Title: PROCESS FOR PREPARATION OF POSACONAZOLE AND CRYSTALLINE POLYMORPHIC FORM V OF POSACONAZOLE

Abstract: The present invention generally relates to a process for the preparation of an antifungal agent posaconazole and to a novel polymorphic form V of antifungal agent posaconazole.

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PROCESS FOR PREPARATION OF POSACONAZOLE AND CRYSTALLINE POLYMORPHIC FORM V OF POSACONAZOLE

FIELD OF THE INVENTION

The present invention generally relates to a process for the preparation of an antifungal agent posaconazole and to a novel crystalline polymorphic form V of antifungal agent posaconazole.

BACKGROUND OF THE INVENTION

Posaconazole is a novel broad-spectrum antifungal agent of the triazole class that has been developed for the treatment of invasive fungal infections. Posaconazole is designated chemically as \((-\)(2R-cis)-4-[4-[4-[4[[-5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)furan-3-yl]methoxy]phenyl]-1-piperaziny]phenyl]-2,4-dihydro-2-[fS)-1-ethyl-2(S)-hydroxypropyl]-3H-1,2,4-triazol-3-one, which is represented by the following general formula (I):

![Chemical Structure](image)

Posaconazole is available as an oral suspension under the trademark Noxafil®, from Schering Corporation.

International patent publication WO95/17407 (the '407 publication) discloses several substituted tetrahydrofuran antifungal compounds including...
posaconazole and their use in treating fungal infections. The publication discloses several processes for preparation of posaconazole.

[0006] According to one process, posaconazole is prepared by condensation of toluene-4-sulfonic acid (-)-(5R-cis)-5-(2,4-difluorophenyl)-5-(1,2,4-triazol-1-ylmethyl)tetrahydro-3-furan methyl ester of formula (IVa)

![IVa](image)

with N-protected triazolone derivative of following formula

![Triazolone Formula](image)

wherein SEM is 2-(trimethyl)silyloxyethyl group in the presence of a strong base and in an aprotic solvent to give the compound of following formula

![Compound Formula](image)

which is then deprotected using hydrochloric acid in methanol followed by N-alkylation with brosylated alcohol of the formula
wherein R represents hydroxyl protecting group (R is 2-(trimethyl)silylethoxymethyl (SEM) or benzyloxymethyl) 
in the presence of a strong base in an aprotic solvent to give hydroxyl protected posaconazole which is then deprotected using hydrochloric acid in methanol to give posaconazole of formula I, which is purified by column chromatography.

The '407 publication discloses a process for preparing posaconazole by reacting (3R-cis)-N-4-[4-[4-[5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-yl)methyl]-furan-3yl]methoxy][phenyl]-l-piperazinyl][phenyl]carbamic acid phenyl ester with 2-[3-(2S,3S)-2-(benzyloxy)pentyl]formic acid hydrazide in the presence of 1,8-diazabicyclo(5,4,0)undec-7-ene under heating to give benzyl posaconazole of formula (Iia)

which on hydrogenolysis with palladium on carbon and formic acid in methanol, affords posaconazole, which is then further purified via preparative thin layer chromatography.

The methods disclosed in the '407 publication lead to the compound of formula I as an amorphous solid.

[0007] United States Patent No. 5625064 (the '064 patent) discloses a process for the preparation of posaconazole, compound of formula (I) comprising the condensation of formula III,
with (0-(5R-cis)-5-(2,4-difluorophenyl)5-[(1H-1,2,4-triazol-1-yl)methyl]tetrahydO-3-furanmethyl ester derivative of following formula (IV),

wherein OB represents a suitable leaving group selected from p-chlorobenzenesulfonyl, p-toluenesulfonyl, methanesulfonyl; in the presence of a base to give benzyl posaconazole, compound of formula IIa which is then deprotected either with palladium on carbon in the presence of formic acid or aqueous hydrobromic acid to form posaconazole, compound of formula I.

International patent publication number WO2009/141837 discloses a process for the preparation of posaconazole, compound of formula I by deprotecting the benzyl posaconazole, compound of formula IIa,

using a mineral acid in the presence of a noble metal catalyst in an organic solvent under hydrogen pressure.
United States Patent No. 6,713,481 discloses three polymorphic forms of posaconazole designated as forms I, II and III. X-ray powder diffractograms are used to describe the three polymorphic forms, where of the three crystalline forms, Form I is the most stable. Crystalline forms II and III were found to be unstable under the conditions investigated.

International patent publication WO2010/000668 discloses crystalline Form IV of posaconazole. X-ray powder diffractogram with the characteristic peaks are likewise used to describe Form IV.

International patent publication WO2009/147075 discloses crystalline Form Y of posaconazole. Herein, the X-ray powder diffractogram is also used to describe Form Y.

The major drawback of the processes disclosed above is that the deprotection of benzyl posaconazole in the presence of formic acid may not go to completion or may require lengthy reaction times, of about 1 to 3 days, even in the presence of a large (>50 wt%) amount of Pd/C. These reaction conditions may lead to the generation of several impurities and require chromatographic purification steps. Similarly, the deprotection of benzyl posaconazole with a mineral acid like hydrochloric acid or hydrobromic acid may result in the degradation of posaconazole, which may necessitate laborious, and additional, purification methods to purify posaconazole, subsequently contributing to loss of yield and purity.

The aforementioned challenges, such as the long reaction times for the deprotection of the benzyl ether, the excess use of Pd/C, and the ensuing chromatographic purifications for the removal of impurities formed in the deprotection reaction are undesirable for a large-scale synthesis of posaconazole. To overcome the above difficulties, the present invention provides an efficient and industrially advantageous process for the synthesis of posaconazole.

There also remains a need for alternative stable polymorphic forms of posaconazole which have properties that make them suitable for bulk preparation and handling as well as for preparing of pharmaceutical compositions on a commercial scale.
SUMMARY OF THE INVENTION

[0015] The present invention provides a process for preparing posaconazole, compound of formula I

![Chemical Structure I](image)

comprising:

a) debenzylating a compound of formula II

![Chemical Structure II](image)

wherein R represents H, alkyl, substituted alkyl, halogen, nitro, amino using a metal catalyst and a hydrogen source in presence of an organic acid selected from the group consisting of a sulfonic acid, a sulfinic acid, a carboxylic acid having two or more carbon atoms and;

b) optionally purifying the posaconazole.

[0016] The present invention provides a process for preparing posaconazole, compound of formula I

![Chemical Structure I](image)
comprising,

a) reacting a compound of formula III

\[
\text{III}
\]

with a compound of formula IV in presence of a base and an organic solvent

\[
\text{IV}
\]

wherein OB represents leaving group selected from the group consisting of p-chlorobenzenesulfonyl, p-bromobenzenesulfonyl, p-toluenesulfonyl, methanesulfonyl, to form compound of formula IIa, benzyl posaconazole

\[
\text{IIa}
\]

b) optionally, isolating the benzyl posaconazole, compound of formula IIa,

c) debenzylating the benzyl posaconazole, compound of formula IIa, and
d) isolating the posaconazole, compound of formula [I].

[0017] The present invention provides a benzyl posaconazole, compound of formula IIa in crystalline Form A.
The present invention provides a process for the preparation of amorphous posaconazole, comprising:

a) providing a solution of posaconazole in one or more solvents capable of dissolving the posaconazole;

b) optionally, filtering the solvent solution to remove any extraneous matter; and

c) substantially removing the solvent from the solution to provide posaconazole substantially in an amorphous form.

