five types of prostanoid receptor. Prostacyclin activates the IP receptor inducing vasodilation and inhibiting proliferation of vascular smooth muscle cells. Selexipag, unlike prostacyclin analogs, is selective for the IP receptor over other prostanoid receptors. In preclinical models selective IP receptor agonist has shown to maintain efficacy and reduce the risk of side effects mediated by activation of other prostanoid receptors, such as EP1 and EP3 receptors.

U.S. Patent No. 7,205,302 B2 discloses Selexipag and its pharmaceutically acceptable salts. Processes to make Selexipag and pharmaceutically acceptable salts are described. Also described are compositions containing Selexipag and method of treating pulmonary arterial hypertension.

U.S. Patent No. 8,791,122 B2 discloses novel crystalline forms of Selexipag viz. Form I, II and III. These novel crystalline forms are characterized by powder X-ray Diffraction (P-XRD) and scanning electron microscope (SEM).

The process described in the prior art reports novel crystalline forms of Selexipag. The prior art methods have failed to describe the process for the preparation of a pure amorphous form of Selexipag. Hence, the need was felt to develop process for preparation of pure amorphous form of Selexipag.

Polymorphism is the ability of a solid material to exist in more than one form or crystal structure. Amorphous solids consist of disordered arrangement of molecules and do not possess a distinguishable crystal lattice. The amorphous form is generally more soluble than the crystalline form and thus contributes more in the bioavailability.
An important solid state property of a pharmaceutical compound is its rate of dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's stomach fluid may have therapeutic consequences since it imposes an upper limit on the rate at which an orally-administered pharmaceutical compound may reach the patient's bloodstream. The rate of dissolution is a consideration in formulating syrups, elixirs and other liquid medicaments. The solid state form of a compound may also affect its behavior on compaction and its storage stability.

It has been disclosed in the art that the amorphous forms of a number of pharmaceutical compounds exhibit superior dissolution characteristics and in some cases different bioavailability patterns compared to crystalline forms [Konno T., Chem. Pharm. Bull., 38, 2003 (1990)]. For some therapeutic indications, one bioavailability pattern may be favored over another.

Solvent medium and mode of isolation play very important roles in obtaining one polymorphic form over another.

Hence, there is a need in the art for highly pure and stable amorphous form of Selexipag, a process for its preparation and a pharmaceutical composition thereof.

**OBJECTS OF THE INVENTION**

An object of the invention is to provide amorphous form of Selexipag.

Another object of the invention is to provide processes for the preparation of amorphous form of Selexipag.

Another object of the invention is to provide amorphous form of Selexipag wherein the amorphous form of selexipag is free from residual solvents.
Another object of the invention is to provide co-precipitates of amorphous Selexipag with the pharmaceutically acceptable excipients.

Another object of the invention is to provide the processes for the preparation of amorphous form of Selexipag with co-precipitates.

Yet another object of the invention is to provide the processes for the preparation of Selexipag or amorphous co-precipitates of Selexipag with the pharmaceutically acceptable excipients.

Yet another object of the invention is to provide pharmaceutical compositions; particularly in powder form; comprising amorphous form of Selexipag or amorphous co-precipitates of Selexipag, having improved solubility properties and hence have improved bioavailability.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Fig.1 shows X-ray powder diffractogram (XRD) of amorphous Selexipag prepared according to the Example 1.

Fig.2 shows X-ray powder diffractogram (XRD) of amorphous Selexipag prepared according to the Example 2.

Fig.3 shows X-ray powder diffractogram (XRD) of amorphous co-precipitate of Selexipag with polyvinylpyrrolidone (PVP) in a weight ratio of 1:1 prepared according to Example 3.
Fig. 4 shows X-ray powder diffractogram (XRD) of amorphous co-precipitate of Selexipag with polyvinylpyrrolidone (PVP) in a weight ratio of 1:0.5 prepared according to Example 4.

