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(54) Title: AMORPHOUS FORM OF VILAZODONE HYDROCHLORIDE AND PROCESS FOR PREPARING THEREOF

(57) Abstract: The present invention relates to an amorphous form of vilazodone hydrochloride and processes for the preparation of amorphous form of vilazodone hydrochloride. The present invention also relates to pharmaceutical compositions that include a therapeutically effective amount of the amorphous form of vilazodone hydrochloride and use of said compositions for the treatment of major depressive disorder (MDD).
AMORPHOUS FORM OF VILAZODONE HYDROCHLORIDE AND PROCESS FOR PREPARING THEREOF

FIELD OF THE INVENTION

The invention relates to an amorphous form of vilazodone hydrochloride and processes for the preparation of amorphous form of vilazodone hydrochloride. The invention also relates to pharmaceutical compositions that include a therapeutically effective amount of the amorphous form of vilazodone hydrochloride and use of said compositions for the treatment of major depressive disorder (MDD).

BACKGROUND OF THE INVENTION

The following discussion of the prior art is intended to present the invention in an appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary, however, reference to any prior art in this specification should be construed as an admission that such art is widely known or forms part of common general knowledge in the field.

Vilazodone i.e. 1-[4-(5-cyanoindol-3-y1)butyl]-4-(2-carbamoyl-benzofuran-5-y1)-piperazine and its physiologically acceptable salts thereof are disclosed in U.S. Patent No. 5,532,241. International PCT Publication No. WO 00/72832 discloses use of Vilazodone in treating certain medical disorders.

U.S. Patent No. 7,834,020 B2 and 7,381,726 B2 disclose fifteen crystalline forms of vilazodone hydrochloride designated as Form-I through Form-XV. It also discloses an amorphous type Form-XVI, which is not a pure amorphous form as it contains characteristic two theta peaks pertaining to crystalline nature of the form.


Yet, there is a need of a commercial process for preparing amorphous form of vilazodone hydrochloride without using spray drying technique.

The present invention provides substantially pure amorphous form of vilazodone hydrochloride having polymorphic purity greater than 99.9% with no detectable amount of any other crystalline forms.

Crystalline solids normally require a significant amount of energy for dissolution due to their highly organized, lattice like structures. For example, the energy required for a drug molecule to escape from a crystal is more than from an amorphous or a non-crystalline form. It is known that the amorphous forms in a number of drugs exhibit different dissolution
characteristics and in some cases different bioavailability patterns compared to the crystalline form (Econno T., Chem. Pharm. Bull., 1990; 38: 2003-2007). For some therapeutic indications, one bioavailability pattern may be favored over another.

An amorphous form of some of the drugs exhibit much higher bioavailability than the crystalline forms, which leads to the selection of the amorphous form as the final drug substance for pharmaceutical dosage from development. Additionally, the aqueous solubility of crystalline form is lower than its amorphous form in some of the drugs, which may resulted in the difference in their in vivo bioavailability. Therefore, it is desirable to have amorphous forms of drugs with high purity to meet the needs of regulatory agencies and also highly reproducible processes for their preparation.

In view of the above, it is therefore, desirable to provide an efficient, economical and eco-friendly process for the preparation of highly pure Vilazodone hydrochloride in amorphous form without using spray drying.

**SUMMARY OF THE INVENTION**

In one general aspect, there is provided an amorphous form of vilazodone hydrochloride of Formula (I).

![Formula](image)

(I)

In another general aspect, there is provided a substantially pure amorphous form of vilazodone hydrochloride of Formula (I).

In another general aspect, there is provided an amorphous form of vilazodone hydrochloride having water content of from about 0.5% to about 10% wt/wt.

In another general aspect, there is provided a process for the preparation of the amorphous form of vilazodone hydrochloride.

In another general aspect, there is provided a process for the preparation of amorphous form of vilazodone hydrochloride of Formula (I) by ball milling vilazodone hydrochloride.

The process includes ball milling of vilazodone hydrochloride using balls in a milling chamber and rotating with high speed for sufficient time and interval. The ball milling may be carried out in pharmacy practice.
Embodiments of the process may include one or more of the following features. For example, vilazodone hydrochloride of Formula (I) may be added in a ball mill; ball milling the mixture below about 50°C for about 30 to 700 minutes, followed by repeating the ball milling cycles.

In another general aspect, there is provided a process for the preparation of amorphous form of vilazodone hydrochloride of Formula (I). The process includes grinding vilazodone hydrochloride in a grinder for sufficient time and interval and isolating amorphous form of vilazodone hydrochloride.

Embodiments of the process may include one or more of the following features. For example, vilazodone hydrochloride of Formula (I) may be added in a grinder; grinding the mixture below about 50°C for about 30 minutes, followed by repeating the grinding cycles.

In another general aspect, amorphous form of vilazodone hydrochloride is characterized by the X-ray diffraction pattern as shown in FIG.1.

In another general aspect, there is provided an one-pot process for preparing vilazodone hydrochloride of Formula (I) without isolation of vilazodone free base.

In another general aspect, there is provided an one-pot process for preparing vilazodone hydrochloride of Formula (I) the process comprising:

1) reacting 5-(1-piperazinyl) benzofuran-2-carboxamide Formula (G) or its salts with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) in an organic solvent in presence of a base;
2) adding the reaction mass of step (i) into a ternary solvent system and hydrochloric acid to obtain vilazodone hydrochloride;
iii) purifying vilazodone hydrochloride in an organic solvent to obtain pure vilazodone hydrochloride;

In a preferred aspect, there is provided use of vilazodone hydrochloride prepared by one pot process of the present invention, in the preparation of amorphous form of vilazodone hydrochloride.

