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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*
— *of inventorship (Rule 4.17(iv)) for US only*

**Published:**

— *with international search report*
— *with amended claims and statement*

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(54) **Title:** NOVEL POLYMORPHS OF ATOVAQUONE AND PROCESS OF PREPARATION THEREOF

(57) **Abstract:** 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 is disclosed herein. This also provides pharmaceutical compositions comprising the said polymorphs of Atovaquone and 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.

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# 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 immuncompromised 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 $\pm$ 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 $\pm$ 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$\pm$ 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 Kα ($\lambda$ = 1.5406 Å) 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 $\pm$ 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 $\pm$ 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$\pm$ 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 2θ 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.

## 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 solublizing 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 solublizing 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 solublizing solvent at room 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 crystals and drying the crystals.
17. The process as claimed in claim 15, wherein the solubilizing solvent is chlorinated solvents like methylene dichloride or ethylene dichloride.
18. The process as claimed in claim 15, 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 17, wherein the anti-solvent is methanol.
20. The process as claimed in claim 17 wherein the anti-solvent added to regenerate the

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

21. The process as claimed in claim 19, wherein said anti solvent is n-heptane.
22. A composition comprising said polymorphs as prepared by process claimed in any of the above 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.

## Statement under Article 19(1)

**Explanation**

We note from the supplemental sheet that, in examiner's opinion, the claims 2, 3, 5-8, 10, 11, 13-16, 18 and 20-26 lack inventive step. Whilst we strongly dispute the examiners opinion in this regard, in the interest of expediting prosecution of our application, we hereby delete the words reported to be "vague" in the claims and replace the same with specific terms with a view to determine the exact scope of the invention, and submit herewith the amended claims.

It is respectfully submitted that the main thrust of cited document (D1) relates to synthetic preparation of atovaquone. The distinctive features of the current application are different from those disclosed in the cited document. The crystalline polymorphic forms are generally more stable than the amorphous or its original crude form. The characteristic properties of polymorphic forms such as good flowability, high rate of dissolution and high bioavailability can be attributed to this stability. The compounds with these characteristics are useful to prepare pharmaceutical preparations and also easy to handle due to its thermal and chemical stability. D1 does not disclose or claim any polymorphic forms of atovaquone or its preparation.

From the above explanation, it is respectfully submitted that the present invention is novel and inventive with respect to the cited D1 document.

It is respectfully submitted that the main thrust of prior art document D2 and D3 pertains to general information regarding the polymorphic forms, its preparation and identification techniques of pharmaceutical compounds.

The main thrust of D4 document relates to the preparation of 2-substituted -3-hydroxy -1, 4-naphthoquinones, its activity against different protozoal species, its therapeutic preparations and use against protozoal disease in animals. The document D5 pertains to 2-substituted derivatives of 3-hydroxy-1,4, naphthoquinone and their use against malarial

infections. The recrystallization of atovaquone was carried out in a mixture of solvents in D4 and D5; which is a common technique to a person skilled in the art to purify the organic compound using suitable solvent. But, the present invention reveals different polymorphic forms and preparation thereof and its characterization which has not been reported till date. From the above explanation it is respectfully submitted that the present invention is inventive with respect to the prior art documents D4 and D5.

It is respectfully submitted that there is no disclosure or teaching till today, about the polymorphic forms of atovaquone as described in the present application and the process as adopted by us to prepare the same. The allegation of lack of inventive step may kindly be reviewed and reassessed in the light of above rationale. We submit that there is merit in our contention for inventive step. We once again, reiterate that our invention meets the standard tests of novelty and inventiveness unambiguously and hence fulfils the patentability criteria.

It is submitted that the above application is now in order to proceed for the publication, however, should the examiner, unexpectedly, have any further objections, the primary examiner is respectfully requested to communicate the same.