The present invention provides posaconazole having a chemical purity of greater than about 99.5 area % as measured by high performance liquid chromatography.

The present invention provides posaconazole having a chiral purity of greater than about 99.8 area % as measured by high performance liquid chromatography.

The present invention provides posaconazole, prepared by the process having less than about 0.15 area % of total impurities as measured by high performance liquid chromatography (HPLC).

The present invention provides posaconazole having less than 0.15 % of benzyl posaconazole of formula IIa.

In yet another aspect, the present invention provides posaconazole having less than 0.15 % of compound of formula V.
In yet another aspect, the present invention provides posaconazole having less than 0.15% of compound of formula [VI]

[0025] In yet another aspect, the present invention provides a pharmaceutical composition comprising posaconazole prepared by processes herein described above, and at least a pharmaceutically acceptable carrier.

The present invention provides a crystalline polymorphic Form V of posaconazole that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ±0.2° at about 6.9, 8.8, 10.3, 21.4 and 22.6.

The present invention provides a process for the preparation of crystalline polymorphic Form V of posaconazole, comprising, a) providing a solution of posaconazole in one or more solvents capable of dissolving the posaconazole and b) substantially removing the solvent from the solution to provide crystalline polymorphic Form V of posaconazole.

**BRIEF DESCRIPTION OF THE DRAWINGS**

[0028] Fig 1: is an X-ray powder diffractogram of form A of benzyl posaconazole.

[0029] Fig 2: is an X-ray powder diffractogram of posaconazole.

[0030] Fig 3: is an X-ray powder diffractogram of crystalline polymorphic Form V of posaconazole according to Example 8.

[0031] Fig 4: is an X-ray powder diffractogram of crystalline polymorphic Form V of posaconazole according to Example 9.

**DETAILED DESCRIPTION OF THE INVENTION**
The present invention provides a process for the preparation of posaconazole, compound of formula I comprising:

a) debenzylating the compound of formula II wherein R represents H, alkyl, substituted alkyl, halogen, nitro, amino using a metal catalyst and a hydrogen source in presence of an organic acid in presence of an organic acid selected from the group consisting of a sulfonic acid, a sulfinic acid, a carboxylic acid having two or more carbon atoms and;

b) optionally purifying the posaconazole.

The halogens may be selected from fluoro, chloro, bromo, iodo. The alkyl group may be selected from methyl, ethyl, isopropyl, t-butyl and may be optionally substituted with one or more halogens.

Preferably the compound of formula (II) is compound of formula (Ila)
The compound of formula (Ha), benzyl posaconazole may be prepared by methods known in the art, as for example in international publication WO 95/1 7407.

[0035] The organic acid is selected from the group comprising sulfonic acid, a sulfinic acid, a carboxylic acid having two or more carbon atoms.

[0036] The sulfonic acid may be selected from the group consisting of methanesulfonic acid, dimethanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-methylbenzenesulfonic acid, p-aminobenzenesulfonic acid, p-bromobenzenesulfonic acid, camphor sulfonic acid, and the like, preferably methanesulfonic acid, benzene sulfonic acid, p-methylbenzenesulfonic acid.

[0037] The sulfinic acid may be selected from the group consisting of methanesulfinic acid, ethanesulfinic acid, benzenesulfinic acid, p-methylbenzenesulfinic acid, p-bromobenzenesulfinic acid, camphorsulfinic acid, and the like, preferably methanesulfinic acid, benzenesulfinic acid, p-methylbenzenesulfinic acid.

[0038] The carboxylic acid having two or more carbon atoms may be selected from the group consisting of aliphatic carboxylic acid and aromatic carboxylic acid. The aliphatic carboxylic acid may be selected from the group further consisting of monocarboxylic acid, dicarboxylic acid and tricarboxylic acid. Preferably the aliphatic carboxylic acid is monocarboxylic acid.

[0039] The aliphatic monocarboxylic acid may be selected from the group consisting of acetic acid, fluoroacetic acid, difluoroacetic acid, trifluoroacetic acid, chloroacetic acid, dichloroacetic acid, trichloroacetic acid, cyanoacetic acid, propionic acid, butyric acid, acrylic acid, glyoxylic acid, glycolic acid, pyruvic acid, lactic acid, glyceric acid, acetoacetic acid, 2-oxobutanoic acid, 2-aminobutanoic acid, 2,4-diaminobutanoic acid, 2-chlorobutanoic acid, 4-cyanobutanoic acid, uric acid, pimelic acid, dianamopimelic acid 2-oxo-3-methylpentanoic acid, gluconic acid and the like. Preferably the mono aliphatic carboxylic acid is acetic acid, trifluoroacetic acid.

[0040] The aliphatic dicarboxylic acid may be selected from the group consisting of succinic acid, fumaric acid, malic acid, dihydroxymalic acid, mucic acid, tartaric acid,
maleic acid, glutamic acid, γ-carboxyglutamic acid, a-ethyl glutamic acid, mesaconic acid, oxalic acid, oxaloacetic acid, malonic acid, dimethylmalonic acid, methylmalonic acid, glutaric acid, adipic acid, 2-amino adipic acid, aspartic acid, 3-methylaspartic acid, citramalic acid and the like, preferably succinic acid, fumaric acid, dihydroxymalic acid. Preferably the aliphatic dicarboxylic acid is selected from succinic acid, fumaric acid, malic acid.

[0041] The aliphatic tricarboxylic acid may be selected from the group consisting of citric acid, hydroxycitric acid, isocitric acid, aconitic acid, propane-1,2,3-tricarboxylic acid. Preferably citric acid.

[0042] The aromatic carboxylic acid may be selected from the group consisting of aromatic monocarboxylic acid, aromatic dicarboxylic acid. Preferably aromatic monocarboxylic acid.

[0043] The aromatic monocarboxylic acid may be selected from the group consisting of 2-furoic acid, benzoic acid, 2-aminobenzoic acid, 4-aminobenzoic acid, 2-bromobenzoic acid, 3-bromobenzoic acid, 2-chlorobenzoic acid, 3-chlorobenzoic acid, 4-chlorobenzoic acid, 4-methylbenzoic acid, 2-nitrobenzoic acid, 3-nitrobenzoic acid, 4-nitrobenzoic acid, 2-iodobenzoic acid, 3-iodobenzoic acid, 2,5-dihydroxybenzoic acid, 2,4,6-trihydroxybenzoic acid, 2-phenylbenzoic acid, hippuric acid, anthranilic acid, salicylic acid, phenylacetic acid, mandelic acid, pamoic acid, pantothentic acid, stearic acid, cinnamic acid, phthalic acid, picolinic acid, nicotinic acid, 1-naphthoic acid, 8-quinoline carboxylic acid and the like, preferably benzoic acid, paramethylbenzoic acid, parachlorobenzoic acid, paranitrobenzoic acid. Preferably benzoic acid, 2-aminobenzoic, 2-bromobenzoic acid.

[0044] The aromatic dicarboxylic acid may be selected from the group consisting of lutidinic acid, quinolinic acid, o-phthalic acid, m-phthalic acid, p-phthalic acid, terephthalic acid. Preferably quinolinic acid, o-phthalic acid.

[0045] The molar equivalent of the acid employed is from about an equimolar to about 5 times the equimolar amount with respect to the compound of formula (II). Preferably about an equimolar to about 3 times the equimolar amount with respect to the compound of formula (II).
The metal catalyst include, but are not limited to, palladium in the form of palladium on carbon or palladium salts such as palladium hydroxide, palladium hydroxide on carbon, and the like, Raney nickel, platinum, iridium, ruthenium, and the like; preferably, a palladium catalyst, or Raney nickel is used and most preferably, the metal catalyst is palladium on carbon. The palladium content in the catalyst may be about 2.5% to about 20% wt/wt% on carbon, preferably about 5% to about 15 wt/wt%, more preferably about 10 wt/wt%.