In another general aspect, there is provided a process for the preparation of amorphous form of vilazodone hydrochloride of Formula (I) the process comprising:

i) reacting 5-(1-piperazinyl) benzofuran-2-carboxamide Formula (G) or its salts with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) in an organic solvent in presence of a base;

ii) adding the reaction mass of step (i) into a ternary solvent system and hydrochloric acid to obtain vilazodone hydrochloride;

iii) purifying vilazodone hydrochloride in an organic solvent to obtain pure vilazodone hydrochloride;

iv) sieving vilazodone hydrochloride of Formula (I);

v) adding vilazodone hydrochloride obtained in step (i) in a ball miller;

vi) ball milling vilazodone hydrochloride to obtain amorphous form of vilazodone hydrochloride.

In another general aspect, there is provided a process for the preparation of amorphous form of vilazodone hydrochloride of Formula (I)
the process comprising:

i) sieving vilazodone hydrochloride of Formula (I);

ii) adding vilazodone hydrochloride obtained in step (i) in a ball miller;

iii) ball milling vilazodone hydrochloride to obtain amorphous form of vilazodone hydrochloride.

In another general aspect, there is provided a process for the preparation of amorphous form of vilazodone hydrochloride of Formula (I)

the process comprising:

i) adding vilazodone hydrochloride in a ball miller;

ii) ball milling vilazodone hydrochloride to obtain amorphous form of vilazodone hydrochloride.

In another general aspect, there is provided a process for the preparation of amorphous form of vilazodone hydrochloride of Formula (I)
the process comprising:

i) sieving vilazodone hydrochloride of Formula (I);

ii) adding vilazodone hydrochloride obtained in step (i) in a grinder or miller;

iii) grinding or milling to obtain amorphous form of vilazodone hydrochloride.

The amorphous form of vilazodone hydrochloride may be obtained by using techniques of sieving, ball milling, grinding, milling and the like. The process may include further forming the product so obtained into a finished dosage form.

The amorphous form of vilazodone hydrochloride can also be recovered from the solution by adding a suitable anti-solvent resulting in the precipitation of the amorphous form and removing the solvent therefrom by filtration, decantation or centrifugation. The anti-solvent may be selected from a group of solvents in which vilazodone hydrochloride is insoluble or poorly soluble or partially soluble and is known to a person of ordinary skills in the art.

In another general aspect there is provided an amorphous form of vilazodone hydrochloride, substantially free from residual organic solvents.

In another general aspect there is provided a stable amorphous form of vilazodone hydrochloride thereof, which is stable during storage and drying.

In another general aspect there is provided storage and packaging conditions for the amorphous form of vilazodone hydrochloride.

In another general aspect there is provided an amorphous form of vilazodone hydrochloride having particle size distributions wherein the 10th volume percentile particle size (D10) is less than about 50 µm, the 50th volume percentile particle size (D50) is less than about 200 µm, or the 90th volume percentile particle size (D90) is less than about 400 µm, or any combination thereof.

In another aspect there is provided an amorphous form of vilazodone hydrochloride having particle size in terms of d95, is preferably less than about 100 microns, more preferably less than about 50 microns and most preferably less than about 30 microns. As used throughout the disclosure, the term d95 means that 95% of the particles (based on volume) are smaller than or equal to the indicated size.

In another aspect there is provided a process for the preparation of the amorphous form of vilazodone hydrochloride having particle size in terms of d95 less than about 100 microns.

In another general aspect there is provided an amorphous form of vilazodone hydrochloride having purity of greater than about 95%, or greater than about 98%, or greater than about 99%, or greater than about 99.5%, or greater than about 99.8%, or greater than about 99.9%, as determined by using high performance liquid chromatography (HPLC).
In another general aspect, there is provided compositions comprising the amorphous form of vilazodone hydrochloride substantially free of one or more of its corresponding impurities as measured by HPLC.

In another general aspect, there is provided pharmaceutical compositions comprising the stable amorphous form of vilazodone hydrochloride together with one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect there is provided a pharmaceutical composition comprising the stabilized amorphous solid dispersion of vilazodone hydrochloride together with one or more pharmaceutically acceptable carriers, optionally with one or more pharmaceutically acceptable excipients.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

FIG.1. shows X-ray diffractogram (XRD) of amorphous form of vilazodone hydrochloride.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term 'substantially pure' amorphous form of vilazodone hydrochloride referred in the present specification relates to there is provided a substantially pure amorphous form of vilazodone hydrochloride having polymorphic purity greater than about 99.9%. It may also provide amorphous form of vilazodone hydrochloride having less than 0.1% of crystalline vilazodone hydrochloride, for example with no detectable amount of any crystalline forms.

All ranges recited herein include the endpoints, including those that recite a range "between" two values. Terms such as "about", "general", "substantially" and the like are to be construed as modifying a term or value such that it is not an absolute. Such terms will be defined by the circumstances and the terms that they modify as those terms are understood by those 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.

The term "controlled humidity" refers to a relative humidity in the range of 50±10%. In particular, the controlled humidity includes grinding process performed under controlled humidity followed by drying under controlled humidity for the preparation of amorphous form of vilazodone hydrochloride.

The product obtained may be further dried to achieve the desired moisture values. For example, the product may be dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier.

As used herein, the term "grinder" includes mixers, mills (ball mill, jet mill etc.), blenders, micronizers, and the like or a combination thereof. The terms "grinding", "ball milling"
"milling", "mixing", "blending" and the like are interchangeable for achieving the homogeneous solid mixture.

As used herein, the term "storage stable" includes the amorphous form of vilazodone hydrochloride after exposure to a relative humidity of 75% at 40°C or relative humidity of 60% at 25°C, for a period of at least three months shows no change in the polymorphic form by X-ray powder diffraction.