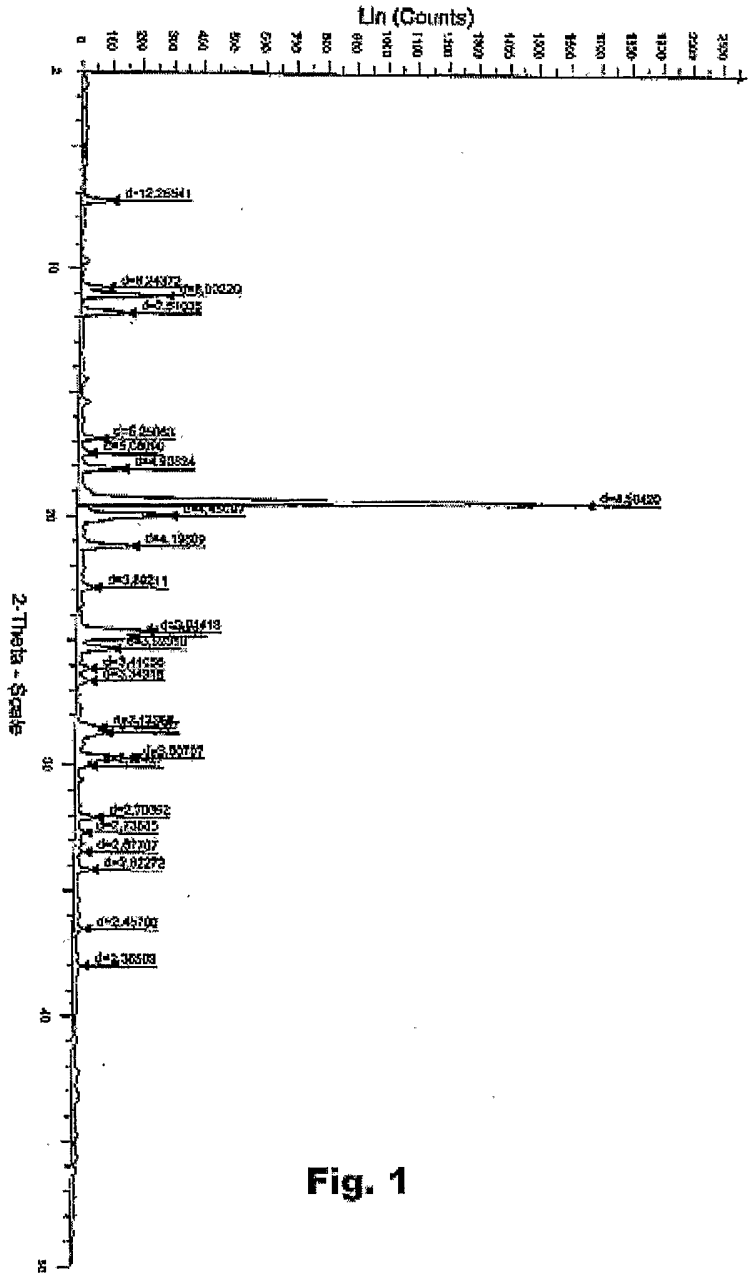


Fig. 1

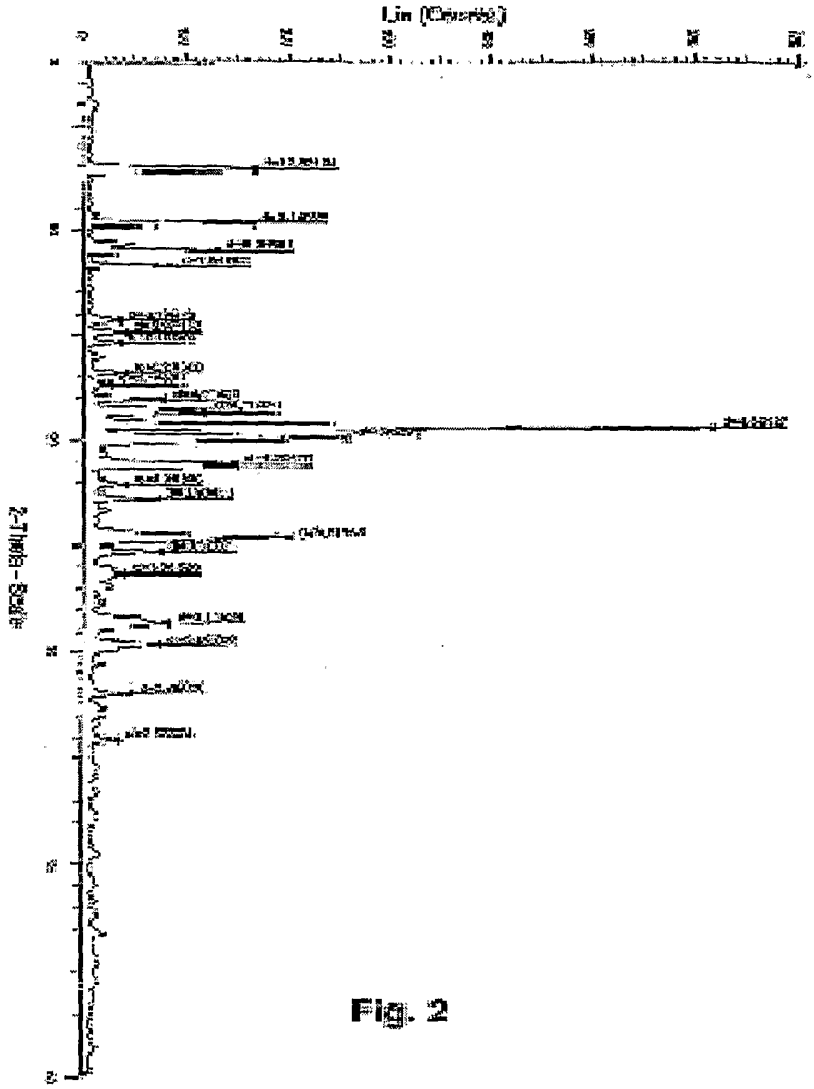

Fig. 2

