

Novel polymorphs of Atovaquone and process of preparation thereof

Technical Field

The present invention relates to novel crystalline forms of anti *Pneumocystis carinii* compound (2-[4-(4-Chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone) commonly known as Atovaquone and methods for producing the same.

Background and Prior Art

Pneumocystis carinii is a parasite, which has a natural habitat in lung tissue, in a host with normal immune system. Without treatment *Pneumocystis carinii* pneumonia is almost always fatal in immunocompromised host. U.S. patent 4,981,874 discloses the process of preparation and the activity of the Atovaquone.

Polymorphs of Atovaquone are not reported yet. The term 'polymorphs', is meant to include different physical forms, crystalline /liquid crystalline/amorphous forms.

Polymorphic studies have become very interesting and important as many active pharmaceutical ingredients exhibit polymorphism and some/one of the polymorphic form exhibit high bio-availability and also much better activity as compared to other polymorphs.

We have focused our research to develop new polymorphic forms with an object to develop novel polymorphic forms of anti *Pneumocystis carinii* compound Atovaquone.

Summary of the invention

U. S. Pat. No. 4,981,874 discloses the recrystallization/purification of Atovaquone using solvent acetonitrile. The polymorphic form obtained by this method is referred hereafter as Form I, characterized by an X-ray powder diffraction pattern having peaks at about 7.2, 11.04, 11.77, 19.34, 21.14, 24.61, 25.28, 28.4 ± 0.2 degrees. The DSC thermogram of Form I shows a small endotherm at 197°C followed by a sharp endotherm at 222°C.

The present invention provides crystalline Atovaquone Form II, characterized by an X-ray powder diffraction pattern having peaks at about 7.02, 9.68, 10.68, 11.70, 14.25, 14.83, 18.60, 19.29, 23.32, 24.54 ± 0.2 degrees. The DSC thermogram of Form II shows a small endotherm at 169°C followed by a sharp endotherm at 222°C

The present invention also provides crystalline Atovaquone Form III, characterized by an X-ray powder diffraction pattern having peaks at about 6.99, 9.65, 12.67, 20.07, 20.65, 20.99, 21.88, 22.10, 25.56 ± 0.2 degrees. The DSC thermogram of Form III shows characteristic sharp endotherm at 222°C

The present invention also provides a process for preparing Form I comprising of dissolution of crude Atovaquone in a solvent; adding anti-solvent to the solution, cooling the resultant solution and, collecting the crystals of Form I.

The present invention also provides a process for converting crystalline Atovaquone Form I to Form II, comprising dissolution of Atovaquone Form I in a solvent by heating; cooling the resultant solution and, collecting the crystals of Form II.

The present invention also provides a process for converting crystalline Atovaquone Form I to Form III, comprising dissolution of Atovaquone Form I in a solvent by heating; cooling the resultant solution and, collecting the crystals of Form III.

The present invention also provides a process for preparing crystalline Atovaquone Form III, comprising dissolution of Atovaquone Form I in a solvent; adding anti-solvent to the solution, cooling the resultant solution and, collecting the crystals of Form III.

Pharmaceutical compositions comprising therapeutically effective amount of polymorphs II and III of Atovaquone are also disclosed herein.

A method of treating *Pneumocystis carinii* pneumonia, the method comprising administering to a warm blooded animal an effective amount of a product-by-process composition of matter comprising polymorphic forms of Atovaquone is also envisaged as part of this invention.

Description of the Invention

The present invention provides new crystal forms of Atovaquone. The discovery of new crystalline form of Active pharmaceutical ingredient will be advantageous with regard to improvement in performance of the product.

The present invention also relates to the solid-state forms (i.e. Polymorphs) of Atovaquone that can be prepared by the methods described herein.

As used herein, a solvent is any liquid substance which has capacity to dissolve the organic compound Atovaquone, either at room temperature or higher. Antisolvent is an organic solvent in which organic compound such as Atovaquone has poor solubility.

As used herein, room temperature means a temperature from about 25°C to 30°C.

X-ray powder diffraction pattern has been obtained on D 8 –Advance, Bruker AXE, Germany, diffractometer equipped with scintillation detector using Copper $K\alpha$ ($\lambda = 1.5406 \text{ \AA}$) radiation with scanning range between 2-50 θ at scanning speed of 2 ° / min.