"Suitable solvent" means a single or a combination of two or more solvents.

In one general aspect there is provided an amorphous form of vilazodone hydrochloride. In another general aspect there is provided a substantially pure amorphous form of vilazodone hydrochloride.

As used herein, the term "substantially pure amorphous form" of vilazodone hydrochloride represents polymorphic purity of amorphous form of vilazodone hydrochloride greater than 99.9%. The amorphous form may not show any detectable amount of any other crystalline forms as determined by using X-ray powder diffraction pattern (XRD).

In another general aspect, there is provided the amorphous form of vilazodone hydrochloride having purity of greater than about 95%, or greater than about 98%, or greater than about 99%, or greater than about 99.5%, or greater than about 99.8%, or greater than about 99.9%, as determined using high performance liquid chromatography (HPLC).

In another general aspect, there is provided a process for the preparation of the amorphous form of vilazodone hydrochloride thereof with simultaneous conversion of crystalline form of vilazodone hydrochloride into the amorphous form.

In another general aspect, amorphous form of vilazodone hydrochloride may be obtained by milling the solid mixture of vilazodone hydrochloride. The milling step may be traditionally carried out in pharmacy practice by compounding using a ball milling, pestle and mortar or a common mixer grinder. According to the invention milling machines that work on substantially the same principle may be used in the present process. Examples of such milling machines include various makes of ball mills, roller mills, gyratory mills, multi-mills, Jet-mills, and the like.

In a preferred aspect, amorphous form of vilazodone hydrochloride may be obtained by ball mill. The ball mill used for obtaining amorphous form may be selected from different makes of ball mill. A few makes of ball mill are covered in the present invention. Alternatively another commercially available ball milling machine can be used.

In a preferred aspect, a few makes of ball mill covered in the present invention are as follows:
1) Lab Ball Mill-lkg GMP Model (available from Prism Pharma Machinery) having technical specification as follows:

<table>
<thead>
<tr>
<th>MODEL</th>
<th>PBM-1 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drum size for 10 Liter</td>
<td>Dia.190 x 190 L- in mm</td>
</tr>
<tr>
<td>Drum MOC</td>
<td>10 MM THICK OF S.S.316</td>
</tr>
<tr>
<td>Drive Motor</td>
<td>1 HP/0.75kw/3phase</td>
</tr>
<tr>
<td>Drum speed</td>
<td>10 to 60 RPM by VFD.</td>
</tr>
</tbody>
</table>

2) Ball Mill (Batch Type) cGMP Model (available from Fab-Tech Engineers)

<table>
<thead>
<tr>
<th>MODEL</th>
<th>Ball Mill (Batch Type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drum size for 100 Liter</td>
<td>500mm O.D. x 600mm Length</td>
</tr>
<tr>
<td>Drum MOC</td>
<td>6 MM THICK OF S.S.316</td>
</tr>
<tr>
<td>Drive Motor</td>
<td>Crompton Make 3 HP with VFD</td>
</tr>
<tr>
<td>Drum speed</td>
<td>10 to 60 RPM by VFD.</td>
</tr>
</tbody>
</table>

3) Ball Mill (with Jacketing) Model (available from Shree Brahmaani Industries (SBI))

<table>
<thead>
<tr>
<th>MODEL</th>
<th>Ball Mill (Batch Type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drum size for 120 Liter</td>
<td>470 mm Dia. x 700 mm Length</td>
</tr>
<tr>
<td>Drum MOC</td>
<td>6 MM THICK OF S.S.316</td>
</tr>
<tr>
<td>Drive Motor</td>
<td>Bharat Bijlee Make KW/3HP/4P/B5/FLP/1420 RPM</td>
</tr>
<tr>
<td>VFD Drive</td>
<td>Amtech Make drive AXPERT-A900</td>
</tr>
<tr>
<td></td>
<td>AC VFD Module-3HP</td>
</tr>
<tr>
<td>Drum speed</td>
<td>10 to 60 RPM by VFD.</td>
</tr>
<tr>
<td>Grinding Midday</td>
<td>S.S. 316L Ball (2 types of balls i.e. cylindrical and spherical with different sizes)</td>
</tr>
<tr>
<td>Spherical Balls (wt.: diameter)</td>
<td>Cylindrical Balls (wt.: diameter)</td>
</tr>
<tr>
<td>38.5 Kg: 25 mm (302 balls) and 19 mm (477 balls)</td>
<td>13.30 Kg: 18 mm Dia., 25 mm L (270 balls) and 17.20 Kg: 14 mm Dia., 20 mm L (703 balls)</td>
</tr>
</tbody>
</table>

In a general aspect, amorphous form of vilazodone hydrochloride may be obtained by using technique of ball milling. The ball milling can be carried out in pharmacy practice by compounding using balls in a milling chamber and rotating it with high speed.
In general aspect of the present invention, vilazodone hydrochloride may be subjected to ball milling involving attrition of the particles and machine surfaces.

The ball milling apparatus may consists of a water jacketed bowl, nitrogen inlet facility with inside surface are made of a stainless steel carbon free material (SS 316). The milling chamber may consist of 40-60% of balls of the total volume which are also made of a stainless steel carbon free material. There are different types of balls used in milling chamber. Mainly cylindrical and spherical types of balls are used having variable range of length and diameter. The size of balls may vary in the range of 10 mm to 50 mm both with respect to diameter and length.

The selection of type of ball defines the formation of amorphous form in the milling chamber. The surface area of spherical balls is narrow as compared to cylindrical balls. The more amount of cylindrical balls leads to east and fast formation of amorphous form in milling chamber.

This milling chamber may be typically charged with feed material in such a way that about 10% to 30% of the effective volume of the grinding chamber is occupied. The speed of rotation is between 10-60 rpm at 50°C. For effective milling 40-60% free space is required.