DETAILED DESCRIPTION OF THE INVENTION

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

Unless stated to the contrary, any use of the words such as "including," "containing," "comprising," "having" and the like, means "including without limitation" and shall not be construed to limit any general statement that it follows to the specific or similar items or matters immediately following it. Embodiments of the invention are not mutually exclusive, but may be implemented in various combinations. The described embodiments of the invention and the disclosed examples are given for the purpose of illustration rather than limitation of the invention as set forth the appended claims.

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

"co-precipitate" means that the compositions comprise amorphous Selexipag together with at least one pharmaceutically acceptable carrier, being prepared by removing solvent from solution containing both of them.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition 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 term "composition" includes, but is not limited to, a powder, a suspension, an emulsion and/or mixtures thereof. The term composition is intended to encompass a product containing the specified ingredients in the specified amounts, as well as any product, which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. A "composition" may contain a single compound or a mixture of compounds. A "compound" is a chemical substance that includes molecules of the same chemical structure regardless of its three dimensional orientation. Thus, it may be used to indicate racemates, stereoisomers, or both.

The term "pharmaceutical composition" is intended to encompass a product including the active ingredient(s), pharmaceutically acceptable excipients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing the active ingredient, additional active ingredient(s), and pharmaceutically acceptable excipients.

The term "excipient" means a component of a pharmaceutical product that is not the active ingredient, such as filler, diluent, carrier, and so on. The excipients that are useful in preparing a pharmaceutical composition are preferably generally safe, non-toxic and neither biologically nor otherwise undesirable, and are acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable
excipient" as used in the specification and claims includes both one and more than one such excipient.

The term "substantially free of" in reference to a composition, as used herein, means that the absent substance cannot be detected in the composition by methods known to those skilled in the art at the time of the filing of this application.

The term "free from residual solvents" as used herein, means that the residual solvents are within permissible ICH limits suitable for pharmaceutical preparations.

According to one aspect of the invention, the present invention provides amorphous Selexipag (I).

Amorphous materials do not exhibit the three-dimensional long-range order found in crystalline materials but are structurally more similar to liquids where the arrangement of molecules is random. Amorphous solids are not crystalline and therefore do not give a definitive x-ray diffraction pattern (XRD), in addition they do not give rise to a melting point and tend to liquefy at some point beyond the glass transition point. A sample of an XRD spectrum of Selexipag obtained by the inventors is shown in Fig.1. As seen there from, the XRD pattern is highly characteristic of an amorphous solid.

According to another embodiment, the present invention provides a process for preparation of the amorphous form of Selexipag, the said process comprising:

a. providing solution of Selexipag in a solvent;

b. removing the said solvent for isolating the amorphous form of Selexipag.
In a preferred embodiment of the present invention, Selexipag used in step (a) can be either in crystalline form, or mixture of crystalline and amorphous form, solvates form or hydrates form thereof.

The solution of Selexipag may be obtained by dissolving Selexipag in a suitable solvent, or such a solution may be obtained directly from a reaction in which Selexipag is formed.

The dissolution temperature to prepare the solution of Selexipag with or without pharmaceutically acceptable excipient can range from about 10°C to reflux temperature of solvent.

The quantity of solvent used for dissolution depends on the solvent and the dissolution temperature adopted. The concentration of Selexipag in the solution may range from about 0.1 to about 0.5g/ml in the solvent, and the volume of the solvent may be kept to a minimum so as to facilitate the effective solvent removal.

The obtained solution can be optionally treated with carbon for removal of undesired color or with sodium sulfate for moisture removal.

The solution obtained above may be treated for removal of any undissolved particles by subjecting the solution to filtration, centrifugation, decantation, and other techniques. The solution may be filtered by passing through paper, glass fiber, or other membrane material, or particulate filtration medium such as celite or calcined diatomaceous earth (Hyflow).
Depending upon the equipment used and the solution properties, such as concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid crystallization.

