(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 June 2012 (14.06.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/077138 Al

(51) **International Patent Classification:**
C07D 209/08 (2006.01) ***BOW 9/02*** (2006.01)

(21) **International Application Number:**
PCT/IN2011/000842

(22) **International Filing Date:**
8 December 2011 (08.12.2011)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
2942/DEL/2010 9 December 2010 (09.12.2010) IN

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2012/077138 A1

(54) Title: METHODS OF CRYSTALLIZING (R) -1- (3 -HYDROXYPROPYL) -5- [2- [2- [2- (2, 2, 2 - TRIFLUOROETHOXY) PHENOXY] ETHYLAMINO] PROPYL] INDOLINE -7 -CARBOXAMIDE

(57) Abstract: The present invention provides a process for crystallization of various forms of silodosin. In particular the present invention provides a process for crystallizing a and β forms of silodosin from various solvents and their mixtures using various crystallization techniques.

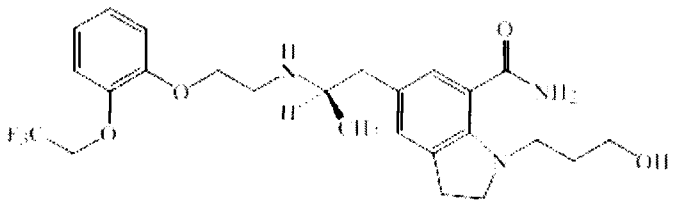
METHODS OF CRYSTALLIZING (R) -1- (3 -HYDROXYPROPYL) -5- [2- [2- [2- (2, 2, 2 - TRIFLUOROETHOXY) PHENOXY] ETHYLAMINO] PROPYL] INDOLINE-7 -CARBOXAMIDE

Field of the invention

The present invention relates to a process for crystallization of Silodosin ((R)-l-(3-hydroxypropyl)-5-[2-[2-[2-(2,2,2-trifluoroemoxy)phenoxy]ethylamino]propyl]indoline-7-carboxamide) using novel crystallization techniques.

Background:

Silodosin is the adopted name of the drug compound chemically known as (R)-l-(3-hydroxypropyl)-5-[2-[2-[2-(2, 2,2-trifluoroethoxy) phenoxy]ethylamino]propyl]indoline-7-carboxamide and is represented by the below structural formula:



Silodosin is a selective alpha-1 adrenergic receptor antagonist, indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Silodosin developed by Kissei, is marketed as tablets for oral administration under the name Rapaflo.

Polymorphism refers to the occurrence of different crystalline forms of the same drug substance. It includes solvation products and amorphous forms. It is often characterized as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystalline solid adducts containing either

stoichiometric or nonstoichiometric amounts of a solvent incorporated within the crystal structure. If the incorporated solvent is water, the solvates are also commonly known as hydrates. (Background Information for the October 2002 ACPS Meeting Scientific Considerations of Polymorphism in Pharmaceutical Solids: Abbreviated New Drug Applications).

Different polymorphs have different physiochemical and biological properties and in pharmaceuticals it is often desired to obtain one particular form that is biologically active and also offers ease of handling during formulation. Hence, it is desired to obtain one particular crystal form in large yield and with high purity.

The formation of different polymorphic forms can be achieved by crystallizing the compound from different solvents under varying conditions. Polymorph formation is influenced by temperature of the solution, rate of stirring, rate of precipitation, mode of mixing and rate of addition of the mixing of solvents and time of stirring. Very often the different polymorphs can be isolated from the same solvent system by simply stirring the mixture for different period of times and one form can be converted into another. In view of the very tight limits of residual solvent specification norms as per ICH guidelines for the Active Pharmaceutical Ingredient (API), only a limited number of solvents, preferably C class solvents are being used for generating the new polymorphs. Thus choice is narrowed down to very few solvent systems. Also seeding plays an important role in crystallizing a specific form of a polymorph from same or different solvent systems in higher yields. There are many techniques that can be used for obtaining a given crystal form in large scale. The choice of the crystallization process may depend on the physiochemical properties of the drug that is intended to be isolated. Many thermodynamic events are associated with the formation of a particular crystal form.