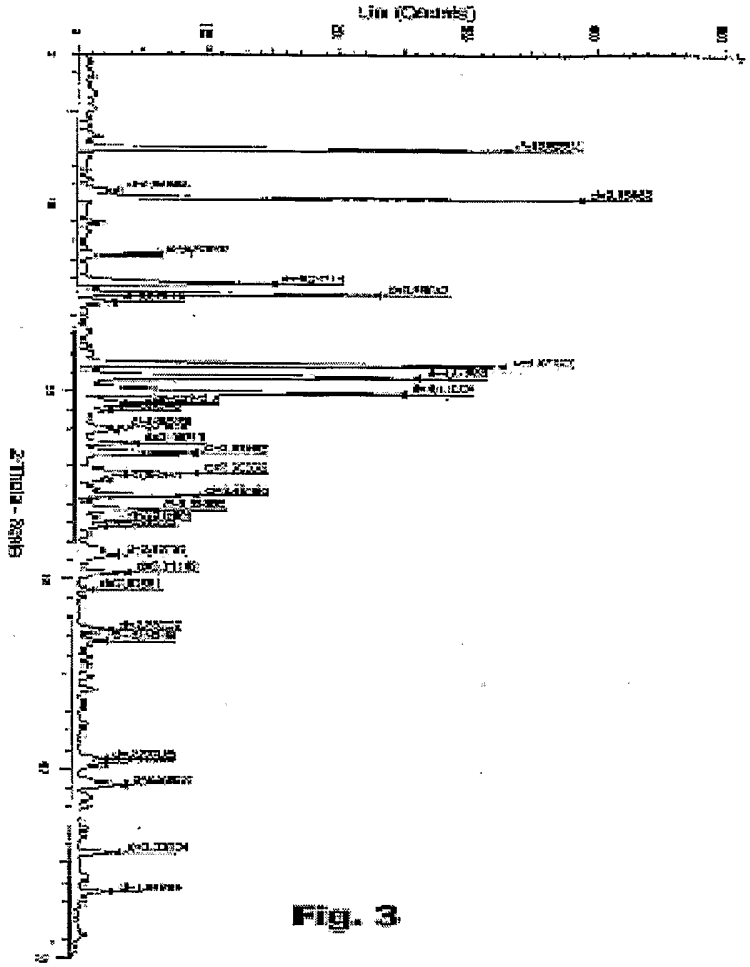


Fig. 3

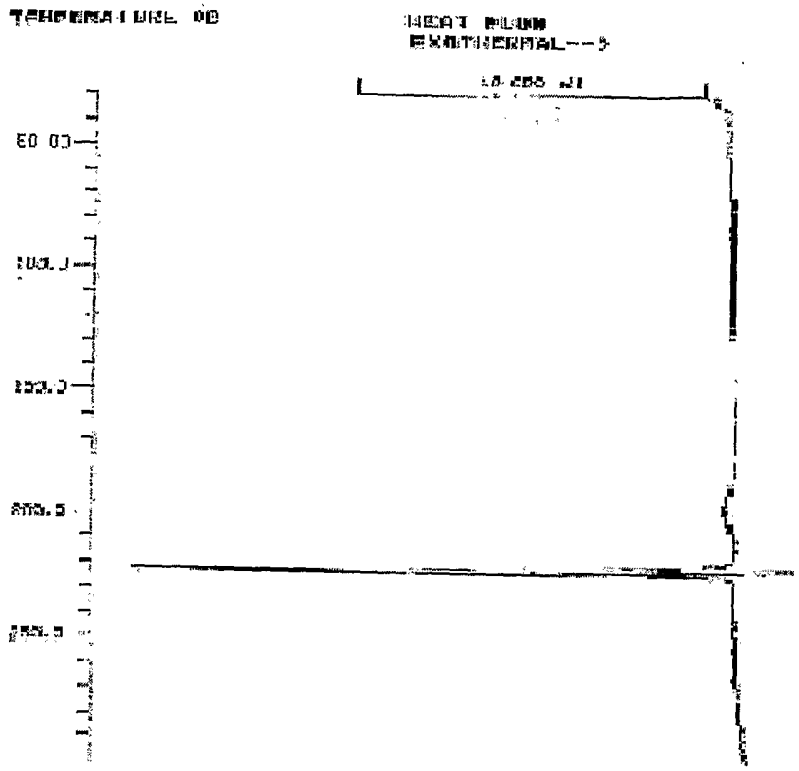

Fig. 4