Distillation of the solvent may be carried under high vacuum such as below 100 mmHg to below 700 mmHg, at elevated temperatures such as about 10°C to about 60°C, depending upon the solvents used for the preparing solution. Any other temperature and vacuum conditions can be used as long as there is no increase in the impurity levels of the products due to decomposition.

The drying may be done at atmospheric pressure or reduced pressures, between 100 mmHg and 700 mmHg, at temperatures such as about 30 °C to about 50°C.

The drying can be carried out for about 1 to 15 hours.

The dried material can be optionally milled to get desired particle size. Milling operation can be performed prior to drying or after the drying. Suitable milling techniques includes, air jet milling, or other conventional milling equipment.

In a preferred embodiment, the solvent used in step (a) includes but does not limit to alcohols like methanol, ethanol, isopropanol, and the like; halogenated hydrocarbons like dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; ketones like acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; esters like ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; ethers like diethyl ether, dimethyl ether, diisopropyl ether and the like; substituted cyclic ethers like 2-methyl tetrahydrofuran, tetrahydrofuran and the like; hydrocarbons such as toluene, xylene, n-heptane, cyclohexane, n-hexane and the
like; nitriles such as acetonitrile, propionitrile and the like; or mixtures thereof. Preferably, the said solvent is dichloromethane and acetone.

The removal of the solvent in step (b) may be affected at an increased temperature, preferably at reflux temperature, and/or reduced pressure.

The removal of solvent is carried out by distillation, evaporation, atmospheric distillation, distillation under vacuum such as rotary evaporator, lyophilization, Freeze drying, spray drying, Agitated thin film drying (ATFD), etc. The solid residue obtained after solvent removal may be isolated and dried using conventional methods such as Air tray drier (ATD), Vacuum Tray Drier (VTD), Fluidized bed drier (FBD), Spin Flash Drier (SFD), Flash Drier (FD), and the like. The advantages of the process include simplicity, eco-friendliness and suitability for commercial use.

According to yet another aspect of the invention there is provided a process of spray drying of selexipag that involves:

a. preparing feed stock;
b. dozing feed stock into the spray-drying instrument; and
c. carrying out the spray drying under the suitable conditions to obtain amorphous selexipag.

In the present invention, the feed stock of selexipag is prepared by either dissolving Selexipag which can be either in crystalline form, or mixture of crystalline and amorphous form, solvates form or hydrates form thereof in a suitable solvent, or such a solution may be obtained directly from a reaction in which Selexipag is formed.

In a preferred embodiment, the solvent used in step (a) includes but does not limit to alcohols like methanol, ethanol, isopropanol, and the like; halogenated hydrocarbons
like dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; ketones like acetone^ ethyl methyl ketone, methyl isobutyl ketone and the like; esters like ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; ethers like diethyl ether, dimethyl ether, diisopropyl ether and the like; substituted cyclic ethers like 2-methyl tetrahydrofuran, tetrahydrofuran and the like hydrocarbons such as toluene, xylene, n-heptane, cyclohexane, n-hexane and the like; nitriles such as acetonitrile, propionitrile and the like; or mixtures thereof. Preferably, the said solvent is dichloromethane and acetone.

The following are the parameters and conditions for carrying our spray drying:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Parameters</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Feed Pump</td>
<td>3-5 ml/min</td>
</tr>
<tr>
<td>2</td>
<td>Inlet temperature</td>
<td>35-70°C</td>
</tr>
<tr>
<td>3</td>
<td>Outlet temperature</td>
<td>35-65°C</td>
</tr>
<tr>
<td>4</td>
<td>Aspirator rate</td>
<td>50-75Nm³/h</td>
</tr>
<tr>
<td>5</td>
<td>Vacuum for conveying the dry product</td>
<td>130-250 mmWC</td>
</tr>
<tr>
<td>6</td>
<td>Atomizer</td>
<td>1.4-1.5 kg/cm²</td>
</tr>
</tbody>
</table>

According to yet another aspect of the invention there is provided a process for preparing co-precipitates of amorphous Selexipag with the pharmaceutically acceptable excipients.