Commonly used techniques for crystallization include solvent evaporation, slow or sudden cooling of the solution, solvent/non-solvent diffusion, anti-solvent, pH shifting, vapor diffusion, sublimation and many variations on these processes.

Silodosin is known to exist in different physical forms referred to as polymorphs.

U.S. Patent no. 5,387,603 discloses Silodosin as therapeutic agents for the treatment of dysuria, urinary disturbance associated with benign prostatic hyperplasia. It also discloses processes for the preparation of Silodosin, wherein it was crystallized using solvents such as a mixture of trifluoroacetic acid and methylene chloride. Further, this patent discloses the physical properties of silodosin on data of IR (Infra Red Absorption Spectrum), specific rotation and NMR (Nuclear Magnetic Resonance Spectrum), but its appearance and crystalline polymorphs have not been reported.

Japanese patent application no. JP 07,330,726 A discloses the crystallization of silodosin by dissolving crude silodosin crystals in heated ethyl acetate followed by drying it over anhydrous magnesium sulfate and allowing the solution to stand at room temperature. The IR of the product obtained gave characteristic peaks at KBr: 3388, 3202, and 1637cm^{-1}.

European patent no. EP 1,541,554 B1 discloses three different crystal forms of silodosin viz., (1) a crystal characterized by main peaks of 5.5° ± 0.2°, 6.1 ° ± 0.2°, 9.8 ° ± 0.2°, 11.1 ° ± 0.2°, 12.2 ° ± 0.2°, 16.4 ° ± 0.2°, 19.7 ° ± 0.2° and 20.0 ° ± 0.2° as 2Θ [hereinafter referred to as crystalline alpha (a) silodosin]; (2) *a* crystal characterized by main peaks of 7.0 ° ± 0.2°, 12.5 ° ± 0.2°, 18.5 ° ± 0.2°, 19.5 ° ± 0.2°, 20.7 ° ± 0.2° and 21.1 ° ± 0.2° as 2Θ [hereinafter referred to as crystalline beta (β) silodosin]; and (3) a crystal characterized by main peaks of 6.0 ° ± 0.2°, 10.6 ° ± 0.2°, 12.6 ° ± 0.2°, 17.1 ° ± 0.2°, 17.9 ° ± 0.2°, 20.7 ° ± 0.2° and 23.7 ° ± 0.2° as 2Θ [hereinafter referred to as crystalline gamma (γ) silodosin.

EP '554 discloses that the crystalline alpha silodosin can be prepared by dissolving crude crystals thereof in appropriate amount of ethylacetate, ethyl formate, acetone, methyl ethyl ketone, acetonitrile, tetrahydrofuran or a mixed solvent of acetone and acetonitrile (1:1), \, preferably ethyl acetate is used under heating, further allowing to stand at room temperature, thereby enabling the gradual precipitation of crystals . The crystalline beta silodosin can be prepared by dissolving crude crystals thereof in an

appropriate amount of methanol under heating, adding petroleum ether as a poor solvent, stirring the mixture vigorously, such that the crystals ate forcibly and suddenly precipitated.. The crystalline beta silodosin can also be prepared by dissolving crude crystal thereof in ethanol or 1-propanol, and cooling quickly. The crystalline gamma silodosin can be prepared by dissolving crude crystal thereof in an appropriate amount of toluene, a mixed solvent of acetonitrile and toluene (1:4) or a mixed solvent of ethyl acetate and toluene (1:19), preferably toluene under heating, allowing to stand at room temperature thereby enabling the crystals to precipitate gradually. The crystalline gamma silodosin can also be prepared by dissolving crude crystal thereof in 2-propanol and adding an appropriate amount of toluene thereto to precipitate a crystal.

The inventors of EP '554 have reported that the crystalline alpha silodosin has improved stability and hygroscopicity, however the crystalline beta silodosin has a manufacturing issue during industrial preparation, since it is prepared by adding a poor solvent into warm solution to make crystal precipitates forcibly and suddenly. EP'554 further reports that since toluene or a mixed solvent comprising mainly of toluene is used for recrystallization crystalline gamma silodosin is, removal of the resuidual solvent becomes troublesome because of toluene's high boiling point.