The period of ball milling may vary depending on the size and number of the balls used in the milling chamber, speed of rotation of the main shaft, type of feed material, quantity of feed material and the free space available in the chamber. The effects of these variables are well known in the art and the invention may be worked over a range of these variables. Typically, the period of ball milling ranges from about 15 minutes to 800 minutes.

In another general aspect, amorphous form of vilazodone hydrochloride may be obtained by using a common milling or grinding technique.

In a preferred aspect, a mill such as a Micros Super Fine Mill (available from Nara Machinery Co. Ltd or Tokyo, Japan), Multi-Mill Sr. No. G. 1.1 32 (available from Grooves International Pharmaceutical & Chemical Machinery), Jet-Mill from Midas Micronizer M-100 Aerosol (No. 154/07-08 (available from microtech Enginering Company) or a common mixer grinder can be used. Alternatively another commercially available milling machine can be used.

In another general aspect, amorphous form of vilazodone hydrochloride may be obtained by using grinding technique. The process parameter includes adding vilazodone hydrochloride in a grinder. A specific grinder used can be small-scale to large-scale mixer grinder which can easily prepare the homogeneous mixture. For example purpose, Quadro dry mixing apparatus for providing lump-free homogenous blending to ensure proper proper mixing.
This grinding apparatus may consist of a water cooled jacketed bowl with the inside surface made of a suitable material such as Zirconium oxide, stainless steel, tungsten carbide, or aluminum oxide. Depending on the size of the grinder, the speed of rotation of the main shaft and the effective volume of the grinding chamber may vary. The effective volume of the grinding chamber may be in the range from about 0.45 liters to about 30 liters. For low capacity mills (such as 0, capacity 0.45 liters; or 5, capacity 4.8 liters), the speed of rotation of the main shaft is typically in the range from about 500 rpm to about 2000 rpm.

The period of milling using the mill may vary depending on the size of the mill, the speed of rotation of the main shaft, the type of feed material, and the quantity of feed material. The effects of these variables are well known in the art and the invention may be worked over a range of these variables. Typically, the period of milling ranges from about 15 minutes to 500 minutes.

In another general aspect, there is provided a process for the preparation of substantially pure amorphous form of vilazodone hydrochloride of Formula (I)

the process comprising:
  i) sieving vilazodone hydrochloride;
  ii) adding vilazodone hydrochloride obtained in step (i) in a ball miller;
  iii) ball milling vilazodone hydrochloride to obtain amorphous form of vilazodone hydrochloride of Formula (I).

Vilazodone hydrochloride before subjecting to sieving step may be prepared by one-pot process as disclosed in the present invention. Embodiments of the process includes, sieving vilazodone hydrochloride through 30 to 60 mesh for obtaining homogeneous solid mixture of vilazodone hydrochloride. Subjecting the obtained sieved solid mixture of vilazodone hydrochloride to a ball miller. Before subjecting the sieved vilazodone hydrochloride to the ball miller the humidity level of the surroundings may be at about 20 to 80%. The ball milling of the sieved vilazodone hydrochloride may be performed below 60°C. The ball milling cycles may be repeated for one or more times. The reaction
being an exothermic reaction, results in rise of temperature. In general, such a mixture may be cooled below 60°C and again the solid mixture may be ball milled below 60°C. The repetition of about two to three ball milling cycles followed by crushing of the solid mixture or sieving of the solid mixture results in substantially pure amorphous form of vilazodone hydrochloride characterized by XRD as depicted in FIG. 1.

The process parameter includes adding solid mixture of vilazodone hydrochloride in a ball mill. A specific ball mill may be used for small-scale to large-scale which can easily prepare the homogeneous mixture. For example purpose, ball mills like Lab Ball Mill-lkg GMP Model, Ball Mill (Batch Type) cGMP Model, Ball Mill (with Jacketing) Model or any other commercially available makes of ball mill may be used. In a preferred aspect, Ball Mill (with Jacketing) Model may be used for commercial production of amorphous form of vilazodone hydrochloride.

In a general aspect of grinding or mixing solid mixture of vilazodone hydrochloride different mixers may be used for example like change-can mixers, Helical-Blade mixers, Double-Arm Kneading Mixers, continuous mixers, Intensive mixers and the like, Mills like multi-mill, jet-mill, ball-mill, hammer mills, and the like, Quadro dry mixing apparatus for providing lump-free homogenous blending to ensure proper mixing. The varieties of mills and mixers provided in Perry's Chemical Engineers' Handbook Seventh Edition by Robert H. Perry and Don W. Green can be used based on suitability are incorporated herein by reference in its entirety.

In a preferred aspect, the vilazodone hydrochloride is ball milled in a Ball Mill (with Jacketing) Model to obtain a homogeneous solid mixture with continuous ball milling below 60°C. In particular, ball milling is performed at about 40°C to 50°C. The time interval may vary from about 30 to 700 minutes. In particular, the reaction may be ball milled for about 60 to 500 minutes.

During the ball milling of vilazodone hydrochloride strong exothermicity may be observed. In general, the mixture may be cooled to less than 45°C, particularly to 35°C to 40°C. Again the mixture may be ball milled to less than about 60°C, particularly at about 40°C to 50°C. This ball milling cycle may be repeated for one or more times. In particular for about 60 to 700 minutes for obtaining amorphous form of vilazodone hydrochloride as monitored by X-ray powder diffraction.

In a general aspect, amorphous form of vilazodone hydrochloride used for solid mixing in a ball miller particularly having water content less than about 3% wt/wt, more particularly less than about 2.5%. 
In a preferred aspect, the process comprises of sieving vilazodone hydrochloride to obtain homogeneous solid mixture of vilazodone hydrochloride. The sieving step may be performed through 30 to 60 mesh for one or two cycles. In a preferred aspect, the sieving may be performed through 36 mesh for one cycle.