The co-precipitates of the invention may have improved physicochemical characteristics that will achieve the effective delivery of Selexipag. The co-precipitates of the present invention increase the stability of the amorphous form of Selexipag and they enhance the integrity of amorphous nature in-totality throughout their life cycle.
According to another embodiment, the present invention provides a process for preparation of amorphous co-precipitate of Selexipag with a pharmaceutically acceptable excipient, the said process comprising:

a) preparation of a solution of the said Selexipag and pharmaceutically acceptable excipients in solvent;

b) removal of solvent from solution obtained in step (a) for isolating solid which is the amorphous co-precipitate of Selexipag with the said pharmaceutically acceptable excipient.

The solution of Selexipag and the pharmaceutically acceptable excipient may be obtained by dissolving the pharmaceutically acceptable excipient in solution containing Selexipag.

In a preferred embodiment of the present invention, the solvent used in step (a) includes but does not limit to alcohols like methanol, ethanol, isopropanol, and the like; halogenated hydrocarbons like dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; ketones like acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; esters like ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; ethers like diethyl ether, dimethyl ether, diisopropyl ether and the like; substituted cyclic ethers like 2-methyl tetrahydrofuran, tetrahydrofuran and the like; hydrocarbons such as toluene, xylene, n-heptane, cyclohexane, n-hexane and the like; nitriles such as acetonitrile, propionitrile and the like; or mixtures thereof.

The removal of the solvent from the solution of Selexipag and a pharmaceutical excipient in step (b) may be affected at an increased temperature, preferably at reflux temperature, and/or reduced pressure.
The removal of solvent is carried out by distillation, evaporation, atmospheric distillation, distillation under vacuum such as rotary evaporator, lyophilization, Freeze drying, spray drying, Agitated thin film drying (ATFD), etc. The solid residue obtained after solvent removal may be isolated and dried using conventional methods such as Air tray drier (ATD), Vacuum Tray Drier (VTD), Fluidized bed drier (FBD), Spin Flash Drier (SFD), Flash Drier (FD), and the like. The advantages of the process include simplicity, eco-friendliness and suitability for commercial use.

The amorphous Selexipag is also prepared by melting procedure with or without pharmaceutical excipients.

The pharmaceutically acceptable excipient that may be used for the preparation of co-precipitants includes; but not limited to, pharmaceutical hydrophilic excipient such as polyvinylprrolidone (homopolymers, also called "povidone", or copolymers of N-vinylprrolidone), gums, cellulose derivatives (including hydroxypropyl methylcellulose, hydroxypropyl cellulose and others), starches, cyclodextrins, gelatins, hycromellose phthalate, sugars, polyhydric alcohols, polyethylene glycol.

In a preferred embodiment, the weight ratio of amorphous form of Selexipag to the pharmaceutically acceptable excipient is in the range of about 1:1 to 1:0.01

The use of mixtures of more than one of the pharmaceutical excipient to provide desired release profiles or for the enhancement of stability is within the scope of this invention. Also, all viscosity grades, molecular weights, commercially available products, their copolymers, mixtures are all within the scope of this invention without limitation.
In present invention, the provided lists of solvents and pharmaceutically acceptable excipient are representative and not intended to be exhaustive or limiting. Generally, the more volatile solvents may be preferred to reduce the energy requirements for subsequent solvent removal.

The solution obtained in step (b) can be optionally treated with carbon for removal of undissolved particles.

The solution obtained above may be treated for removal of any undissolved particles by subjecting the solution to filtration, centrifugation, decantation, and other techniques. The solution may be filtered by passing through paper, glass fiber, or other membrane material, or particulate filtration medium such as celite or calcined diatomaceous earth (Hyflow).

Depending upon the equipment used and the solution properties, such as concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid crystallization.