The reaction is normally and preferably effected in the presence of an inert solvent. The solvents that can be used include, but are not limited to, C1-C5 alcohols for example methanol, ethanol, isopropyl alcohol, isobutyl alcohol and the like; haloalkanes for example dichloromethane, chloroform, carbon tetrachloride, dichloroethane and the like; esters such as methyl acetate, ethylacetate and the like; ethers for example diethyl ether, diisopropyl ether, methyl isobutyl ether tetrahydrofuran and the like; ketones for example acetone, methyl isobutyl ketone and the like; nitriles for example acetonitrile, propionitrile, butyronitrile and the like; dimethylformamide, dimethylacetamide, and dimethylsulfoxide. Preferably the solvent is selected from methanol, ethanol, isopropyl alcohol, dichloromethane, dichloroethane, diethyl ether, diisopropyl ether, acetone, acetonitrile, dimethylformamide, tetrahydrofuran. More preferably the solvent is methanol.

The hydrogen source is selected from the group consisting of hydrogen gas, cyclohexane, cyclohexadiene, or ammonium formate mixed with formic acid. Preferably, the hydrogen source is hydrogen gas.

The hydrogen gas pressure for the deprotection reaction can range from about 2 kg/cm² to about 10 kg/cm² by using hydrogen gas. Preferably at about 5 kg/cm² to about 8 kg/cm², more preferably at about 5 kg/cm².

The reaction can take place over a wide range of temperatures. The temperature can range from about 10°C to about 50°C. Preferably, from about 20°C to about 35°C.

The hydrogenation process may take from about 2 hours to about 10 hours. Preferably about 3 hours to about 6 hours depending upon the catalyst, pressure and temperature chosen.
The time required for the completion of the reaction also varies widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvents employed. The reaction period may transpire from about 1 hour to about 10 hours. Preferably from about 2 hours to about 5 hours.

The completion of reaction may be monitored by thin layer chromatography (TLC) or high performance liquid chromatography (HPLC). After completion of reaction the metal catalyst may be separated or recovered from the reaction mixture any method known in the art, for example by filtering the reaction mixture to remove the catalyst. The solvent is distilled out and the resulting residue is further dissolved in a suitable solvent or mixture of solvents such as an alcohol and water. Then the pH of the solution may be adjusted to 6.5 to 7.5 with a base to isolate posaconazole in high yield. The base used can be any of those that are known in the art, for example sodium hydroxide, potassium hydroxide and the like, sodium carbonate, potassium carbonate and the like. Preferably the base is sodium carbonate.

Sulfonic acid or sulfinic acid or organic acid having two or more carbon atoms during deprotection reaction is advantageous because the product is isolated directly from reaction solution without doing chromatographic separation and reaction is completed in lesser time as compared to the prior art processes and hence degradation of product and impurity formation is reduced.

In one embodiment, the present invention provides a process for preparing posaconazole, compound of formula I comprising debenzylation compound of formula Ila, using a metal catalyst and a hydrogen source in presence of an organic acid selected from the group consisting of a sulfonic acid, a sulfinic acid, a carboxylic acid having two or more carbon atoms.

In one embodiment, the present invention provides a process for preparing posaconazole, compound of formula I, comprising debenzylation compound of formula Ila, using a metal catalyst and a hydrogen source in presence of sulfonic acid selected form the group consisting of methanesulfonic acid, benzenesulfonic acid, p-methylbenzenesulfonic acid.
In one embodiment, the present invention provides a process for preparing posaconazole, compound of formula I comprising debenzylation of compound of formula Ia, using a metal catalyst and a hydrogen source in presence of sulfonic acid.

In one embodiment, the present invention provides a process for preparing posaconazole, compound of formula I, comprising debenzylation of compound of formula IIa, using a 10% Pd/C with hydrogen gas under pressure in the presence of sulfonic acid selected from the group consisting of methanesulfonic acid, benzenesulfonic acid, p-methylbenzenesulfonic acid in an alcoholic solvent. Preferably hydrogen gas pressure is in the range of about 5kg/cm$^2$ to about 8 kg/cm$^2$. The temperature at which the debenzylation can take place can range from about 10°C to about 50°C. Preferably, the temperature is in the range from about 20°C to about 35°C. Preferably the alcoholic solvent is methanol.

The present invention provides a process for preparation of posaconazole, compound of formula I

![Chemical Structure of I]

comprising,

a) reacting a compound of formula III

![Chemical Structure of III]

with a compound of formula IV in presence of a base and an organic solvent
wherein OB represents a suitable leaving group selected from the group consisting of p-chlorobenzenesulfonyl, p-bromobenzenesulfonyl, p-toluenesulfonyl, methanesulfonyl,
5 b) optionally, isolating the benzyl posaconazole, compound of formula IIa,
c) debenzyllating the benzyl posaconazole, compound of formula IIa, and
d) isolating the posaconazole, compound of formula I.

The reaction of compound of formula (III) with compound of formula (IV) may be carried out in the presence of a suitable base and suitable solvent.

The suitable base may be selected from either an inorganic or organic base.

The inorganic base may be selected from the group consisting of hydroxides, carbonates, bicarbonates, acetates for example lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium acetate and potassium acetate and the like.

The organic base may be selected from an aliphatic or an aromatic amine. Aromatic amines include pyridine, methyl morpholine; while the aliphatic amines can be selected from alkyl amine like triethylamine, monomethylamine or isopropylamine and the like.

Preferably the base is selected from the sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate; more preferably the base is sodium hydroxide. The molar ratio of the amounts of the compound of formula III and the base may be about 1:1 to about 1:3. The mole ratio of the compounds of formula III and IV would generally be from about an equimolar amount to about 2 times. Preferably, about an equimolar amount to about 1.3 molars.
The reaction solvent may be selected from aprotic solvents like tetrahydrofuran (THF), dimethylformamide (DMF), dimethylsulfoxide (DMSO) and mixtures thereof. Preferably, the solvent is dimethylsulfoxide.

The reaction is carried out at a temperature of about 20°C to about 55°C. The reaction time can vary from between about 3 hours to about 24 hours. Preferably, the reaction transpires between about 5 hours to about 15 hours.

The completion of reaction may be monitored by thin layer chromatography (TLC) or high performance liquid chromatography (HPLC). After completion of the reaction, the reaction mass may be diluted with water or with an organic solvent or with a mixture of water and an organic solvent. The organic solvent may be selected from the group consisting of haloalkanes such as dichloromethane, dichloroethane, chloroform and the like; esters such as ethyl acetate, methylisobutyl acetate and the like. Preferably the organic solvent is dichloromethane. The precipitated product may be isolated by filtration or the layers obtained are separated; the organic layer is washed with water. The solvent is removed by distillation under vacuum at temperatures below about 70°C. Preferably, below about 40°C.

The starting compound of formula (III) may be prepared by methods known in the art. Illustratively, the method may be that as in US Patent No. 5625064, which is incorporated herein as reference in its entirety.