Despite the development and research of crystallization methods, control over crystallization based on structural understanding and the ability to design crystals and other solid-forms is still limited. The control on nucleation, growth, dissolution, and morphology of molecular crystals remains primarily a matter of "mix and try"The prior known methods of silodosin crystallization did not provide complete purification, especially in terms of the final crystalline form and produced material with inconsistent physical properties. Thus, there is a need to explore various routes of obtaining these polymorphs in large yield and purity.

The instant invention describes a method for crystallizing silodosin from a solvent and anti-solvent system and producing the pure crystalline product. The desired final crystal form may be pure Form a and/or pure Form β.

Summary:

The present invention relates to a process of preparation of various crystalline forms of silodosin using novel crystallization techniques.

The present invention relates to a process of preparation of various crystalline forms of silodosin from crude and pure silodosin using various crystallization techniques such as solvent evaporation, slow or sudden/rapid cooling, solvent/non-solvent diffusion, anti-solvent, pH shifting, vapor diffusion, sublimation and many variations on these processes.

In an aspect, the present invention provides a process for the crystallization of silodosin comprising the use of a solvent to effect the dissolution of silodosin followed by the addition of an anti-solvent to initiate the crystallization.

The present invention provides a process for the preparation of chemically pure silodosin comprising crystalising silodosin free base from a solvent selected from a group consisting of methyl isobutyl ketone (MIBK), dichloromethane (DCM), methyl t-butyl ether (MTBE), ethyl acetate (EtOAc), methanol (MeOH), ethanol, petroleum ether, hexane, heptane (HEP), cyclohexane, methyl ethyl ketone (MEK), methyl acetate, iso-butyl acetate, isopropyl acetate, toluene, 1-propanol, 1-butanol, 2-butanol, 1-pentanol, 2-methyl-l-propanaol (iso amyl alcohol), tetrahydrofuran (THF), 2-methyl THF and isopropyl alcohol (IPA) and/or their mixtures.

In one aspect the present invention relates to a process of preparing crystalline alpha Silodosin (Form a).

In *a* specific aspect of the present invention crystalline alpha silodosin is prepared by dissolving silodosin base in an alcohol and adding an anti-solvent which is an alkane solvent.

In a further specific embodiment of the present invention crystalline alpha silodosin is prepared by dissolving silodosin base in an alcohol like methanol, ethanol and the like and further adding an anti-solvent which is an alkane solvent selected from a group comprising of heptane, hexane, petroleum ether, cyclohexane and the like.

In another specific aspect of the present invention crystalline alpha silodosin is prepared by using halogenated solvents.

In a further specific embodiment of the present invention crystalline alpha silodosin is prepared by using halogenated solvents selected from a group comprising of MDC, chloroform and the like.

The present invention further relates to a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in ethyl acetate by heating followed by sudden cooling.

The present invention further relates to a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in ethyl acetate by heating and cooling to room temperature.

The present invention further relates to a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in a solvent mixture of methanol and petroleum ether, heating and stirring for 12 h at room temperature.

The present invention further relates to a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in a solvent mixture having methanol and ethyl acetate by heating and cooling to room temperature.

The present invention further relates to a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in a solvent mixture having ethyl acetate and heptane by heating and adding heptane to the heated mixture.

The present invention further relates to a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in DCM (dichloromethane) by heating and cooling to room temperature.

The present invention further relates to a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in MEK (methyl ethyl ketone) by heating followed by stirring at room temperature.

In another aspect, the present invention relates to a process of preparing crystalline beta silodosin. (Form β).

In a specific aspect of the present invention crystalline beta silodosin is prepared by dissolving crude silodosin or silodosin base in an alcohol and adding an anti-solvent which is an alkane solvent.