Distillation of the solvent may be carried under high vacuum such as below 100 mmHg to below 600 mmHg, at elevated temperature from 15°C to about reflux temperature of solvent, depending upon the solvents used for the preparing solution. Any other temperature and vacuum conditions can be used as long as there is no increase in the impurity levels of the products due to decompositions etc.

According to the invention, there is provided amorphous form of Selexipag (I). Figure 1 illustrates X-ray powder diffraction (XRD) pattern of polymorph of Selexipag (I), prepared according to example 1. It demonstrates the amorphous nature of Selexipag. The X-ray diffractogram was measured on Bruker Axe, DS
advance Power X-ray Diffractometer with Cu K alpha-1 Radiation source having the wavelength 1.541 Å.

According to the invention, there is provided amorphous form of Selexipag (I). Figure 2 illustrates X-ray powder diffraction (XRD) pattern of polymorph of Selexipag (I), prepared according to example 2. It demonstrates the amorphous nature of Selexipag. The X-ray diffractogram was measured on Bruker Axe, DS advance Power X-ray Diffractometer with Cu K alpha-1 Radiation source having the wavelength 1.541 Å.

According to the invention, there is provided amorphous form of Selexipag (I) with polyvinylpyrrolidone (povidone) (1:1). Figure 3 illustrates X-ray powder diffraction (XRD) pattern of polymorph of Selexipag (I) with polyvinylpyrrolidone (povidone) (1:1), prepared according to example 3. It demonstrates the amorphous nature of Selexipag with polyvinylpyrrolidone (povidone) (1:1). The X-ray diffractogram was measured on Bruker Axe, DS advance Power X-ray Diffractometer with Cu K alpha-1 Radiation source having the wavelength 1.541 Å.

According to the invention, there is provided amorphous form of Selexipag (I) with polyvinylpyrrolidone (povidone) (1:0.5). Figure 4 illustrates X-ray powder diffraction (XRD) pattern of polymorph of Selexipag (I) with polyvinylpyrrolidone (povidone) (1:0.5), prepared according to example 4. It demonstrates the amorphous nature of Selexipag with polyvinylpyrrolidone (povidone) (1:0.5). The X-ray diffractogram was measured on Bruker Axe, DS advance Power X-ray Diffractometer with Cu K alpha-1 Radiation source having the wavelength 1.541 Å.
According to the invention, there is provided an amorphous selexipag, wherein the
D (90) particle size distributions is about 1 to 400 µ.

According to the invention, there is provided amorphous selexipag having purity of
about 99.5% or more, as determined by High Performance liquid chromatography
(HPLC).

In another aspect of the invention, the selexipag may be micronized to achieve the
better particle size distribution in order to make suitable formulation. Selexipag may be
micronized by using one or combination of the methods known in the art.

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 disclosure in any manner.

**BEST MODE OR EXAMPLES FOR WORKING OF THE INVENTION**

The present invention is described in the examples given below; further these are
provided only to illustrate the invention and therefore should not be construed to
limit the scope of the invention.

**Example 1: Preparation of Amorphous Selexipag (conversion of crystalline form
to amorphous form)**

Selexipag (5.0 gm) was dissolved in acetone (100.0 ml). The obtained solution was then
subjected to spray-drying in a spray dryer (Labultima-LU228) at an inlet temperature of
about 70° C. and an outlet temperature of about 65° C , and flow rate of 5 ml/minute
using air to produce 3.6 g of amorphous Selexipag as a white powder.

**Characterization Data:**
The resulting amorphous Selexipag is characterised by X-ray powder diffraction pattern, showing a plain halo with no well-defined peaks, as shown in Fig. 1.

**Example 2: Preparation of Amorphous Selexipag (conversion of crystalline form to amorphous form)**

Selexipag (5.0 gm) was dissolved in Dichloromethane (50.0 ml). The obtained solution was then subjected to spray-drying in a spray dryer (Labultima-LU228) at an inlet temperature of about 50° C, and an outlet temperature of about 42° C, and flow rate of 5ml/minute using air to produce 1.73 g of amorphous Selexipag as a white powder.