The starting compound of formula (IV) is preferably compound of formula (IVa).

where OTs represents p-toluenesulfonyl

The compound of formula (IVa) may be prepared by methods known in the art. Illustratively, the method may be that as described in international publication WO 95/17407, which is incorporated herein as reference.
In one embodiment the compound of formula (III) is reacted with compound of formula (IVa) in the presence of a suitable inorganic base and an aprotic solvent to form benzyl posaconazole, compound of formula Ila. The obtained crude benzyl posaconazole compound of formula Ila, without isolation, may be used for debenzylation to form posaconazole in the same vessel. The process for debenzylation of the benzyl posaconazole is as previously described.

In one embodiment the compound of formula (III) is reacted with compound of formula (IVa) in the presence of sodium hydroxide and dimethyl sulfoxide (DMSO) to form benzyl posaconazole, compound of formula Ila. After completion of the reaction, the reaction mass may be diluted with water or with an organic solvent or with a mixture of water and an organic solvent. The organic solvent may be selected from the group consisting of haloalkanes such as dichloromethane, dichloroethane, chloroform and the like; esters such as ethyl acetate, methylisobutyl acetate and the like. Preferably, the organic solvent is dichloromethane. The precipitated product may be isolated by filtration or the layers obtained are separated; the organic layer is washed with water. The solvent is removed by distillation under vacuum at temperatures below about 70°C. Preferably, below about 40°C. The obtained crude benzyl posaconazole, compound of formula Ila, without isolation, may be used for debenzylation to form posaconazole in the same vessel. The process for debenzylation of the benzyl posaconazole is as previously described.

The obtained crude benzyl posaconazole, compound of formula Ila may be crystallized from suitable organic solvents to get pure benzyl posaconazole. Suitable organic solvents for crystallization of benzyl posaconazole are selected from, but are not limited to, water; C1- C4 alcohols for example, methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutyl alcohol, tertiary butyl alcohol and the like and mixtures thereof; esters such as methyl acetate, ethyl acetate, isopropyl acetate, tertiary butyl acetate and the like; ketones such as acetone, ethyl methyl ketone, and the like and mixtures thereof; hydrocarbons such as n-hexane, n-heptane, cyclohexane, toluene, xylene and the like and mixtures thereof. Preferably the solvent used for dissolution is selected from methanol, ethanol, isopropanol, acetone, ethyl acetate, n-hexane, water and
mixtures thereof. More preferably, the solvent used for dissolution is methanol or isopropanol.

[0074] The benzyl posaconazole, compound of formula Ila can be recovered by any conventional technique known in the art, for example filtration. Typically, if stirring is involved, the temperature during stirring can range from about -10°C to about 30°C. Preferably, at about 20°C to about 25°C. More preferably, at about 0°C to 10°C.

[0075] The resultant product may optionally be further dried. Suitably, drying can be carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer and the like. The drying can be carried out at a temperature ranging from about 30°C to about 70°C. The drying can be carried out for any desired time until the required product purity is achieved, e.g., a time period ranging from about 1 hour to about 50 hours, preferably about 20 hours.

[0076] The benzyl posaconazole recovered using the purification process of the present invention is in crystalline Form A.

[0077] The present invention provides a benzyl posaconazole in crystalline Form A characterized by peaks expressed in degrees 2θ±0.2°θ at about 2.04, 6.1, 12.24, 15.06, 15.73, 17.171 7.37, 18.15, 19.42, 19.97, 24.34, 26.0.

[0078] The present invention provides benzyl posaconazole in a crystalline form A characterized via X-ray powder diffraction pattern. The X-Ray powder diffraction can be measured by an X-ray powder Diffractometer equipped with a Cu-anode (λ=1.54 Angstrom), X-ray source operated at 45kV, 40 mA and a Ni filter is used to strip K-beta radiation. Two-theta calibration is performed using an NIST SRM 640c Si standard. The sample was analyzed using the following instrument parameters: measuring range=2-50° 2θ, step width=0.017°; and measuring time per step=5 sec.

[0079] In one embodiment, the present invention provides a process for the preparation of amorphous posaconazole, comprising, a) providing a solution of posaconazole in one or more solvents capable of dissolving the posaconazole, b) optionally, filtering the solvent solution to remove any extraneous matter, and c) substantially removing the solvent from the solution to provide posaconazole substantially in an amorphous form.
In a) of the process directly described, a solution is formed containing posaconazole and a solvent capable of dissolving the posaconazole. The posaconazole used as a starting material in the process can be, for example, hydrates, solvates, polymorphic forms and the like. Suitable solvents capable of dissolving posaconazole for use herein include, but are not limited to, alcoholic solvents having from 1 to 6 carbon atoms, e.g., methanol, ethanol, propanol, and the like, haloalkanes solvents such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane and the like ether solvents selected from tetrahydrofuran, 1,4-dioxane, diisopropyl ether, methyl tertiary butyl ether and mixtures thereof. Preferably, the solvent is dichloromethane. The dissolution can be carried out at a temperature ranging from about 25°C to about 100°C and preferably at a temperature ranging from about 45°C to about 70°C.

After the dissolution of the posaconazole in the solvent, the solution may optionally be filtered in order to remove any extraneous matter present in the solution using any standard filtration techniques known in the art. If desired, a filtering aid such as celite can be added to the solution.

In (c) of the process directly described, the solvent is substantially removed to provide amorphous posaconazole. The solvent may be removed by substantial evaporation of the solvent, concentrating the solution, cooling to obtain amorphous form and filtering the solid under an inert atmosphere, e.g., a nitrogen atmosphere. Evaporation may be achieved by techniques known in the art, e.g., by completely evaporating the solution in a rotavapor, a vacuum paddle dryer or in a conventional reactor under vacuum above about 720 mm Hg by flash evaporation techniques by using an agitated thin-film dryer, lyophilization at about sub-zero temperatures or freeze-drying techniques or evaporated by spray drying to obtain a dry amorphous powder.

Preferably the substantial removal of the solvent can be carried out by completely evaporating the solution in a rotavapor under vacuum above about 720 mm Hg. This process includes loading a solution containing posaconazole and the solvent capable of dissolving posaconazole into a rotavapor and the solution may be heated to a temperature ranging from about 25°C to about 80°C. Preferably at a temperature ranging from about 45°C to about 60°C and concentrated under vacuum.
In one embodiment, the present invention provides a process for the preparation of amorphous posaconazole, comprising, a) providing a solution of posaconazole in dichloromethane b) optionally, filtering the solvent solution to remove any extraneous matter, and c) substantially removing the solvent from the solution by evaporating the solution in a rotavapor under vacuum above to provide posaconazole substantially in an amorphous form.

In another method, the removal of the solvent is carried out via spray-drying. This process includes at least loading a solution containing posaconazole and the solvent capable of dissolving posaconazole into a spray drier and spraying the solution at a flow rate ranging from about 10 ml/hour to about 300 ml/hour. Preferably, from about 40 ml/hour to about 200 ml/hour. The air inlet temperature to the spray drier may range from about 25°C to about 150°C. Preferably, from about 60°C to 110°C. The outlet air temperature used may range from about 30°C to about 90°C.

If desired, the substantially pure amorphous posaconazole obtained by the above processes may be further dried in, for example, a vacuum tray dryer, rotovac vacuum dryer, vacuum paddle dryer or pilot plant rotavapor, to further lower residual solvents.

The present invention provides posaconazole having a chemical purity of greater than or equal to about 97% as measured by high performance liquid chromatography (HPLC). Preferably greater than or equal to about 99%. More preferably greater than or equal to about 99.8%.

Preferably, the chiral purity of the posaconazole is about at least 99% as measured by area under HPLC. More preferably about at least 99.5% as measured by area under HPLC. More preferably about at least 99.8% as measured by area under HPLC. More preferably about at least 99.9% as measured by area under HPLC.