In a further specific embodiment of the present invention crystalline beta silodosin is prepared by dissolving crude silodosin or silodosin base in an alcohol like methanol, ethanol, isopropylalcohol and the like and further adding an anti-solvent which is an alkane solvent selected from a group comprising of heptane, hexane, cyclohexane, petroleum ether and the like.

In another specific aspect of the present invention crystalline beta silodosin is prepared by using ketone solvents.

In another very specific aspect of the present invention crystalline beta silodosin is prepared by using ketone solvents like methyl isobutyl ketone, acetone and the like.

In yet another specific aspect of the present invention crystalline beta silodosin is prepared by dissolving crude silodosin or silodosin base in a ketone solvent and adding an anti-solvent which is an alkane solvent.

In yet another very specific aspect of the present invention crystalline beta silodosin is prepared by dissolving crude silodosin or silodosin base in a ketone solvent selected

from a group comprising of methyl isobutyl ketone, acetone, methyl ethyl ketone and the like and further adding an anti-solvent which is an alkane solvent selected from a group comprising of heptane, hexane, petroleum ether, cyclohexane and the like.

In still another aspect of the present invention crystalline beta silodosin is prepared by dissolving crude silodosin or silodosin base in a ketone solvent and adding an anti-solvent which is an ether solvent.

In still another specific aspect of the present invention crystalline beta silodosin is prepared by dissolving crude silodosin or silodosin base in a ketone solvent selected from a group comprising of methyl isobutyl ketone, acetone, methyl ethyl ketone and the like and further adding an anti-solvent which is an ether solvent selected from a group comprising of diethyl ether, isopropyl ether, methyl t-butyl ether and the like.

In another aspect of the present invention crystalline beta silodosin is prepared by dissolving crude silodosin or silodosin base in an halogenated solvent and adding an anti-solvent which is an ether solvent.

In a specific aspect of the present invention crystalline beta silodosin is prepared by dissolving crude silodosin or silodosin base in an halogenated solvent like DCM and further adding an anti-solvent which is an ether solvent selected from a group comprising of diethyl ether, isopropyl ether, methyl t-butyl ether and the like.

In further aspects of the present invention, crystalline silodosin can be prepared using a combination of solvents which may be DCM and MTBE, or DCM, MTBE and hexane.

The present invention further relates to a process of preparing crystalline beta silodosin comprising: dissolving crude silodosin in methanol under heating at 50°C; adding petroleum ether as an antisolvent (methanol: petroleum ether ratio: 1: 3-5); and evaporating the solvent mixture under reducing pressure.

The present invention further relates to a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in ethanol by heating; and

(ii) adding petroleum ether or hexane to the heated mixture.

The present invention further relates to a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in IPA (isopropyl alcohol) by heating;

(ii) adding petroleum ether or hexane as anti solvent; and

(iii) stirring at room temperature for **1** day.

The present invention further relates to a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in MIBK (methyl isobutyl ketone) by heating; and

(ii) adding petroleum ether or hexane to the heated mixture.

The present invention further relates to a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in DCM (dichloromethane) by heating; and

(ii) adding MTBE (methyl t-butyl ether)and petroleum ether to the heated mixture.

The present invention further relates to process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in MEK (methyl ethyl ketone) by heating; and

(ii) adding pettroleum ether or hexane to the heated mixture.

The present invention further relates to a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in IPA (isopropyl alcohol); and

(ii) adding heptane to the heated mixture.

The present invention further relates to a process of preparing crystalline beta silodosin comprising dissolving crude silodosin in MIBK (methyl isobutyl ketone) by heating followed by cooling to room temperature

The present invention further relates to a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in MIBK; and

(ii) adding heptane to the heated mixture.

The present invention further relates to a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in MIBK; and

(ii) adding MTBE to the heated mixture.

The present invention further relates to process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in acetone; and

(ii) adding MTBE to the heated mixture.

The present invention further relates to process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in MEKby heating; and

(ii) adding MTBE to the heated mixture.

The present invention further relates to process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in MEK by heating; and

(ii) adding Heptane to the heated mixture.

The present invention further relates to a process of preparing crystalline beta silodosin comprising:

(i) dissolving the crude silodosin in ethyl acetate; and

(ii) concentrating the solution completely to dryness.