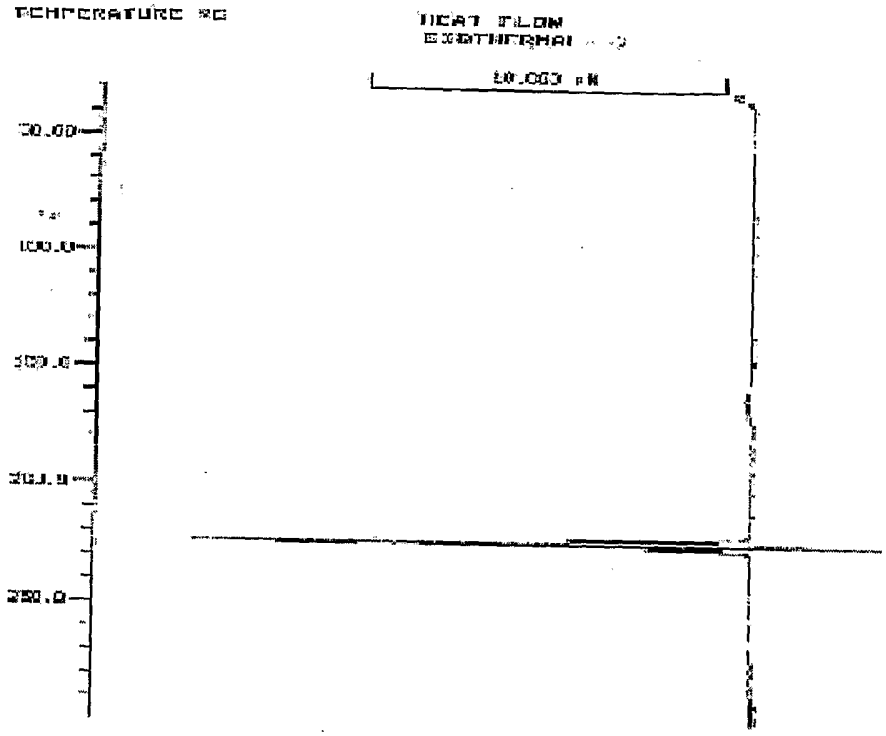
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Fig.5