In another aspect, the present invention provides posaconazole, prepared by the process herein described above, having less than about 0.5 area % of total impurities as measured by high performance liquid chromatography. Preferably less than about 0.15 area % of total impurities as measured by high performance liquid chromatography.
In yet another aspect, the present invention provides posaconazole having less than 0.15% of benzyl posaconazole of formula IIa.

In yet another aspect, the present invention provides posaconazole having less than 0.15% of compound of formula [V]

In yet another aspect, the present invention provides posaconazole having less than 0.15% of compound of formula [VI]

The present invention further provides posaconazole, obtained by the processes described herein, having relatively low content of one or more organic volatile impurities.

The present invention provides posaconazole, obtained using the processes described herein, may have a residual solvent content that is within the limits given by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines. The guideline solvent
The present invention provides posaconazole, obtained by the process disclosed herein, having less than about 800 parts per million (ppm) C_{1-4} alcohols such as methanol, ethanol, isopropanol, preferably less than about 200 ppm; less than about 500 ppm dichloromethane, preferably less than about 100 ppm; less than about 500 ppm dichloromethane, preferably less than about 100 ppm; less than about 500 ppm dimethyl sulfoxide, preferably less than about 100 ppm.

In yet another aspect of the present invention provides a pharmaceutical composition comprising posaconazole prepared by processes herein described above, and at least a pharmaceutically acceptable carrier.

The present invention further provides posaconazole as disclosed herein for use in a pharmaceutical composition, previously described, which may independently have a D_{50} and D_{90} particle size less than about 300 microns, preferably less than about 200 microns, more preferably less than about 150 microns, still more preferably less than about 50 microns and most preferably less than about 10 microns. Whereupon, the notation D_{x} means that X\% of particles have a diameter less than a specified diameter D. Thus, a D_{50} of about 300 microns means that 50\% of the micronized particles in a composition have a diameter less than about 300 microns. Any milling, grinding, micronizing or other particle size reduction method known in the art can be used to bring the solid state posaconazole into any desired particle size range set forth above.

The present invention provides a pharmaceutical composition comprising posaconazole prepared by processes herein described above, and at least a pharmaceutically acceptable carrier. Such pharmaceutical compositions may be administered to a mammalian patient in any dosage form, e.g., liquid, powder, elixir, injectable solution, etc. Dosage forms may be adapted for administration to the patient by oral, buccal, parenteral, ophthalmic, rectal and transdermal routes. Oral dosage forms include, but are not limited to, tablets, pills, capsules, troches, sachets, suspensions, powders, lozenges, elixirs and the like.
The present invention provides a crystalline polymorphic Form V of posaconazole that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees $2\theta \pm 0.2^\circ$ at about 6.9, 8.8, 10.3, 21.4 and 22.6.

In one embodiment, the present invention provides a crystalline polymorphic Form V of posaconazole characterized by peaks expressed in degrees $2\theta \pm 0.2^\circ$ at about 6.9, 8.8, 10.3, 10.8, 16.1, 17.1, 18.8, 20.2, 20.7, 21.4 and 22.6.

The present invention provides a crystalline polymorphic Form V of posaconazole having an X-ray diffraction pattern, substantially in accordance with Fig. 3 and Fig. 4.

The present invention provides characterization via X-ray powder diffraction pattern of crystalline polymorphic Form V of posaconazole. The X-Ray powder diffraction can be measured by an X-ray powder Diffractometer equipped with a Cu-anode ($\lambda = 1.54$ Angstrom), X-ray source operated at 45kV, 40 mA and a Ni filter is used to strip K-beta radiation. Two-theta calibration is performed using an NIST SRM 640c Si standard. The sample was analyzed using the following instrument parameters: measuring range=2-50° $2\Theta$; step width=0.017°; and measuring time per step=5 sec.

The comparative X-ray powder diffraction pattern characteristic peaks of the novel crystalline polymorphic Form V of posaconazole and the known polymorphic forms described in the background of the invention is tabulated below; Table I: X-ray powder diffraction pattern

<p>| Form I | Form II | Form III | Form IV | Form V | | | | |
|--------|---------|----------|---------|--------|---------|---------|</p>
<table>
<thead>
<tr>
<th>d value</th>
<th>% RI</th>
<th>d value</th>
<th>% RI</th>
<th>d value</th>
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[00104] In one embodiment, the present invention provides a process for the preparation of crystalline polymorphic Form V of posaconazole, comprising, a) providing a solution of posaconazole in one or more solvents capable of dissolving the posaconazole and b) substantially removing the solvent from the solution to provide crystalline polymorphic Form V of posaconazole.

[00105] In step a) of the process directly described, a solution is formed containing at least posaconazole and a solvent capable of dissolving the posaconazole. The posaconazole used as a starting material in the process can be, for example, hydrates, solvates, polymorphic forms and the like. Suitable solvents capable of dissolving posaconazole for use herein include, but are not limited to, alcoholic solvents having from 1 to 6 carbon atoms, e.g., methanol, ethanol, propanol, and the like, haloalkanes solvents such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane and the like or their mixtures. Preferably, the solvent is dichloromethane. The dissolution can be carried out at a temperature ranging from about 25°C to about 100°C and...
preferably at a temperature ranging from about 45°C to about 75°C. If required the solution of posaconazole in the solvent is filtered so that it is particle free. In step b) of the process directly described, the solvent is substantially removed to provide crystalline polymorphic Form V of posaconazole. The solvent may be removed substantially by evaporation of the solvent. Evaporation may be achieved by techniques known in the art, e.g., by completely evaporating the solution in a rotavapor using a rotational evaporator device such as a Buchi Rotavapor, by flash evaporation techniques by using an agitated thin-film dryer, or by spray drying.

Evaporation of the solvent may be conducted under a vacuum, at about 550 mm Hg to about 760 mm Hg, at elevated temperatures such as about 50°C to about 75°C. The temperature and vacuum conditions should not lend to a deleterious increase in the impurity levels of the product. The concentration, solvent type, temperature, vacuums, and feeding rate are set at conditions where the posaconazole coming from the inlet precipitates virtually instantly.

Preferably the substantial removal of the solvent can be carried out by rapid evaporation technique by completely evaporating the solution in a rotavapor which is preheated in the temperature range of about 40°C to about 80°C and under vacuum about 700 mm Hg. This process includes loading a solution containing posaconazole and the solvent capable of dissolving posaconazole into a rotavapor which is preheated in the temperature range of about 40°C to about 75°C drop wise, portion-wise or continuously and concentrating the solution under vacuum. The speed of the addition of the solution is about 10 ml per minute.

In one preferred embodiment, the present invention provides a process comprising a) dissolving posaconazole in haloalkane and b) pouring the solution portion wise in a preheated Buchi flask which is under vacuum in the range of about 700 mm Hg to about 750 mm Hg and wherein the temperature is in the range of about 50°C to about 75°C; c) evaporating the solution almost instantaneously to give the desired crystalline form V of posaconazole; and d) adding the next portion in the flask and repeating the process.

Preferably dichloromethane is used for dissolving posaconazole. After complete addition of all the portions of the solution of posaconazole, the Buchi flask is
maintained under vacuum in the range of about 650 mmHg to about 750 mmHg and at a
temperature in the range of about 50°C to about 75 °C; for a period of about 1 hour to 2
hours and the crystalline form V' of posaconazole is isolated.