The sieving step is followed by subjecting vilazodone hydrochloride to a ball miller in pharmacy practice. The ball milling step may be performed below 60°C. The ball milling step may be performed using a ball mill at a temperature of about 30°C to 50°C. The preferred temperature for ball milling may be from 40°C to 50°C. The ball milling cycles may be repeated for two or more times after an interval of 2 hours. The time duration between the two cycles of ball milling may vary from 60 minutes to 700 minutes. The ball milling may be performed for about 30 minutes to 900 minutes.

The reaction being an exothermic reaction, results in rise of temperature. In general, such a mixture may be cooled below 60°C and again the solid mixture may be ball milled below 60°C. The repetition of about two to three ball milling cycles followed by crushing of the solid mixture or sieving of the solid mixture results in amorphous form of vilazodone hydrochloride. Vilazodone hydrochloride obtained after ball milling leads to substantially pure amorphous vilazodone hydrochloride as depicted in FIG. 1.

In another general aspect, there is provided a one pot process for preparing vilazodone hydrochloride of Formula (I) without isolation of vilazodone free base.

In another general aspect, there is provided an one-pot process for preparing vilazodone hydrochloride of Formula (I)

the process comprising:

i) reacting 5-(1-piperazinyl) benzofuran-2-carboxamide Formula (G) or its salts with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) in an organic solvent in presence of a base;

ii) adding the reaction mass of step (i) into a ternary solvent system and hydrochloric acid to obtain vilazodone hydrochloride;
iii) purifying vilazodone hydrochloride in an organic solvent to obtain pure vilazodone hydrochloride;

The suitable solvent for step (i) comprises one or more of hydrocarbons, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl sulfoxide, dimethyl acetamide, acetonitrile, C_4 straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate and butyl acetate and the like. Particularly, the solvent may be dimethyl sulfoxide.

The suitable base for step (i) comprises an organic or inorganic base; an organic base may be selected from diisopropylethylamine, diisopropylamine, trimethylamine, diethylamine, piperidine, morpholine, pyridine, DBU, DABCO and the like; the inorganic base comprises of an alkali and alkaline metal hydroxide and carbonate, in particular the suitable alkali metal hydroxide comprises of sodium hydroxide, potassium hydroxide, lithium hydroxide, and the like, carbonate comprises of sodium carbonate, potassium carbonate, cesium carbonate and the like. Particularly, the base may be diisopropylethylamine.

The suitable solvent for ternary solvent system in step (ii) comprises one or more of hydrocarbons, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl sulfoxide, dimethyl acetamide, acetonitrile, C_4 straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate and butyl acetate or a mixture thereof. Particularly, the ternary solvent system may be ethyl acetate: methanol: acetone with ratio of 1.5:1:1 respectively.

The preferred solvent for isolation of vilazodone hydrochloride may be methanol. The suitable solvent for purifying vilazodone hydrochloride in step (iii) may be selected from one or more of hydrocarbons, nitriles, amides, alcohol, ketones, ester and the like. In particular, the suitable solvent comprises toluene, xylene, ethylbenzene dimethyl formamide, dimethyl sulfoxide, dimethyl acetamide, acetonitrile, C_4 straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate, butyl acetate and mixture thereof. Particularly, the solvent may be mixture of acetone-water.
In a preferred aspect, there is provided use of vilazodone hydrochloride prepared by one pot process as per the present invention, in the preparation of amorphous form of vilazodone hydrochloride.

In another general aspect, there is provided a process for the preparation of substantially pure amorphous form of vilazodone hydrochloride of Formula (I).

\[
\text{(I)}
\]

the process comprising:

i) sieving vilazodone hydrochloride of Formula (I);

ii) adding vilazodone hydrochloride obtained in step (i) in grinder or miller;

iii) grinding or milling vilazodone hydrochloride to obtain amorphous form of vilazodone hydrochloride of Formula (I).

The sieving may be performed through 30 to 60 mesh for one or two cycles. In particular the sieving may be performed through 36 mesh for one cycle.

The grinding or milling step may be performed using a common miller like ball mill, jet mill, mixers and grinders, preferably ball mill may be used.

In particular Ball Mill (with Jacketing) Model may be used for preparing amorphous form of vilazodone hydrochloride.

The ball milling may be performed at a temperature of about 20°C to 40°C for about 30 minutes to 900 minutes for two or more cycles.

The milling step may be performed using a jet mill with feeding pressure of about 3 kg and grading pressure of about 4 kg.

The grinding or jet milling cycles may vary from 1 to 5 cycles to obtain substantially pure amorphous form of vilazodone hydrochloride as depicted in FIG.1.

In another general aspect, there is provided a process for the preparation of amorphous form of vilazodone hydrochloride of Formula (I)
the process comprising:

i) reacting 5-(1-piperazinyl) benzofuran-2-carboxamide Formula (G) or its salts with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) in an organic solvent in presence of a base;

ii) adding the reaction mass of step (i) into a ternary solvent system (ethyl acetate: methanol: acetone with mole ratio of 1.5:1:1 respectively) and hydrochloric acid to obtain vilazodone hydrochloride;

iii) purifying vilazodone hydrochloride in an organic solvent to obtain pure vilazodone hydrochloride;

iv) sieving vilazodone hydrochloride of Formula (I);

v) adding vilazodone hydrochloride obtained in step (i) in a ball miller;

vi) ball milling vilazodone hydrochloride to obtain amorphous form of vilazodone hydrochloride.

