Title: POLYMORPHIC FORM I OF LUMEFANTRINE AND PROCESSES FOR ITS PREPARATION

Abstract: The invention relates to a novel polymorphic form of lumefantrine and processes for its preparation. More particularly, it relates to the preparation of polymorphic form of lumefantrine designated as Form I. The invention also relates to pharmaceutical compositions that include the polymorphic Form I and use of said compositions for treatment of malaria.
POLYMORPHIC FORM I OF LUMEFANTRINE AND PROCESSES FOR ITS PREPARATION

Field of the Invention

5 The field of the invention relates to a novel polymorphic form of lumefantrine and processes for its preparation. More particularly, it relates to the preparation of polymorphic form of lumefantrine designated as Form I. The invention also relates to pharmaceutical compositions that include the polymorphic Form I and use of said compositions for treatment of malaria.

Background of the Invention

Lumefantrine is chemically, (Z)-2,7-dichloro-9-[(4-chlorophenyl)methylene]-α-[(dibutylamino)methyl]-9H-fluorene-4-methanol having the structural Formula I.

\[ \text{FORMULA I} \]

15 Lumefantrine belongs to the class of antimalarial agents and is reported to be originally synthesized in the 1970's by the Academy of Military Medical Sciences, China. Artemether + Lumefantrine, a fixed dose combination of two active ingredients, artemether, a sesquiterpene lactone derivative of a naturally occurring substance, artemisinin, and lumefantrine, a synthetic racemic fluorene derivative, is indicated in artemisinin-based combination therapy (ACT) used to treat malaria including the stand by-emerging treatment of adults and children with infections due
to *Plasmodium falciparum* or mixed infections including *Plasmodium falciparum* -the deadliest form of the disease. The combination has gametocytocidal action.

*Plasmodium falciparum* and *Plasmodium vivax* are the two dominant species with relative frequency of 60% and 40%, respectively. However, this proportion varies from place to place and from season to season. In malaria epidemic situations, *Plasmodium falciparum* is the dominant parasite species and almost all malaria deaths happen due to infections by this species. Moreover, the biological diversity of *Plasmodium falciparum*, its ability to develop resistance to a number of anti-malarial drugs has been a major challenge in malaria chemotherapy.

Chinese Patent No. CN 1029680C discloses a five-step process for the preparation of lumefantrine, which is obtained as yellow crystals. However, the lumefantrine is not obtained in pure form.

**Summary of the Invention**

The present inventors have found a new polymorphic form of lumefantrine and have developed a process for preparation of the polymorphic form. The new polymorphic form of lumefantrine is designated as Form I of lumefantrine.

In one general aspect there is provided a polymorphic Form I of lumefantrine.

The Form I of lumefantrine may have the X-ray diffraction pattern of Figure 1, differential scanning calorimetry thermogram of Figure 2, and infrared spectrum of Figure 3.

In one general aspect there is provided a process for the preparation of Form I of lumefantrine. The process includes obtaining a solution of lumefantrine in one or more organic solvents; cooling the solution to 25°C or less; and isolating the polymorphic Form I of lumefantrine by the removal of the solvents.

Removing the solvents may include, for example, one or more of filtration, filtration under vacuum, decantation, centrifugation, distillation and distillation under vacuum.

The process may include further drying the product obtained.
In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of the polymorphic Form I of lumefantrine; and one or more pharmaceutically acceptable carriers, excipients or diluents.

The present inventors have noticed that lumefantrine when prepared as per the process reported in the prior art is not pure and has a purity of about 90% or less. The present inventors have now developed a process to get lumefantrine in pure form which is suitable for making dosage forms.

In another general aspect there is provided a pure lumefantrine.

In another general aspect there is provided a process for preparing pure lumefantrine. The process includes treating 2-(dibutylamino)-1-(2,7-dichloro-9H-fluoren-4-yi)ethanol with p-chlorobenzaldehyde in the presence of a base and one or more organic solvents; cooling reaction mixture of to 10°C or less; isolating lumefantrine from the reaction mass; obtaining a solution of lumefantrine so obtained in one or more organic solvents; cooling the solution to 25°C or less; and isolating the pure lumefantrine by the removal of the solvents.