[00110] If desired, crystalline polymorphic Form V of posaconazole obtained by
the above processes may be, optionally, further dried. Suitably, drying can be carried out
in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer
and the like. The drying can be carried out at a temperature ranging from about 30°C to
about 70°C. The drying can be carried out for any desired time until the required product
purity is achieved, e.g., a time period ranging from about 1 hour to about 50 hours,
preferably about 20 hours.

[00111] In yet another aspect, the present invention provides a pharmaceutical
composition comprising crystalline polymorphic Form V of posaconazole and at least a
pharmaceutically acceptable carrier.

[00112] Such pharmaceutical compositions may be administered to a mammalian
patient in any dosage form, e.g., liquid, powder, elixir, injectable solution, etc. Dosage
forms may be adapted for administration to the patient by oral, buccal, parenteral,
ophthalmic, rectal and transdermal routes. Oral dosage forms include, but are not limited
to, tablets, pills, capsules, troches, sachets, suspensions, powders, lozenges, elixirs and
the like.

[00113] The following examples are provided to enable one skilled in the art to
practice the invention and are merely illustrative of the invention. The examples should
not be read as limiting the scope of the invention as defined in the features and
advantages.
COMPARATIVE EXAMPLE 1
DEBENZYLATION USING HYDROBROMIC ACID

In a clean, dry 250 ml round bottom flask 5 gm of benzyl posaconazole, 125 ml of hydrobromic acid were charged and stirred at about 30°C for 24 hours. After completion of the reaction, the reaction mass was cooled to about 5°C. The pH of the solution was adjusted to 7.5 using 4N NaOH solution and stirred for about 1 hour at about 5°C and stirred for about 30 minutes. 75 ml of dichloromethane was added to the reaction mass and stirred for about 30 minutes. The organic and aqueous layers were separated, where the aqueous layer was extracted with 30 ml of dichloromethane. All dichloromethane layers were combined and washed with water and brine solution and dried over sodium sulphate. The dichloromethane layer was completely concentrated under vacuum at about 35°C and 10 ml of acetone was added the solution was heated to about 40°C to get clear solution. 50 ml of water was added to the solution and stirred for about 12 hours. The formed precipitate was filtered and washed with water and dried to yield 1.1 gm of posaconazole. Purity by HPLC: 90%.

COMPARATIVE EXAMPLE 2
DEBENZYLATION USING FORMIC ACID

In a clean, dry 250 ml round bottom flask 5 gm of benzyl posaconazole, 106 ml of methanol were charged, a clear solution was obtained. Then 0.5 gm of 10% Pd/C and 54 ml of formic acid were added. The reaction mass was heated slowly to about 60°C and maintained for about 4 hours. After completion of the reaction, the reaction mass was cooled to about room temperature and filtered and washed with 50 ml of methanol. The filtrate was quenched into 600 ml of ice cooled water under stirring. The pH of the solution was adjusted to about 4.0 to about 5.0 using liquid ammonia. The solution was extracted twice with 100 ml of ethyl acetate each time and all of the combined ethyl acetate layers were dried over sodium sulphate. The ethyl acetate layer was concentrated completely under vacuum to get 3 gms of oily mass.

Purity by HPLC: 57.30%.
EXAMPLES

EXAMPLE 1

PREPARATION OF BENZYL POSACONAZOLE OF FORMULA (IIa)

In a clean, dry round bottomed flask 37.5 ml of dimethylsulfoxide and 4.74 gm of compound of formula (III) were charged at room temperature and stirred for about 15 minutes. Added previously prepared NaOH solution (0.53 gm of NaOH dissolved in 3.74 ml of water) into the flask at room temperature and stirred for about 30 minutes. 5 gm of compound of formula (IVa) was added to the reaction solution and stirred at room temperature for about 12 hours. After completion of the reaction the reaction solution was cooled to about 0°C and 50 ml of dichloromethane was added and stirred for about 15 minutes. 50 ml of water was added drop wise and stirred for about 30 minutes. The layers were separated, aqueous layer was extracted three times, each time with 30 ml of dichloromethane. All organic layers were combined and washed twice with 50 ml each of water. The organic layer was concentrated under vacuum at below about 40°C. 5 ml of isopropyl alcohol was added and distilled out under vacuum. 25 ml of isopropyl alcohol was added and stirred for about 10 hours. The mass was filtered and washed the solid with 5 ml of isopropyl alcohol. The solid was dried in air oven at about 45°C to yield 6.3 gm of the title compound. Purity by HPLC: 90%

EXAMPLE 2

PREPARATION OF BENZYL POSACONAZOLE OF FORMULA (IIa)

In a clean, dry round bottomed flask 23 ml of dimethylsulfoxide and 4.74 gm of compound of formula (III) were charged at room temperature and stirred for about 15 minutes. Previously prepared NaOH solution (0.53 gm of NaOH dissolved in 3.74 ml of water) was added into the flask at about room temperature and stirred for about 30 minutes. 5 gm of compound of formula (IVa) was added to the reaction solution and stirred at about 35°C to about 40°C for about 12 hours. After completion of the reaction, the reaction solution was cooled to about 0°C and 50 ml of water was added dropwise and stirred for about 30 minutes. The formed precipitate was filtered and washed with 80
ml of water. The solid was dried in air oven at about 45°C to about 50°C to yield 6.6 gm of the title compound. Purity by HPLC: 92%

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<td>2.72</td>
<td>2.62</td>
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**EXAMPLE 3**

**PREPARATION OF POSACONAZOLE OF FORMULA (I)**

In a clean, dry Pari shaker bottle 5 gm of benzyl posaconazole, 50 ml of methanol were charged and 3.1 ml of methane sulfonic acid and 0.5 gm of 10% Pd/C were added at about room temperature. 5 kg/cm² of hydrogen gas pressure was applied and stirred for about 4 hours at about room temperature. After completion of the reaction, the pressure was released and the reaction solution was filtered and the catalyst was washed with 15 ml of methanol. The methanol solution was concentrated completely under vacuum. Then
15 ml of isopropyl alcohol and 25 ml of water were added to the residue and stirred for about 15 minutes and cooled to about 5°C. The pH of the solution was adjusted to 7.5 using 4N NaOH solution and stirred for about 1 hour at about 5°C. The solid obtained was filtered and washed with 30 ml of water. The wet material was dried in a vacuum oven at about 50°C for about 12 hours to yield 4.3 gm of the title compound. Purity by HPLC: 95%

EXAMPLE 4
PREPARATION OF POSACONAZOLE OF FORMULA (I)

In a clean, dry Pari shaker bottle, 1 gm of benzyl posaconazole, 10 ml of methanol were charged and 1 gm of p-methylbenzene sulfonic acid and 0.1 gm of 10% Pd/C were added at about room temperature. 5 kg/cm² of hydrogen gas pressure was applied and stirred for about 4 hours at about room temperature. After completion of the reaction, the pressure was released and the reaction solution was filtered and the catalyst was washed with 15 ml of methanol. The methanol solution was concentrated completely under vacuum. Then 15 ml of isopropyl alcohol and 25 ml of water were added to the residue and stirred for about 15 minutes and cooled to about 5°C. The pH of the solution was adjusted to 7.5 using 4N NaOH solution and stirred for about 1 hour at about 5°C. The solid obtained was filtered and washed with 30 ml of water. The wet material was dried in a vacuum oven.