**Characterization Data:**
The resulting amorphous Selexipag is characterised by an X-ray powder diffraction pattern, showing a plain halo with no well-defined peaks, as shown in Fig.2.

**Example-3: Preparation of Amorphous coprecipitate of Selexipag with polyvinylpyrrolidone (PVP) (conversion of Selexipag to amorphous Selexipag with polyvinylpyrrolidone (PVP), 1:1)**

Selexipag (2.0 gm) and polyvinylpyrrolidone (PVP) (2.0 gm) were dissolved in 100 ml acetone. The obtained solution was filtered to remove the foreign particle followed by distillation of solvent using Buchi Rotavapor apparatus under vacuum. The amorphous co-precipitate of Selexipag (3.0 gm) was dried to obtain co-precipitate of amorphous Selexipag with polyvinylpyrrolidone (PVP) as pharmaceutically acceptable excipient as white solid.

**Characterization Data:**
The resulting amorphous co-precipitate of Selexipag with polyvinylpyrrolidone (1:1) is characterised by an X-ray powder diffraction pattern, showing a plain halo with no well-defined peaks, as shown in Fig.3.
Example-4: Preparation of Amorphous coprecipitate of Selexipag with polyvinylpyrrolidone (PVP) (conversion of Selixpag to amorphous Selexipag with polyvinylpyrrolidone (PVP), 1:0.5)

Selexipag (2.0 gm) and polyvinylpyrrolidone (PVP) (1.0 gm) were dissolved in 80 ml acetone. The obtained solution was filtered to remove the foreign particle followed by distillation of solvent using Buchi Rotavapor apparatus under vacuum. The amorphous co-precipitate of Selexipag (2.5 gm) was dried to obtain co-precipitate of amorphous Selexipag with polyvinylpyrrolidone (PVP) as pharmaceutically acceptable excipient as white solid.

Characterization Data:
The resulting amorphous co-precipitate of Selexipag with polyvinylpyrrolidone (1:0.5) is characterised by an X-ray powder diffraction pattern, showing a plain halo with no well-defined peaks, as shown in Fig.4.

Example 5: Preparation of Amorphous Selexipag (conversion of crystalline form to amorphous form)

In 2.0 L four necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, Selexipag (50.0 gm) was charged in dichloromethane (1000.0 ml) and the reaction mass was stirred for 10-15 mins to obtain clear solution. The obtained reaction mass was filtered. The obtained filtrate was then subjected to spray-drying in a spray dryer (Labultima-LU228) under the below conditions:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Parameters</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Feed Pump</td>
<td>3-5 ml/min</td>
</tr>
<tr>
<td>2</td>
<td>Inlet temperature</td>
<td>37-39°C</td>
</tr>
<tr>
<td>3</td>
<td>Outlet temperature</td>
<td>35-37°C</td>
</tr>
<tr>
<td>4</td>
<td>Aspirator rate</td>
<td>50-75 Nm³/h</td>
</tr>
<tr>
<td>5</td>
<td>Vacuum for conveying the dry product</td>
<td>130-250 mmWC</td>
</tr>
<tr>
<td>6</td>
<td>Atomizer</td>
<td>1.4-1.5 kg/cm²</td>
</tr>
</tbody>
</table>
Cool the cyclone at 15-25 °C and product was collected from cyclone, and further dried at 30-35°C under vacuum for 10-12 hrs to obtain 30 g of amorphous Selexipag. The obtained product is free from residual solvents.

**Characterization Data:**
The resulting amorphous Selexipag is characterized by an X-ray powder diffraction pattern, showing a plain halo with no well-defined peaks, as shown in Fig.2.