The suitable solvent for step (i) comprises one or more of hydrocarbons, nitriles, amides, alcohol, ketones, ester and the like. Particularly, the solvent may be dimethyl sulfoxide.

The suitable base for step (i) comprises of an organic or inorganic base. Particularly, the base may be diisopropylethylamine.

The preferred solvent for isolation of vilazodone hydrochloride in step (ii) may be methanol.

The suitable solvent for purifying vilazodone hydrochloride in step (iii) may be selected from one or more of hydrocarbons, nitriles, amides, alcohol, ketones, ester and the like. Particularly, the solvent may be mixture of acetone-water.

The sieving in step (iv) may be performed through 36 mesh for one cycle.
The ball miller in step (v) may be selected from common makes of ball mill comprising of Lab Ball Mill-lkg GMP Model, Ball Mill (Batch Type) cGMP Model, Ball Mill (with Jacketing) Model or any other commercially available makes of ball mill. Particularly, Ball Mill (with Jacketing) Model may be used.

The ball milling in step (vi) may be performed at a temperature of about 40°C to 50°C. The ball milling cycles may be repeated for two or more times after an interval of 2 hours. The ball milling may be performed for about 30 minutes to 900 minutes.

In another general aspect there is provided a process for the preparation of amorphous form of vilazodone hydrochloride, which includes one or more of the following steps:

a) providing a solution of vilazodone hydrochloride in one or more solvents;
b) adding a suitable anti-solvent; and

c) isolating the amorphous form of vilazodone hydrochloride.

The solution of vilazodone hydrochloride can be obtained by the known methods that include direct use of a reaction mixture containing vilazodone hydrochloride that is obtained in the course of its synthesis, or dissolving vilazodone hydrochloride in a suitable solvent or mixture of solvents.

Suitable solvents may include but are not limited to water; alcohols such as methanol, ethanol, isopropanol, 2-propanol, 1-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, amyl alcohol, ethylene glycol, glycerol and the like; ketones such as acetone, butanone, 2-pentanone, 3-pentanone, methyl butyl ketone, methyl isobutyl ketone, and the like; esters such as ethyl formate, methyl acetate, ethyl acetate, propyl acetate, t-butyl acetate, isobutyl acetate, hydrocarbons like toluene, xylene, methylene dichloride, ethylene dichloride, chlorobenzene, and the like, nitrites like acetonitrile, ethers like diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,4-dioxane, 2-methoxyethanol, polar aprotic solvents, like N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, pyridine, dimethylsulfoxide, sulfolane, formamide, acetamide, propanamide, pyridine, and the like; and mixtures thereof.

Suitable anti-solvents may include one or more of hydrocarbons like hexanes, n-heptane, n-pentane, cyclohexane, methylcyclohexane and the like; aromatic hydrocarbons like toluene, xylene, chlorobenzene, ethylbenzene and the like; ethers like diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,4-dioxane, 2-methoxyethanol, and the like.

In another general aspect there is provided the amorphous form of vilazodone hydrochloride having water content from about 0.5% to about 10% wt/wt.
In a preferred aspect there is provided the amorphous form of vilazodone hydrochloride having water content of about 4% wt/wt.

In another general aspect there is provided the amorphous form of vilazodone hydrochloride substantially free from residual organic solvents.

In general there is provided a process for the preparation of the amorphous form of vilazodone hydrochloride, substantially free from residual organic solvents. The process includes:

a) providing vilazodone hydrochloride having less than 10% residual organic solvent;

b) triturating vilazodone hydrochloride in water, or contacting vilazodone hydrochloride with humid air in a fluidized bed drier, or drying vilazodone hydrochloride under reduced pressure of less than about 30 mmHg at less than 60°C;

c) optionally micronizing vilazodone hydrochloride; and

d) drying the product obtain in step c) to obtain the amorphous form of vilazodone hydrochloride substantially free of residual organic solvents.

In another general aspect the invention provides the amorphous form of vilazodone hydrochloride having particle size distributions wherein the 10th volume percentile particle size (D10) is less than about 50 \( \mu \text{m} \), the 50th volume percentile particle size (D50) is less than about 200 \( \mu \text{m} \), or the 90th volume percentile particle size (D90) is less than about 400 \( \mu \text{m} \), or any combination thereof.

In another aspect there is provided the amorphous form of vilazodone hydrochloride having particle size in terms of \( d_{95} \), preferably less than about 100 microns, more preferably less than about 50 microns and most preferably less than about 30 microns. As used throughout the disclosure, the term \( d_{95} \) means that 95% of the particles (based on volume) are smaller than or equal to the indicated size.

In another aspect there is provided amorphous form of vilazodone hydrochloride having particle size in terms of \( d_{95} \), less than about 100 microns.

In another general aspect, there is provided a stable amorphous form of vilazodone hydrochloride which is stable during storage and drying.

In another general aspect, the stable amorphous form of vilazodone hydrochloride, is stored under nitrogen atmosphere and packed in a double polythene bag tied with a thread, keeping primary packing containing amorphous vilazodone hydrochloride or salts thereof inside a black color polyethylene bag containing oxygen busters and sealing it, placing above the double polyethylene bag inside a triple laminated bag optionally containing oxygen busters and sealing it, and placing the sealed triple laminated bag inside a closed high density
polyethylene (HDPE) container and storing in controlled environment chamber at about 25°C and/or 40°C.

In another general aspect there is provided an amorphous form of vilazodone hydrochloride having purity of greater than about 95%, or greater than about 98%, or greater than about 99%, or greater than about 99.5%, or greater than about 99.8%, or greater than about 99.9%, as determined by using high performance liquid chromatography (HPLC).

In another general aspect, there is provided compositions comprising the amorphous form of vilazodone hydrochloride substantially free of one or more of its corresponding impurities as measured by HPLC.