EXAMPLE 5
PREPARATION OF POSACONAZOLE OF FORMULA (I)

In a clean, dry Pari shaker bottle, 1 gm of benzyl posaconazole, 10 ml of methanol were charged and 0.9 gm of benzene sulfonic acid and 0.1 gm of 10% Pd/C were added at about room temperature. 5 kg/cm² of hydrogen gas pressure was applied and stirred for about 4 hours at about room temperature. After completion of the reaction, the pressure was released and the reaction solution was filtered and the catalyst was washed with 15 ml of methanol. The methanol solution was concentrated completely under vacuum. Then 15 ml of isopropyl alcohol and 25 ml of water were added to the residue and stirred for about 15 minutes and cooled to about 5°C. The pH of the solution was adjusted to 7.5
using 4N NaOH solution and stirred for about 1 hour at about 5°C. The solid obtained was filtered and washed with 30 ml of water. The wet material was dried in vacuum oven.

**EXAMPLE 6**

**PREPARATION OF POSACONAZOLE (I) WITHOUT ISOLATING THE INTERMEDIATE BENZYL POSACONAZOLE**

In a clean, dry round bottom flask charge 37.5 ml of dimethylsulfoxide and 4.74 gm of compound of formula (III) at room temperature and stir for about 15 minutes. Add previously prepared NaOH solution (0.53 gm of NaOH dissolved in 3.74 ml of water) in to the flask at about room temperature and stir for about 30 minutes. Add 5 gm of compound of formula (IVa) in the reaction solution and stir at room temperature for about 12 hours. After completion of the reaction, cool the reaction solution to about 0°C and add 50 ml of dichloromethane and stir for about 15 minutes. Then add 50 ml of water dropwise and stir for about 30 minutes. Separate the layers, then extract the aqueous layer three times, each time with 30 ml of dichloromethane. Combine all organic layers and wash twice with 50 ml each of water. Concentrate the organic layer under vacuum at below about 40°C. Then add 5 ml of methanol and distill out under vacuum. Then added 50 ml of methanol and transfer the solution into a Pari shaker bottle. Add 3.1 ml of methane sulfonic acid and 0.5 gm of Pd/C at room temperature. Apply 5 kg/cm² of hydrogen gas pressure and stir for about 4 hours at about room temperature. After completion of the reaction, release the pressure and filter the reaction solution and wash the catalyst with about 15 ml of methanol. Concentrate the methanol solution completely under vacuum. Then add 15 ml of isopropyl alcohol and 25 ml of water to the residue and stir for about 15 minutes and cool to about 5°C. Adjust the pH of the solution to 7.5 using 4N NaOH solution and stir for about 1 hour at about 5°C. Filter the solid obtained and wash with 30 ml of water. Dry the wet material in a vacuum oven at about 50°C for about 12 hours.

**EXAMPLE 7**

**PREPARATION OF AMORPHOUS POSACONAZOLE**
5 gm of posaconazole was dissolved in 50 ml of dichloromethane and the solution was filtered through Whatman paper to remove any particles. The solution was transferred into a Buchi flask and heated the water bath of the rotavapor to about 70°C. Concentrated the solution completely under vacuum and degassed the solid obtained well under same conditions for about 3 hours. The material was unloaded from the Buchi flask and dried in a vacuum oven at about 45°C for about 10 hours to give 4.5 gm of amorphous posaconazole. Purity by HPLC: 99.85%.

**EXAMPLE 8**

**PREPARATION OF CRYSTALLINE POSACONAZOLE POLYMORPHIC FORM V**

10 gm of posaconazole was charged in 100.0 ml dichloromethane at about 25°C to about 30°C and stirred for dissolution for about 15-20 minutes. The solution was filtered and was transferred in to a conical flask. An empty clean and dry 1.0 liter Buchi flask was fixed to rotavapour and vacuum was applied and heated to about 70°C to about 75°C under rotation. At the temperature of about 70°C to about 75°C and vacuum of not less than 650 mmHg, dichloromethane solution was sucked out with a pipe attached to the rotavapour knob into Buchi flask portion-wise at 10 ml/ min. After completion of suction of solution, the crystallized material was dried for about another 120 minutes at same conditions.

Unloaded material was subjected to drying in vacuum oven for about 12 hrs at about 40°C to about 45°C.

**Yield: 9.2 gm**

The x-ray powder diffractogram pattern distinctive for crystalline polymorphic Form V of posaconazole is tabulated below

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<thead>
<tr>
<th>Crystal form V</th>
</tr>
</thead>
<tbody>
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| 8.83 | 10.01 | 1.89 |
| 10.32 | 8.58 | 7.39 |
| 10.86 | 8.15 | 12.03 |
| 11.54 | 7.67 | 5.22 |
| 12.25 | 7.23 | 7.65 |
| 13.30 | 6.66 | 0.84 |
| 14.31 | 6.19 | 6.83 |
| 14.78 | 5.99 | 4.87 |
| 15.30 | 5.79 | 8.42 |
| 16.07 | 5.51 | 100 |
| 17.16 | 5.17 | 12.32 |
| 17.93 | 4.95 | 7.05 |
| 18.85 | 4.71 | 13 |
| 19.16 | 4.63 | 8.52 |
| 20.18 | 4.40 | 13.66 |
| 20.74 | 4.28 | 26.28 |
| 21.33 | 4.17 | 12.5 |
| 22.57 | 3.94 | 12.31 |
| 23.96 | 3.71 | 9.76 |
| 24.90 | 3.58 | 8.97 |
| 25.56 | 3.48 | 9.08 |
| 26.53 | 3.36 | 3.34 |
| 27.11 | 3.29 | 3.46 |
| 28.23 | 3.16 | 0.63 |
| 29.43 | 3.03 | 1.15 |
| 31.31 | 2.86 | 2.87 |
| 32.83 | 2.73 | 1.04 |
| 34.22 | 2.62 | 0.97 |
| 36.43 | 2.47 | 0.68 |
| 37.55 | 2.40 | 0.76 |

EXAMPLE 9
PREPARATION OF CRYSTALLINE POSACONAZOLE POLYMORPHIC FORM V

10 gm of posaconazole was charged in 100.0 ml dichloromethane at about 25°C to about 30°C and stirred for dissolution for about 15-20 minutes. The solution was filtered and was transferred into conical flask. An empty clean and dry 1.0 lit Buchi flask was fixed to rotavapour and vacuum was applied and heated to about 70°C to about 75°C under rotation. At the temperature of about 70°C to about 75°C and vacuum of not less than 650
mmHg, dichloromethane solution was sucked out with a pipe attached to the rotavapour knob into Buchi flask portion-wise at 10 ml/minutes. After completion of suction of solution, the crystallized material was dried for about another 60 minutes at same conditions.

Unloaded material subjected to dried in vacuum oven for 12 hrs at 40-45°C.