**Example 6:**

**Preparation of Amorphous Selexipag (conversion of crystalline form to amorphous form)**

In 3.0 L four necked round bottom flask equipped with mechanical stirrer, thermometer and an addition funnel, Selexipag (140.0 gm) was charged in dichloromethane (2.1 L) under nitrogen atmosphere and the reaction mass was stirred for 30 mins at 25°C to obtain clear solution. The obtained reaction mass was filtered. The obtained filtrate was then distilled at 35-40°C under 710 mmHg vacuum pressure under constant stirring, degased at 35-40°C under 710 mmHg vacuum pressure, cooled to 15-20°C under constant stirring at 710 mmHg vacuum pressure to obtain wet material. The wet material is further grinded, and dry the material under vacuum at 30-35°C cooled to room temperature at nitrogen atmosphere to obtain 110 g of amorphous Selexipag. The obtained product is free from residual solvents.

**Characterization Data:**
The resulting amorphous Selexipag is characterized by an X-ray powder diffraction pattern, showing a plain halo with no well-defined peaks, as shown in Fig.2.
We claim:

1. An Amorphous Selexipag.

2. The amorphous form of Selexipag according to claim 1, is characterized by PXRD pattern as shown in Figures 1 and 2.

3. The amorphous form of Selexipag according to claim 1, wherein the amorphous form of Selexipag is free from residual solvents.

4. The amorphous form of Selexipag according to claim 1, wherein the D(90) particle size distribution is about 1 to 400 μ.

5. A process for preparation of an amorphous form of Selexipag, the process comprising:
   a. providing a solution of Selexipag in a solvent; and
   b. removing the said solvent for isolating the solid mass, which is the amorphous form of Selexipag.

6. The process according to claim 5, wherein Selexipag used can be either in crystalline form, or mixture of crystalline and amorphous form, solvates form or hydrates form thereof.

7. The process according to claim 5, wherein the solution of Selexipag may be obtained by dissolving Selexipag in a suitable solvent, or such a solution may be obtained directly from a reaction in which Selexipag is formed.

8. The process according to claim 5, wherein the solvent is selected from group consisting of alcohols, halogenated hydrocarbons, ketones, esters, ethers,
substituted cyclic ethers, hydrocarbons including aromatic hydrocarbons, aliphatic hydrocarbons; nitriles; or mixtures thereof.

9. The process according to claim 5, wherein the removal of solvent is carried out by at least one of the following methods distillation, evaporation, atmospheric distillation, distillation under vacuum such as rotary evaporator, lyophilization, Freeze drying, spray drying, Agitated thin film drying (ATFD), etc. The solid residue obtained after solvent removal may be isolated and dried using conventional methods such as Air tray drier (ATD), Vacuum Tray Drier (VTD), Fluidized bed drier (FBD), Spin Flash Drier (SFD), and Flash Drier (FD).

10. A co-precipitate of amorphous Selexipag with a pharmaceutically acceptable excipient.

11. A co-precipitate of amorphous Selexipag with a pharmaceutically acceptable excipient namely, polyvinylpyrrolidine; characterized by their X-ray diffraction (XRD) pattern as shown in figure 3 and 4 respectively.

12. The co-precipitate of claim 10, wherein the said pharmaceutically acceptable excipients is selected from pharmaceutical hydrophilic excipients consisting of polyvinylpyrrolidone; gums; cellulose derivatives including hydroxypropyl methylcellulose and hydroxypropyl cellulose; starches; cyclodextrins; gelatins; hypromellose phthalate; sugars; polyhydric alcohols, and polyethylene glycol.

13. The co-precipitate of claim 10, wherein the weight ratio of amorphous form of Selexipag to the pharmaceutically acceptable excipient is in the range of about 1:1 to 1:0.01.
14. A process for preparation of amorphous co-precipitate of Selexipag with a pharmaceutically acceptable excipient, the said process comprising the steps of:
a) preparation of a solution of Selexipag and pharmaceutically acceptable excipients in at least one solvent; and
b) removal of solvent from solution obtained in step (a) for isolating solid mass, which is the amorphous co-precipitate of Selexipag with the said pharmaceutically acceptable excipient.

15. The process as claimed in claim 14, wherein the said Selexipag can be either in crystalline form, or mixture of crystalline and amorphous form, solvates form or hydrates form thereof.