Detailed description:

The present invention relates to a process of preparation of various crystalline forms of silodosin from crude and pure silodosin.

Definitions:

The invention is described herein in detail using the terms defined below unless otherwise specified.

The term "petroleum ether" refers to the following distillation fractions of petroleum ether: 30 to 40 °C, 40 to 60 °C, 60 to 80 °C, 80 to 100 °C, 80 to 120 °C and sometimes 100 to 120 °C.

The term "crude" is defined as less pure material (starting material) having purity of 98% and less.

The term "room temperature" refers to a temperature of about 20°C to about 40°C.

The term "sudden cooling" refers to a process of dissolving the crude material in an appropriate solvent followed by quickly cooling the solution to 0-5°C in an ice bath.

It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. As well, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising", "including", "characterized by" and "having" can be used interchangeably.

The present invention relates to a process of preparing various crystalline forms of silodosin by various crystallization methods such as gradual or sudden cooling, anti-solvent technique, rapid evaporation and sudden crystallization. Preferably, the present invention relates to a process of preparing various forms of silodosin by anti-solvent technique.

The crude or pure compound used as starting material (herein after referred to as "starting material") for obtaining pure crystals using crystallization process of the present invention can be obtained from different sources.

The starting material is dissolved in a solvent or mixture of solvents by heating to obtain a heated solution and any or all of the following actions may be performed on the heated solution:

a) rapidly cooled;
b) gradually cooled;
c) left at room temperature;
d) stirred at room temperature;
e) subjected to evaporation; and/or
f) a second solvent or solvent mixture is added to the heated solution.

Common solvent (s) used for dissolving the starting material are selected from but are not limited to methyl isobutyl ketone (MIBK), dichloromethane (DCM), methyl t-butyl ether (MTBE), ethyl acetate (EtOAc), methanol (MeOH), ethanol, , methyl ethyl ketone (MEK), methyl acetate, iso-butyl acetate, isopropyl acetate, toluene, 1-propanol, 1-butanol, 2-butanol, 1-pentanol, 2-methyl-l-propanaol (iso amyl alcohol), tetrahydrofuran (THF), 2-methyl THF and isopropyl alcohol (IPA) and/or their mixtures.

Heating temperature may vary from 30-100°C depending on the solubility of crude silodosin in the particular solvent. Preferably heating is done at a temperature range varying from 30-70°C.

The instant invention further describes a method for crystallizing silodosin by carrying out crystallization under specific cooling conditions and producing the pure crystalline product. The desired final crystal form may be pure Form a and/or pure Form β. The cooling condition may be slow or rapid cooling. Cooling may be carried out by dissolving the crude material in an appropriate solvent followed by quickly cooling the

solution to 0-5°C in an ice bath. Alternatively cooling can also be gradual over a prior of time at a specific temperature (e.g 20-30°C) or at a gradient of temperature.

The second solvent /solvent mixture as used in the process is selected from but is not limited to petroleum ether, heptane, methyl t-butyl ether, cyclohexane, hexane, diethyl ether, toluene, xylene, isopropyl ether and mixtures thereof.

In one embodiment the present invention provides a process of preparing crystalline alpha silodosin (Form a).

In an embodiment, the present invention provides a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in ethyl acetate by heating followed by sudden cooling.

In a preferred embodiment, the present invention provides a process of preparing crystalline alpha silodosin comprising

(i) preparing a solution of crude silodosin by dissolving in ethyl acetate by heating;
(ii) drying the said solution on sodium sulphate;
(iii) concentrating the solution obtained in step (ii) to reduce the volume; and
(iv) sudden cooling.

Preferably, the concentration in step (iii) is done until the volume is reduced to one third. In an embodiment, the dissolution of crude silodosin in ethyl acetate is done by heating at 60°C for 5 hours followed by heating at 40°C for 18 hours and at room temperature for 2 days.

In another embodiment, the present invention provides a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in ethyl acetate by heating and cooling to room temperature.

In another embodiment, the present invention provides a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in a solvent mixture of methanol and petroleum ether by heating and stirring overnight at room temperature.