Differential Scanning Calorimeter was performed on Mettler DSC 20 instrument. Samples of 2 mg to 3 mg weighed in aluminum crucible with holes were scanned at a heating rate of 10°C per minute under Nitrogen atmosphere at a rate of 35 ml / min.

Atovaquone Form I

Atovaquone is prepared by the method described in US, 4,981,874 which is referred as Form I. The X-ray powder diffraction diagram and DSC thermograms of Form I are shown in Figs. 1 and 4 respectively.

Preparation of Atovaquone Form I

Example 1

1g. of crude Atovaquone Form I was dissolved in 10 mL methylene dichloride at room temperature. To this solution 20 mL of methanol was added drop wise under stirring at same temperature. The slurry obtained was stirred for 4 hrs. at the same temperature. The solid was filtered and dried to get Form I.

Example 2

1g. of crude Atovaquone Form I was dissolved in 10 mL methylene dichloride at room temperature. To this solution 20 mL of n-Heptane was added drop wise under stirring at same temperature. The slurry obtained was stirred for 4 hrs. at the same temperature. The solid was filtered and dried to get Form I.

Preparation of Atovaquone Form II

Atovaquone Form II is prepared from Form I by the method described below and the DSC thermogram, X-ray powder diffraction diagram of Form II are shown in Figs. 2 and 5 respectively

Example 3

1g. of Atovaquone Form I was dissolved in 5 mL 1,4-Dioxane under reflux condition. The clear solution was allowed to cool to room temperature for 30 minutes and then cooled at 5°C for 4 hours. The solid obtained was then recovered on Buchner funnel and dried to get Form II.

Preparation of Atovaquone Form III

Atovaquone Form III is prepared from Form I by the method described below and the DSC thermogram, X-ray powder diffraction diagram of Form III are shown in Figs. 3 and 6 respectively

Example 4

0.5 g Atovaquone Form I was dissolved in 20 mL Acetone under reflux condition. 40 ml of water was maintained at 0°C and to this cold water, the hot solution of the Atovaquone was added dropwise with stirring. The solution was maintained at the same temperature for 1 hr. The solid thus obtained was filtered and dried to get Form III.

Example 5

0.5 g. Atovaquone Form I was dissolved in 15 mL chloroform at room temperature. To this solution 20 mL of methanol was added drop wise under stirring at same temperature. The slurry obtained was stirred for 4 hrs. at the same temperature. The solid was filtered and dried to get Form III.

Example 6

0.5 g. Atovaquone Form I was dissolved in 80 mL diisopropyl ether under reflux condition. The solution was cooled to room temperature and maintained at same temperature for 4 hrs. The solid was filtered and dried to get Form III.

Description of the figures:

Fig. 1 Shows the X-ray Diffraction Diagram of Atovaquone Form I

Fig. 2 Shows the X-ray Diffraction Diagram of Atovaquone Form II

Fig. 3 Shows the X-ray Diffraction Diagram of Atovaquone Form III

Fig. 4 Shows the DSC Thermogram of Atovaquone Form I

Fig. 5 Shows the DSC Thermogram of Atovaquone Form II

Fig. 6 Shows the DSC Thermogram of Atovaquone Form III

The polymorphic form I obtained by this method is characterized by an X-ray powder diffraction pattern (Fig. 1) having peaks at about 7.2, 11.04, 11.77, 19.34, 21.14, 24.61, 25.28, 28.4 ± 0.2 degrees. The DSC thermogram of Form I (Fig. 2) shows a small endotherm at 197°C followed by a sharp endotherm at 222°C.

The present invention provides crystalline Atovaquone Form II, characterized by an X-ray powder diffraction pattern having peaks at about 7.02, 9.68, 10.68, 11.70, 14.25, 14.83, 18.60, 19.29, 23.32, 24.54 ± 0.2 degrees as shown in Fig. 2. The DSC thermogram of Form II in Fig. 3 shows a small endotherm at 169°C followed by a sharp endotherm at 222°C

The present invention also provides crystalline Atovaquone Form III, characterized by an X-ray powder diffraction pattern (Fig. 4) having peaks at about 6.99, 9.65, 12.67, 20.07, 20.65, 20.99, 21.88, 22.10, 25.56 ± 0.2 degrees. The DSC thermogram of Form III (Fig. 5) shows characteristic sharp endotherm at 222°C

Pharmaceutical compositions comprising therapeutically effective amount of polymorphs II and III of Atovaquone are prepared by conventional methods.