**Yield: 9.0 g**

The x-ray powder diffractogram pattern distinctive for crystalline polymorphic Form V of posaconazole is tabulated below

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<td>18.86</td>
<td>4.70</td>
</tr>
<tr>
<td>19.22</td>
<td>4.62</td>
</tr>
<tr>
<td>20.26</td>
<td>4.38</td>
</tr>
<tr>
<td>20.80</td>
<td>4.27</td>
</tr>
<tr>
<td>21.42</td>
<td>4.15</td>
</tr>
<tr>
<td>22.64</td>
<td>3.93</td>
</tr>
<tr>
<td>24.03</td>
<td>3.70</td>
</tr>
<tr>
<td>25.13</td>
<td>3.54</td>
</tr>
</tbody>
</table>
EXAMPLE 10

Posaconazole formulations

Formulation A

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredient</th>
<th>mg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Posaconazole crystalline form V</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>Hydroxypropyl Betacyclodextrin</td>
<td>500</td>
</tr>
<tr>
<td>3</td>
<td>Sodium benzoate</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Sodium citrate dihydrate</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>Citric acid monohydrate</td>
<td>2.5</td>
</tr>
<tr>
<td>6</td>
<td>Artificial cherry flavor</td>
<td>0.5</td>
</tr>
<tr>
<td>7</td>
<td>Purified water</td>
<td>1000</td>
</tr>
</tbody>
</table>

Dissolve Hydroxypropyl Betacyclodextrin into purified water using mechanical stirrer. Add Posaconazole crystalline form V and stir for about 20 hours. Add sodium benzoate, sodium citrate dihydrate, citric acid monohydrate, artificial cherry flavor into solution & stir well to obtain posaconazole formulation.
Formulation B

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredient</th>
<th>I mg/ml</th>
<th>II mg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Posaconazole crystalline form V</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>SLS (sodium lauryl sulfate)</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Polysorbate</td>
<td>0</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>Simethicone</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Sodium benzoate</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Sodium citrate dihydrate</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>6</td>
<td>Citric acid monohydrate</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>7</td>
<td>Glycerin</td>
<td>107.5</td>
<td>107.5</td>
</tr>
<tr>
<td>8</td>
<td>Xanthan gum 180</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>Liquid glucose</td>
<td>350</td>
<td>350</td>
</tr>
<tr>
<td>10</td>
<td>Titanium dioxide</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>Artificial cherry flavor</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>Purified water to q.s.</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

1) Partial quantity of water is taken and to it SLS/polysorbate is added with continuous stirring till dissolved.

2) To 1, Simethicone is added and mixed with stirring.

3) Crystalline form V posaconazole is added to 2 under continuous stirring.

4) Sodium Benzoate, sodium citrate monohydrate, citric acid monohydrate is added to 3 under stirring.

5) Xanthan gum is dispersed into 4 under continuous stirring and allowed to hydrate for about 30 minutes.

6) Glycerin is added to 5 with continuous stirring.

7) Partial quantity of purified water is added to the 6 suspension under continuous stirring.

8) Liquid glucose is added to 7, followed by the addition of titanium dioxide and cherry flavor.

9) Remaining quantity of purified water is added to 8 to make up the volume and mixed well to obtain a uniform suspension.
CLAIMS

1. A process for preparing posaconazole, compound of formula I

![Formula I]

wherein R represents H, alkyl, substituted alkyl, halogen, nitro, amino using a metal catalyst and a hydrogen source in presence of an organic acid selected from the group consisting of a sulfonic acid, a sulfmic acid, a carboxylic acid having two or more carbon atoms and;

b) optionally purifying the posaconazole.

2. The process as claimed in claim 1 wherein the sulfonic acid is selected from the group consisting of methane sulfonic acid, methane disulfonic acid, ethane sulfonic acid, benzene sulfonic acid, paramethylbenzene sulfonic acid, paraaminobenzene sulfonic acid, camphor sulfonic acid.

3. The process as claimed in claim 1 wherein the metal catalyst is selected from the group consisting of palladium on carbon, palladium hydroxide, palladium hydroxide on carbon, Raney nickel, platinum, iridium, ruthenium.
4. A process as claimed in claim 1 wherein R is H, the sulfonic acid is methane sulfonic acid and hydrogen source is hydrogen gas.

5. A process for preparing posaconazole, compound of formula I

![Chemical Structure](image1)

comprising,

a) reacting a compound of formula III

![Chemical Structure](image2)

with a compound of formula IV in presence of a base and an organic solvent

![Chemical Structure](image3)

wherein OB represents leaving group selected from the group consisting of p-chlorobenzenesulfonyl, p-bromobenzenesulfonyl, p-toluenesulfonyl methanesulfonyl, to form compound of formula IIa, benzyl posaconazole
b) optionally, isolating the benzyl posaconazole, compound of formula Ila,
c) debenzylating the benzyl posaconazole, compound of formula Ila, and

d) isolating the posaconazole, compound of formula [I].

6. The process as claimed in claim 5, wherein the benzyl posaconazole, compound of formula Ila is not isolated and the debenzylation is carried out using a metal catalyst and a hydrogen source in presence of an organic acid selected from a sulfonic acid, a sulfinic acid, a carboxylic acid having two or more carbon atoms.

7. A process for preparing amorphous form of posaconazole, comprising:
a) providing a solution of posaconazole in one or more solvents capable of dissolving the posaconazole;
b) optionally, filtering the solvent solution to remove any extraneous matter; and
c) substantially removing the solvent from the solution to provide posaconazole substantially in an amorphous form.

8. The process as claimed in claim 7, wherein the solvent is selected from the group consisting of C1-C5 alcohol solvents selected from methanol, ethanol, isopropyl alcohol, isobutyl alcohol; haloalkane solvents selected from diechloromethane, chloroform, carbon tetrachloride, dichloroethane; ether solvents selected from tetrahydrofuran, 1,4-dioxane, diisopropyl ether, methyl tertiary butyl ether and mixtures thereof.

9. The process as claimed in claim 8, wherein the haloalkane solvent is diechloromethane.

10. The process as claimed in claim 7, wherein the removal of solvent is done by
evaporating the solution under vacuum.

11. Crystalline benzyl posaconazole Form A, wherein the Form A has an XRD pattern substantially in accordance with Figure 1.

12. Crystalline benzyl posaconazole Form A characterized by peaks expressed in degrees 2θ± 0.2° at about 2.04, 6.1, 12.24, 15.06, 15.73, 17.17, 17.37, 18.15, 19.42, 19.97, 24.34, 26.0.

13. Posaconazole having a chemical purity of greater than about 99.5 area % as measured by high performance liquid chromatography.

14. Posaconazole having a chiral purity of greater than about 99.8 area % as measured by high performance liquid chromatography.

15. Posaconazole having less than about 0.15 area % of total impurities as measured by high performance liquid chromatography

16. Posaconazole having less than 0.15 area % of benzyl posaconazole of formula [IIa] as measured by high performance liquid chromatography

17. Posaconazole having less than 0.15 area % of compound of formula [V] as measured by high performance liquid chromatography
18. Posaconazole having less than 0.15 area % of compound of formula [VI] as 
measured by high performance liquid chromatography

\[
\text{VI}
\]

19. A pharmaceutical composition comprising posaconazole prepared by process as 
claimed in claim 1 and at least a pharmaceutically acceptable carrier.

20. A crystalline polymorphic Form V of posaconazole that exhibits an X-ray powder 
diffraction pattern having characteristic peaks expressed in degrees 2\(\theta\) \(\pm\) 0.2° \(\theta\) at about 
6.9, 8.8, 10.3, 21.4 and 22.6.

21. A crystalline polymorphic Form V of posaconazole as claimed in claim 20 further 
characterized by peaks expressed in degrees 2\(\theta\) \(\pm\) 0.2° \(\theta\) at about 10.8, 16.1, 17.1, 18.8, 
20.2 and 20.7.

22. A process for the preparation of crystalline polymorphic Form V of posaconazole, 
comprising, a) providing a solution of posaconazole in one or more solvents capable of 
dissolving the posaconazole and b) substantially removing the solvent from the solution 
to provide crystalline polymorphic Form V of posaconazole.

23. A process as claimed in claim 22 wherein in b) the solvent is removed by rapid 
evaporation.

24. A pharmaceutical composition comprising crystalline polymorphic Form V of 
posaconazole and at least a pharmaceutically acceptable carrier.