In another embodiment, the present invention provides a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in a solvent mixture having methanol and ethyl acetate by heating and cooling to room temperature.

In another embodiment, the present invention provides a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in a solvent mixture having ethyl acetate and heptane by heating and adding heptane to the heated mixture.

In another embodiment, the present invention provides a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in DCM (dichloromethane) by heating and cooling to room temperature.

In another embodiment, the present invention provides a process of preparing crystalline alpha silodosin comprising dissolving crude silodosin in MEK (methyl ethyl ketone) by heating followed by stirring at room temperature.

In another embodiment, the present invention relates to a process of preparing crystalline beta silodosin. (Form β).

In an embodiment, the present invention provides a process of preparing crystalline beta silodosin comprising dissolving crude silodosin in methanol under heating at 50°C; adding petroleum ether as an anti solvent (methanol : petroleum ether ratio: 1: 3-5); and evaporating the solvent mixture under reducing pressure.

In another embodiment, the present invention provides a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in ethanol by heating; and

(ii) adding petroleum ether (petroleum ether) or hexane to the heated mixture.

In an embodiment, the present invention provides a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in IPA (isopropyl alcohol) by heating;

(ii) adding petroleum ether or hexane ; and

(iii) stirring at room temperature for 1 day.

In a further embodiment, the present invention provides a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in MIBK (methyl isobutyl ketone) by heating; and

(ii) adding petroleum ether or hexane to the heated mixture.

The present invention further relates to a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in DCM by heating; and

(ii) adding MTBE and petroleum ether to the heated mixture.

In another embodiment, the present invention provides a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in MEK by heating; and

(ii) adding petroleum ether or hexane to the heated mixture.

In yet another embodiment, the present invention provides a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in IPA; and

(ii) adding heptane to the heated mixture.

In an embodiment, the present invention further relates to a process of preparing crystalline beta silodosin comprising dissolving crude silodosin in MIBK (methyl isobutyl ketone) by heating followed by cooling to room temperature

In an embodiment, the present invention provides a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in MIBK; and

(ii) adding heptane to the heated mixture.

In an embodiment, the present invention further relates to a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in MIBK; and

(ii) adding MTBE to the heated mixture.

In another embodiment, the present invention provides a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in acetone; and

(ii) adding MTBE to the heated mixture.

In an embodiment, the present invention provides a process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in MEK by heating; and

(ii) adding MTBE to the heated mixture.

In an embodiment, the present invention further relates to process of preparing crystalline beta silodosin comprising:

(i) dissolving crude silodosin in MEK by heating; and

(ii) adding Heptane to the heated mixture.

In yet another embodiment, the present invention provides a process of preparing crystalline beta silodosin comprising:

(i) dissolving the crude silodosin in ethyl acetate; and

(ii) concentrating the solution completely to dryness.

Examples:

The invention is explained in detail in the following examples which are given solely for the purpose of illustration and therefore should not be construed to limit the scope of the invention. The silodsin product was obtained as per following examples were identified by matching the IR values the alpha (a) and beta (β) forms of silodosin reported in EP 1,541,554 B1 and US5,387603. The prominent peaks in alpha (a) form IR (KBr) is 3484, 3202, 1636 cm^{-1} and in beta (β) form is 3384, 3202, 1636 cm^{-1}.

Example-1: Silodosin crude (0.5 g) was dissolved in 20 ml of ethyl acetate at 50°C and maintained for 30 min at 50°C. The solution was cooled to room temperature (20-30°C) and stirred for 1 hour. Solid obtained was filtered and dried to give 0.25 g of crystalline alpha silodosin (HPLC purity: 98.30 %).

Example-2: Silodosin crude (0.5 g) was dissolved in 20 ml of ethyl acetate at 50°C and the clear solution was dried by adding sodium sulphate. The solution was filtered and concentrated to half the volume and stirred for 1h at room temperature (20-30°C). The solid obtained was filtered and dried to give 0.3 g of crystalline alpha silodosin (HPLC purity: 98.31%).