In another general aspect, there is provided pharmaceutical compositions comprising a therapeutically effective amount of amorphous vilazodone hydrochloride substantially free from crystalline form, and one or more pharmaceutically acceptable carriers, excipients or diluents.

The invention also encompasses pharmaceutical compositions comprising vilazodone or salts thereof of the invention. As used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" includes tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

Pharmaceutical compositions containing the vilazodone hydrochloride of the invention may be prepared by using diluents or excipients such as fillers, bulking agents, binders, wetting agents, disintegrating agents, surface active agents, and lubricants. Various modes of administration of the pharmaceutical compositions of the invention can be selected depending on the therapeutic purpose, for example tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

Any excipient commonly known and used widely in the art can be used in the pharmaceutical composition. Carriers may include, but are not limited to, lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, and the like. Binders may include, but are not limited to, water, ethanol, propanol, simple syrup, glucose solutions, starch solutions, gelatin solutions, carboxymethyl cellulose, shelac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone, and the like.

Disintegrating agents may include, but are not limited to, dried starch, sodium alginate, agar powder, laminalia powder, sodium hydrogen carbonate, calcium carbonate, fatty acid esters of polyoxyethylene sorbitan, sodium laurylsulfate, monoglyceride of stearic acid, starch, lactose, and the like.
Disintegration inhibitors may include, but are not limited to, white sugar, stearin, coconut butter, hydrogenated oils, and the like. Absorption accelerators used include, but are not limited to, quaternary ammonium base, sodium laurylsulfate, and the like.

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification.

The process for preparation of the amorphous form of vilazodone hydrochloride is demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of invention.

**Example-1: Preparation of Amorphous form of Vilazodone Hydrochloride**

Methanol (850 ml) was added to Vilazodone free base (150 g) in a four-neck two litre round bottom flask at 35°C and heated to 60-65°C followed by addition of acetic acid (115 g). The reaction mass was stirred for 30 minutes and stirred for 1 hour. The reaction mass was filtered and washed with methanol (75 ml) and treated with DMSO (300 ml) at 25-30°C and heated to 80-85°C. The reaction mass was cooled to 25-30°C followed by addition of 25% sodium methoxide solution (35 g). The reaction mass was filtered and washed with methanol (75 ml) and treated with acetone (200 ml) and heated to 50-55°C. An another assembly was arranged in a tub using diisopropyl ether (1000 ml) and cone, hydrochloric acid (16 ml) at 0-5°C. First reaction mass was added into second reaction mass within 45 minutes and stirred for 30 minutes. The reaction mass was filtered and washed with chilled DIPE (120 ml) at 0-5°C afforded vilazodone hydrochloride.

Vilazodone hydrochloride was sieved through 30 to 40 mesh and further grinded for 60 minutes at 25-30°C. The grinding cycle may be repeated 3 to 4 times afforded substantially pure amorphous form as depicted by XRD (FIG. 1).

**Example-2: Preparation of Amorphous form of Vilazodone Hydrochloride**

3-(4-chlorobutyl)-IH-indole-5-carbonitrile (7 Kg) and 5-(piperazin-l-yl)benzofuran-2-carboxamide (8.5 Kg) in dimethyl sulfoxide (75 L) & diisopropylethyl amine (100 L) were added in a RBF at 25-30°C. The reaction mixture was stirred at 80-85°C. Another assembly was arranged in tub using ethyl acetate (105 L); methanol (65 L ml); acetone (65 L) and cone, hydrochloric acid (14 L). First reaction mass was treated with second reaction mass within 60 minutes and stirred for 60 minutes. The reaction mixture was filtered and washed with methanol and treated with water (170 L); DMSO (14 L) at 50-55°C. The reaction mass was stirred for 10 minutes and filtered. To the filtrate methanol (65 L) was added and heated at 50-
55°C for 30 minutes and cooled to 25-30°C. The reaction mass was filtered and washed with methanol (7 L). Vilazodone hydrochloride was obtained by treating the reaction mass with a mixture of acetone: water (2:1) (45 L) at 55-60°C for 30 minutes. The reaction mass was cooled to 25-30°C, filtered and washed with water (5 L).

Vilazodone hydrochloride was sieved through 36 mesh and 1.0 Kg of vilazodone hydrochloride was subjected to ball mill containing 68.5 Kg balls of different sizes [(Spherical (38.5 Kg): 25 mm (302 balls), 19 mm (477 balls) and cylindrical 30 Kg (13.30 Kg: 270 balls with diameter: 8 mm and length: 25 mm); and 17.20 Kg:703 balls with diameter: 14 mm and length: 20 mm] at humidity of about 20 to 80%. The chamber was flushed with nitrogen and ball mill was rotated at 51 rpm/min for 2 hours. Ball milling cycles were repeated for 8-12 hours. After 12 hours substantially pure amorphous form vilazodone hydrochloride was obtained (0.92Kg). XRD substantially as depicted in FIG. 1.
We Claim:

1. A process for preparing amorphous form of vilazodone hydrochloride of Formula (I) having X-ray powder diffraction (XRD) pattern substantially as depicted in FIG. 1

   ![Formula (I)](image)

   the process comprising:

   i) sieving vilazodone hydrochloride of Formula (I);

   ii) adding vilazodone hydrochloride obtained in step (i) in a ball miller;

   iii) ball milling vilazodone hydrochloride to obtain amorphous form of vilazodone hydrochloride.

2. The process as claimed in claim 1, wherein sieving may be performed through 30 to 60 mesh for one or two cycles.

3. The process as claimed in claim 2, wherein sieving may be performed through 36 mesh for one cycle.

4. The process as claimed in claim 1, wherein ball milling may be performed using a commercial makes of ball mill selected from Lab Ball Mill-1kg GMP Model (Prism Pharma Machinery), Ball Mill (with Jacketing) Model (Shree Brahmani Industries) and Ball Mill (Batch Type) cGMP Model (Fab-Tech Engineers).