16. The process as claimed in claim 14, wherein the said solvent is selected from the group consisting of alcohols; halogenated hydrocarbons; ketones; esters; ethers; substituted cyclic ethers; hydrocarbons including aromatic hydrocarbons, aliphatic hydrocarbons; nitriles; or mixtures thereof.

17. The process as claimed in claim 14, wherein the said pharmaceutically acceptable excipients is selected from pharmaceutical hydrophilic excipients consisting of polyvinylpyrrolidone; gums; cellulose derivatives including hydroxypropyl methylcellulose and hydroxypropyl cellulose; starches; cyclodextrins; gelatins; hypromellose phthalate; sugars; polyhydric alcohols, and polyethylene glycol.

18. The process of claim 14, wherein the weight ratio of amorphous form of Selexipag to the pharmaceutically acceptable excipient is in the range of about 1:1 to 1:0.01
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D241/20 A61K31/495 A61P9/12

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>5-9, 14-18</td>
</tr>
<tr>
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<td>17 April 2007 (2007-04-17) cited in the application example 84</td>
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E* earlier application or patent but published on or after the international filing date

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A* document member of the same patent family

Date of the actual completion of the international search

8 September 2016

Date of mailing of the international search report

16/09/2016

Name and mailing address of the ISA

European Patent Office, P.B. 5816 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

Hoepfner, Wolfgang
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<td></td>
<td>AU 2010263569 Al 02-02-2012</td>
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<td>CA 2764475 Al 29-12-2010</td>
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<td>CN 102459198 A 16-05-2012</td>
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<td>CN 104326991 A 04-02-2015</td>
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<td>CO 6430432 A2 30-04-2012</td>
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<td></td>
<td>EP 2447254 Al 02-05-2012</td>
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<td>KR 20120109457 A 08-10-2012</td>
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<td>MA 33637 Bl 01-10-2012</td>
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<td>NZ 597352 A 25-01-2013</td>
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<td></td>
<td>RU 2012102678 A 10-08-2013</td>
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<td>SG 176915 Al 30-01-2012</td>
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<td>SG 1020140313 W 30-10-2014</td>
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<tr>
<td>ME 01111352 A</td>
<td></td>
<td>01-04-2011</td>
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<td></td>
<td>US 2012101276 Al 26-04-2012</td>
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<td>US 2014148469 Al 29-05-2014</td>
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<td>US 2014155414 Al 05-06-2014</td>
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<td></td>
<td>US 2015266830 Al 24-09-2015</td>
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<td></td>
<td>WO 2010150865 Al 29-12-2010</td>
<td></td>
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<td></td>
<td>ZA 201109099 B 29-08-2012</td>
<td></td>
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<td></td>
<td>CA 2445344 Al 07-11-2002</td>
<td></td>
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<td></td>
<td></td>
<td>CN 1516690 A 28-07-2004</td>
<td></td>
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<td></td>
<td></td>
<td>DE 60217674 T2 11-10-2007</td>
<td></td>
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<td>DK 1400518 T3 26-03-2007</td>
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<td></td>
<td>EP 1400518 Al 24-03-2004</td>
<td></td>
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<td></td>
<td>ES 2276931 T3 01-07-2007</td>
<td></td>
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<td></td>
<td>JP 4479152 B2 09-06-2010</td>
<td></td>
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<td></td>
<td></td>
<td>KR 20040014174 A 18-02-2004</td>
<td></td>
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<td></td>
<td></td>
<td>MX PA03009800 A 29-01-2004</td>
<td></td>
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<td></td>
<td>PT 1400518 E 36-03-2007</td>
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<td></td>
<td>RU 2283835 C2 29-09-2006</td>
<td></td>
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<td></td>
<td>TW 1316055 B 21-10-2009</td>
<td></td>
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<td></td>
<td>US 2004102436 Al 27-05-2004</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>WO 02088084 Al 07-11-2002</td>
<td></td>
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