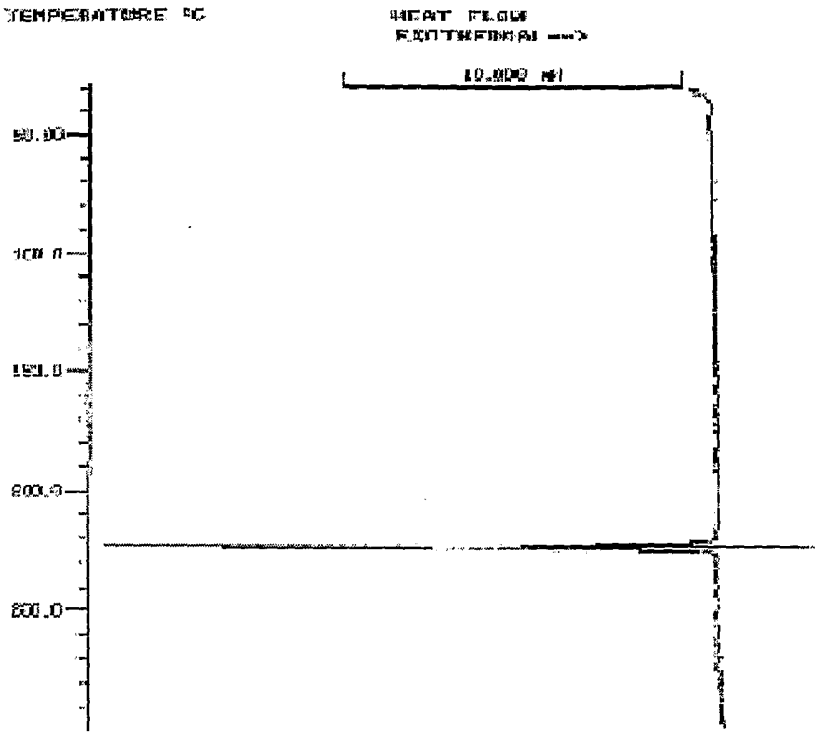


Fig. 6

# INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/IN2004/000213

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C46/10 C07C50/32

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br><br>Y | US 4 981 874 A (LATTER ET AL)<br>1 January 1991 (1991-01-01)<br>cited in the application<br>especially example 1, part (c) and claim 1<br>the whole document | 1,4,9,<br>12,17,<br>19,27,28<br>2,3,5-8,<br>10,11,<br>13-16,<br>18,20-26 |
| Y | BERNSTEIN J: "Polymorphism of pharmaceuticals"<br>POLYMORPHISM IN MOLECULAR CRYSTALS, 2002,<br>pages 253-255, XP002308143<br>especially on page 252, last paragraph<br>the whole document | 2,3,5-8,<br>10,11,<br>13-16,<br>18,20-26 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 6 September 2005 | 07. 10. 2005 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Seelmann, M |

Form PCT/ISA/210 (second sheet) (January 2004)

# INTERNATIONAL SEARCH REPORT

Inte nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| Y | US 2 553 647 A (FIESER LOUIS F ET AL) 22 May 1951 (1951-05-22) compound III-6, table III, col.3-4 column 1, line 48 - line 59; examples 1,2,5 column 7, line 70 - column 8, line 4 | 22-26 |

# INTERNATIONAL SEARCH REPORT

ational application No.
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## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/IN2004 /000213

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8,27(part),28(part)

   atovaquone polymorphic form I I, preparation process and pharmaceutical composition or use thereof

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2. claims: 9-21,27(part),28(part)

   atovaquone polymorphic form I II, preparation process and pharmaceutical composition or use thereof

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3. claims: 22-26,27(part),28(part)

   preparation process of atovaquone polymorphic form I and pharmaceutical composition or use thereof

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