Example-3: Silodosin crude (0.5 g) was dissolved in 5 ml of DCM at 35°C and maintained for 30 min at same temperature. The solution was cooled to 0°C and stirred for 1 h. Solid obtained was filtered and dried to give 0.3 g of crystalline alpha silodosin (HPLC urity: 98.37%).

Example-4: Silodosin crude (0.5 g) was dissolved in 10 ml of Isopropyl alcohol at 65°C and maintained for 30 min at same temperature. The solution was cooled to 0°C and stirred for 1 h. The Solid obtained was filtered and dried to give 0.25 g of crystalline beta silodosin (HPLC purity 98.42%).

Example-5: Silodosin crude (2 g) was dissolved in 8 ml of Isopropyl alcohol at 65°C and the solution was allowed to cool to room temperature (20-30°C). To the mixture 8 ml of n-heptane was added and stirred for 30 min. The solid obtained was filtered and dried to give 1.35 g of crystalline beta silodosin (HPLC purity: 99.65%).

Example-6: Silodosin crude (0.5 g) was dissolved in 5 ml of MIBK at 65°C and maintained for 30 min at 65°C. The solution was allowed to cool to room temperature (20-30°C) and stirred for 2 h. Solid obtained was filtered and dried to give 0.18 g of crystalline beta silodosin (HPLC purity: 98.23%).

Example-7: Silodosin crude (0.5 g) was dissolved in 2 ml of MEK at 60°C and the solution was allowed to cool to room temperature (20-30°C). To the mixture 5 ml of MTBE was added and stirred for 30 min. The solid obtained was filtered and dried to give 0.26 g of crystalline beta silodosin (HPLC purity: 97.36%).

Example-8: Silodosin crude (0.5 g) was dissolved in 2 ml of MIBK at 60°C and the solution was allowed to cool to room temperature (20-30°C). To the mixture 5 ml of petroleum ether or n-Heptane was added and stirred for 10 min. The solid obtained was filtered and dried to give 0.23 g of crystalline beta silodosin (HPLC purity: 98.94%).

Example-9: Silodosin crude (0.5 g) was dissolved in 2 ml of MEK at 60°C and the solution was allowed to cool to room temperature (20-30°C). To the mixture 5 ml of Petroleum ether or n-Heptane was added and stirred for 10 min. The solid obtained was filtered and dried to give 0.25 g of crystalline beta silodosin (HPLC purity: 96.43%).

Example-10: Silodosin crude (0.5 g) was dissolved in 5 ml of MEK at 60°C and the solution was allowed to cool to room temperature (20-30°C). The mixture was stirred for 10 min. The solid obtained was filtered and dried to give 0.18 g of crystalline alpha silodosin (HPLC purity: 98.56%)

Example-11: Silodosin crude (0.5 g) was dissolved in 2 ml of acetone at 40°C and the solution was allowed to cool to room temperature (20-30°C). To the mixture 10 ml of MTBE was added and stirred for 30 min. The solid obtained was filtered and dried to give 0.4 gm of crystalline beta silodosin (HPLC purity 98.56%).

CLAIMS

1. A process for preparing crystalline alpha silodosin by dissolving crude silodosin in an alcohol and adding an anti-solvent which is an alkane solvent.

2. A process according to claim 1 wherein alcohol solvent is selected from methanol, ethanol and the like and the alkane anti-solvent is selected from heptane, hexane, petroleum ether, cyclohexane and the like.

3. A process for preparing crystalline alpha silodosin using halogenated solvents.

4. A process according to claim 3 wherein the halogenated solvent may be dichloromethane, chloroform and the like.

5. A process for preparing crystalline beta silodosin by dissolving crude silodosin in an alcohol and adding an anti-solvent which is an alkane solvent.

6. A process according to claim 5 wherein alcohol solvent is selected from methanol, ethanol, isopropylalcohol and the like and the alkane anti-solvent is selected from heptane, hexane, petroleum ether, cyclohexane and the like.

