

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 α ($\lambda = 1.5406 \text{ \AA}$) radiation with scanning range between 2-50 θ at scanning speed of 2 $^\circ$ / 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 $^\circ$ 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

We claim,

1. Atovaquone polymorphic Form II
2. Atovaquone Form II as claimed in claim 1 having Characteristic X-ray diffraction peaks at values of 2θ values of about 7.02, 9.68, 10.68, 11.70, 14.25, 14.83, 18.60, 19.29, 23.32, 24.54.
3. Atovaquone Form II as claimed in claim 1 exhibiting a DSC thermogram that has small endotherm at 169°C followed by sharp endotherm at 222°C
4. A process for making Atovaquone Form II comprising:
 - a) Dissolving Atovaquone Form I in a solublizing solvent at an elevated temp to form a solution.
 - b) Cooling the solution to precipitate Atovaquone
 - c) Collecting the precipitated product at suction
 - d) Drying the product
5. The process as claimed in claim 4 wherein the solublizing solvent is a cyclic ether preferably 1,4-Dioxane
6. The process as claimed in claim 4 wherein the elevated temperature that is between 35°C and about 90°C, preferably 70°C.
7. The process as claimed in claim 4 wherein the cooling is done between 0°C to 30°C, preferably 5°C.
8. The process as claimed in claim 4 wherein the drying is done between 50°C to 90°C, preferably 65°C.

9. Atovaquone polymorphic Form III
10. Atovaquone Form III as claimed in claim 9 having characteristic X-ray diffraction peaks at values of 2 θ values of about 6.99, 9.65, 12.67, 20.07, 20.65, 20.99, 21.88, 22.10, 25.56,
11. Atovaquone Form III as claimed in claim 9 exhibiting a DSC thermogram that has characteristic sharp endotherm at 222°C
12. A process for making Atovaquone Form III comprising of the steps of
 - a) Dissolving Atovaquone Form I in a solublizing solvent at an elevated temperature
to form a solution.
 - b) Cooling the solution to precipitate Atovaquone
 - c) Collecting the precipitated product at suction
 - d) Drying the product
13. The process as claimed in claim 12 wherein the solublizing solvent is an ether, preferably diisopropyl ether.
14. The process as claimed in claim 12 wherein the elevated temperature that is between 35°C and about 80°C, preferably at 70°C.
15. The process as claimed in claim 12 wherein the cooling is done between 0°C to 30°C, preferably 5°C.
16. The process as claimed in claim 12 wherein the drying is done between 50°C to 90°C, preferably 65°C.

17. A process of making Atovaquone Form III also comprising:
 - a) Dissolving Atovaquone Form I in Solublizing solvent at an elevated temperature to form a solution.
 - b) Adding an anti-solvent to the solution till turbidity is obtained.
 - c) Stirring the solution while cooling
 - d) Collecting the precipitated solid and drying
18. The process as claimed in claim 17 wherein the solublizing solvent is either chlorinated solvent like chloroform or a ketone preferably acetone.
19. The process as claimed in claim 17 wherein the dissolving is at an elevated temperature that is between 25° and about 70°C, preferably at 70°C.
20. The process as claimed in claim 17 wherein the anti-solvent added to regenerate the solid is selected from the group consisting of methanol, ethanol, isopropanol, preferably methanol.
21. The process as claimed in claim 17 wherein the anti-solvent added to regenerate the solid is water.
22. A process of making Atovaquone Form I comprising
 - a) Dissolving crude Atovaquone in Solublizing solvent at an elevated temperature to form a solution.
 - b) Adding an anti-solvent to the solution till turbidity is seen
 - c) Stirring the solution while cooling
 - d) Collecting the precipitated solid and drying

23. The process as claimed in claim 22 wherein the solublizing solvent is chlorinated solvents like methylene dichloride, ethylene dichloride preferably methylene dichloride.
24. The process as claimed in claim 22 wherein the dissolving is at an elevated temperature that is between 25° and 50°C, preferably at 50°C.
25. The process as claimed in claim 22 wherein the anti-solvent added to regenerate the solid is selected from the group consisting of methanol, ethanol, isopropanol, preferably methanol.
26. The process as claimed in claim 22 wherein the anti-solvent added to regenerate the solid is selected from the group consisting of aliphatic hydrocarbon like n-pentane, n-hexane, n-heptane, preferably n-heptane.
27. A composition comprising the said polymorphs as prepared by process claimed in any of the above claims.
28. 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 wherein the said polymorphic forms of Atovaquone manufactured by the process as claimed in any of the claims 1 to 26.