A method of treating *Pneumocystis carinii* pneumonia, the method comprising administering to a warm blooded animal an effective amount of a product-by-process composition of matter comprising polymorphic forms of Atovaquone is also envisaged as part of this invention

AMENDED CLAIMS

[received by the International Bureau on 15 November 2005 (15.11.05);
original claims 1-28 replaced by new claims 1-23 (3 pages)].

1. A crystalline Atovaquone polymorphic Form II characterized by XPRD pattern with peaks at 2θ values of 7.02, 9.68, 10.68, 11.70, 14.25, 14.83, 18.60, 19.29, 23.32, 24.54.
2. The crystalline Atovaquone Form II as claimed in claim 1 exhibiting a DSC thermogram that has an endotherm at 169°C followed by another endotherm at 222°C.
3. A process for making crystalline Atovaquone Form II of claim 1 and 2 comprising the steps of:
 - a) dissolving Atovaquone Form I in a solublizing solvent at reflux temperature of the solvent to form a solution;
 - b) cooling the solution to precipitate Atovaquone crystals;
 - c) collecting the precipitated crystals at suction and
 - d) drying the crystals.
4. The process as claimed in claim 3, wherein the solublizing solvent is a cyclic ether, 1,4-Dioxane.
5. The process as claimed in claim 3, wherein the cooling is done at 5°C.
6. A crystalline Atovaquone polymorphic Form III, having characteristic X-ray diffraction peaks at 2θ values of 6.99, 9.65, 12.67, 20.07, 20.65, 20.99, 21.88, 22.10, 25.56.
7. The crystalline Atovaquone polymorphic Form III as claimed in claim 6, exhibiting DSC thermogram that has a characteristic endotherm at 222°C.
8. A process for making crystalline Atovaquone Form III as claimed in claims 6 and comprising the steps of:
 - a) dissolving Atovaquone Form I in a solublizing solvent at reflux temperature of the solvent to form a solution.
 - b) cooling the solution to precipitate Atovaquone crystals;
 - c) collecting the precipitated crystals at suction; and
 - d) drying the crystals.

9. The process as claimed in claim 8, wherein the solubilizing solvent is diisopropyl ether.
10. The process as claimed in claim 8, wherein the cooling is done to room temperature.
11. A process of making Atovaquone Form III as claimed in claims 6 and 7 comprising the steps of:
 - a) dissolving Atovaquone Form I in solubilizing solvent at room temperature or at reflux temperature based on the solvent used to form a solution;
 - b) adding an anti-solvent in which Atovaquone has poor solubility; to the solution till turbidity is obtained;
 - c) stirring the solution while cooling;
 - d) collecting the precipitated crystals and drying.
12. The process as claimed in claim 11, wherein the solubilizing solvent is selected from chlorinated solvent like chloroform or a ketone like acetone.
13. The process as claimed in claim 11, wherein the anti-solvent added to regenerate the solid is selected from the group consisting of methanol, ethanol and isopropanol.
14. The process as claimed in claim 13, wherein said anti solvent is methanol.
15. The process as claimed in claim 11, wherein the anti-solvent added to regenerate the solid is water.
16. A process of making Atovaquone Form I comprising the steps of;
 - a) dissolving Atovaquone in solubilizing solvent at room temperature to form a solution;
 - b) adding an anti-solvent to the solution till turbidity is seen;
 - c) stirring the solution;
 - d) collecting the precipitated crystals and drying the crystals.
17. The process as claimed in claim 16, wherein the solubilizing solvent is chlorinated solvent selected from methylene dichloride or ethylene dichloride.
18. The process as claimed in claim 16, wherein the anti-solvent added to regenerate the solid is selected from the group consisting of methanol, ethanol and isopropanol.
19. The process as claimed in claim 18, wherein the anti-solvent is methanol.
20. The process as claimed in claim 16 wherein the anti-solvent added to regenerate the

solid is selected from the group consisting of n-pentane, n- hexane and n-heptane.

21. The process as claimed in claim 20, wherein said anti solvent is n-heptane.
22. A composition comprising Atovaquone polymorph I or II or III or combination thereof, prepared by process claimed in any of the preceding claims.
23. Atovaquone polymorphs II and III either alone or in combination with polymorphic form I for the formulation of medicament for use in *Pneumocystis carinii* pneumonia infections.