7. A process for preparing crystalline beta silodosin using ketone solvents.

8. A process according to claim 7 wherein ketone solvent is selected from methyl isobutyl ketone, acetone and the like.

9. A process for preparing crystalline beta silodosin by dissolving crude silodosin in a ketone solvent and adding an anti-solvent which is an alkane solvent.

10. A process according to claim 9 wherein ketone solvent is selected from methyl isobutyl ketone, acetone, methyl ethyl ketone and the like and the alkane anti-solvent is selected from heptane, hexane, petroleum ether, cyclohexane and the like.

11. A process for preparing crystalline beta silodosin by dissolving crude silodosin in a ketone solvent and adding an anti-solvent which is an ether solvent.

12. A process according to claim 11 wherein ketone solvent is selected from methyl isobutyl ketone, acetone, methyl ethyl ketone and the like and the ether anti-solvent is selected from diethyl ether, isopropyl ether, methyl t-butyl ether and the like.

13. A process for preparing crystalline beta silodosin by dissolving crude silodosin in a halogenated solvent and adding an anti-solvent which is ether solvent.

14. A process according to claim 13 wherein the halogenated solvent is dichloromethane and the ether anti-solvent is selected from diethyl ether, isopropyl ether, methyl t-butyl ether and the like.

15. A process of preparing crystalline alpha silodosin comprising:

a) dissolving crude silodosin in a solvent mixture of methanol and Petroleum ether heating and stirring overnight at room temperature;

or

b) dissolving crude silodosin in a solvent mixture having methanol and ethyl acetate by heating and cooling to room temperature;

or

c) dissolving crude silodosin in a solvent mixture having ethyl acetate and heptane by heating and adding heptane to the heated mixture;

or

d) dissolving crude silodosin in DCM (Dichloromethane) by heating and cooling to room temperature;

or

e) dissolving crude silodosin in MEK (methyl ethyl ketone) by heating followed by stirring at room temperature;

16. A process of preparing crystalline beta silodosin comprising:

a) dissolving crude silodosin in methanol under heating at 50°C and followed by addition of petroleum ether or hexane as an anti-solvent and subjecting the solvent mixture to evaporation under reducing pressure;

or

b) (i) dissolving crude silodosin in EtOH by heating; and

(ii) adding petroleum ether or hexane to the heated mixture;

or

c) (i) dissolving crude silodosin in a mixture of isopropyl alcohol by heating;

(ii) adding petroleum ether or hexane as anti solvent; and

(iii) stirring at room temperature for 1 day;

or

d) (i) dissolving crude silodosin in methyl isobutyl ketone by heating; and

(ii) adding petroleum ether or hexane to the heated mixture;

or

e) (i) dissolving crude silodosin in DCM by heating; and

(ii) adding MTBE and petroleum ether to the heated mixture;

or

f) (i) dissolving crude silodosin in methyl ethyl ketone; and

(ii) adding petroleum ether or hexane to the heated mixture;

or

g) (i) dissolving crude silodosin in isopropyl alcohol; and

(ii) adding heptane to the heated mixture;

or

h) Dissolving the crude silodosin in methyl isobutyl ketone solvent and cooling the solution to room temperature

or

i) (i) dissolving crude silodosin in a mixture of solvent having methyl isobutyl ketone; and

(ii) adding heptane to the heated mixture;

or

j) (i) dissolving crude silodosin in methyl isobutyl ketone; and
(ii) adding MTBE to the heated mixture;
or
k) (i) dissolving crude silodosin in acetone; and
(ii) adding MTBE to the heated mixture;
or
1) (i) dissolving crude silodosin in MEK by heating; and
(ii) adding MTBE to the heated mixture;
or
m) (i) dissolving crude silodosin in MEK by heating; and
(ii) adding Heptane to the heated mixture.

17. A process according to claim 16, wherein in process a), the ratio of methanol to petroleum ether is in the range of 1: 3-5.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2011/0OQ842

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/08 B01D9/02
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D B01D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2012	29/03/2012

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2011/0OQ842

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X, P	CN 102 229 558 A (Z0U QIA0GEN) 2 November 2011 (2011-11-02) the whole document	5-14, 16, 17
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