5. The process as claimed in claim 4, wherein ball milling may be performed using Ball Mill (with Jacketing) Model (Makes Shree Brahmani Industries).

6. The process as claimed in claim 1, wherein ball milling may be performed with variable size of spherical and cylindrical balls selected from 10 mm to 50 mm both with respect to diameter and length.

7. The process as claimed in claim 1, wherein ball milling may be performed at a temperature of about 30°C to 60°C.
8. The process as claimed in claim 7, wherein ball milling may be performed at a temperature of about 40°C to 50°C.

9. The process as claimed in claim 1, wherein ball milling may be performed at rotation of about 10 to 60 rpm/min.

10. The process as claimed in claim 9, wherein ball milling may be performed at rotation of about 51 rpm/min.

11. The process as claimed in claim 1, wherein ball milling may be performed for about 30 to 900 minutes.

12. The process as claimed in claim 1, wherein ball milling may be performed for about two or more cycles.

13. The process as claimed in claim 12, wherein the time duration between the two cycles of ball milling may vary from 60 minutes to 700 minutes.

14. The process as claimed in claim 1, amorphous vilazodone hydrochloride obtained from ball mill having water content less than about 6%.

15. The process as claimed in claim 1, amorphous vilazodone hydrochloride obtained from ball mill may be milled in common mixer grinder.

16. An one-pot process for preparing vilazodone hydrochloride of Formula (I)

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the process comprising:

i) reacting 5-(1-piperazinyl) benzofuran-2-carboxamide Formula (G) or its salts with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) in an organic solvent in presence of a base;

ii) adding the reaction mass of step (i) into a ternary solvent system and hydrochloric acid to obtain vilazodone hydrochloride;
iii) purifying vilazodone hydrochloride in an organic solvent to obtain pure vilazodone hydrochloride;

17. The process as claimed 16, wherein solvent comprises of comprises one or more of hydrocarbons, nitriles, amides, alcohol, ketones and esters.

18. The process as claimed 17, wherein solvent comprises of toluene, xylene, ethylbenzene dimethyl formamide, dimethyl sulfoxide, dimethyl acetamide, acetonitrile, C1-C4 straight chain or branched alcohols, acetone, methyl isobutyl ketone, methyl ethyl ketone, ethyl acetate, isopropyl acetate and butyl acetate.

19. The process as claimed 18, wherein solvent may be dimethyl sulfoxide.

20. The process as claimed 16, wherein base comprises of an organic or inorganic base selected from diisopropylethylamine, diisopropylamine, trimethylamine, diethylamine, piperidine, morpholine, pyridine, DBU, DABCO, alkali metal hydroxides and carbonates like sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate and cesium carbonate.

21. The process as claimed 20, wherein base may be diisopropylethylamine.

22. The process as claimed 16, wherein ternary solvent system comprises of mixture of solvents selected from one or more of hydrocarbons, nitriles, amides, alcohol, ketones and esters.

23. The process as claimed 22, wherein ternary solvent system comprises of ethyl acetate: methanol: acetone with ratio of 1.5:1:1 respectively.

24. The process as claimed 16, wherein solvent for isolating crude vilazodone hydrochloride may be methanol.
25. The process as claimed 16, wherein solvent for purifying vilazodone hydrochloride comprises of one or more of hydrocarbons, nitriles, amides, alcohol, ketones, esters and mixture thereof.

26. The process as claimed 25, wherein solvent for purifying vilazodone hydrochloride may be a mixture of acetone water.

27. A process for the preparation of the amorphous form of vilazodone hydrochloride, substantially free from residual organic solvents, the process includes:

i) providing vilazodone hydrochloride having less than 10% residual organic solvent;

ii) triturating vilazodone hydrochloride in water, or contacting vilazodone hydrochloride with humid air in a fluidized bed drier, or drying vilazodone hydrochloride under reduced pressure of less than about 30 mmHg at less than 60°C;

iii) optionally micronizing vilazodone hydrochloride; and

iv) drying the product obtained in step c) to obtain the amorphous form of vilazodone hydrochloride substantially free of residual organic solvents.

28. A process for the preparation of amorphous form of vilazodone hydrochloride of Formula (I)

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\text{(I)}
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the process comprising:

i) reacting 5-(1-piperazinyl) benzofuran-2-carboxamide Formula (G) or its salts with 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula (H) in an organic solvent in presence of a base;

ii) adding the reaction mass of step (i) into a ternary solvent system (ethyl acetate: methanol: acetone with mole ratio of 1.5:1:1 respectively) and hydrochloric acid to obtain vilazodone hydrochloride;
iii) purifying vilazodone hydrochloride in an organic solvent to obtain pure vilazodone hydrochloride;

iv) sieving vilazodone hydrochloride of Formula (I);

v) adding vilazodone hydrochloride obtained in step (i) in a ball miller;

vi) ball milling vilazodone hydrochloride to obtain amorphous form of vilazodone hydrochloride.

29. The process as claimed in claim 28, wherein steps (i) to (iii) may be corresponding to the process as claimed in claim 16.

30. The process as claimed in claim 28, wherein steps (iv) to (vi) may be corresponding to the process as claimed in claim 1.

31. A pharmaceutical composition comprising a therapeutically effective amount of an amorphous form of vilazodone hydrochloride prepared as per the process claimed in claim 1 and one or more pharmaceutically acceptable carriers, excipients, or diluents.

32. Use of an amorphous form of vilazodone hydrochloride prepared as per the process claimed in claim 1 for the treatment of major depressive disorders.