The process may produce the pure lumefantrine having purity more than 95%. In particular, it may produce the pure lumefantrine having purity more than 98%, for example more than 99%.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of the pure lumefantrine; and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect there is provided a method of treating or preventing malaria in a warm blooded animal, the method comprising providing a dosage form to the warm blooded animal that includes pure lumefantrine.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description and claims.
Description of the Drawings

Figure 1 is an X-ray powder diffraction pattern of polymorphic Form I of lumefantrine.

Figure 2 is a differential scanning calorimetric (DSC) thermogram of polymorphic Form I of lumefantrine.

Figure 3 is a Fourier Transform Infrared (FTIR) spectrum of polymorphic Form I of lumefantrine.

Detailed Description of the Invention

The inventors have developed a process for the preparation of a new polymorphic form of lumefantrine. More particularly, the inventors have developed a process for the preparation of a polymorphic Form I of lumefantrine.

The term "Form I" of lumefantrine refers to a polymorph of lumefantrine having X-ray diffraction pattern as depicted in Figure 1.

A first aspect of the invention provides a process for the preparation of polymorphic Form I of lumefantrine wherein the process includes the steps of:

a) obtaining a solution of lumefantrine in one or more organic solvents:

b) cooling the solution to 25°C or less; and

c) isolating the polymorphic Form I of lumefantrine by the removal of the solvents.

The inventors also have developed pharmaceutical compositions that contain the polymorphic Form I of lumefantrine in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients.

In general, the solution of lumefantrine may be obtained by dissolving lumefantrine in a suitable solvent. Alternatively, such a solution may be obtained directly from a reaction in which lumefantrine is formed. The solvent containing lumefantrine may be heated to obtain a solution. It may be heated from about 30°C to about reflux temperature of the solvent used, for example from about 50°C to about
100°C. It may be heated from about 10 minutes to about 24 hours. More particularly, it may be heated for about 1-2 hours.

The lumefantrine which is used as the starting material can be prepared by any of the known processes, for example, process as disclosed in CN 1029680C.

The term “obtaining” includes dissolving, slurrying, stirring or a combination thereof.

The term “suitable solvents” includes any solvent or solvent mixture in which lumefantrine can be solubilized, including, for example, alkanols, ketones, nitriles, chlorinated hydrocarbons, polar aprotic solvents, esters, ethers, or mixtures thereof.

The alkanol may include one or more of methanol, ethanol, n-propanol, isopropanol and butanol. The ketone may include one or more of acetone, ethyl methyl ketone, methyl isobutyl ketone, and diisobutyl ketone.

Examples of nitrile include acetonitrile. A suitable chlorinated hydrocarbon includes one or more of chloroform, dichloromethane, and 1,2-dichloroethane.

Examples of polar aprotic solvents include solvents such as dimethylsulfoxide and dimethylformamide. Examples of esters include solvents such as methyl acetate, ethyl acetate, and isopropyl acetate. Examples of ethers include solvents such as dioxane and tetrahydrofuran. Mixtures of all of these solvents are also contemplated.

In general, the solution may be cooled to obtain Form I of lumefantrine. It may be cooled to about room temperature or less, for example from about 25°C to about -10°C.

In one aspect, the solution may be seeded with crystals of Form I resulting in the precipitation of the Form I of lumefantrine and removing the solvent there from by filtration, filtration under vacuum, decantation or centrifugation.

The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be further or additionally dried in a tray drier, dried under vacuum and/or in a Fluid Bed Dryer.

In general, the polymorphic Form I of lumefantrine may be characterized by X-ray diffraction peaks at about 5.50, 10.76, 11.06, 13.50, 14.30, 14.90, 15.42, 16.98, 18.00, 18.50, 19.12, 19.78, 20.08, 20.90, 21.54, 21.92, 22.98, 23.70, 24.20, 25.32,
26.48, 26.98, 27.50, 28.16, 28.54, 28.98, 30.14, 31.48, 31.96, 32.10, 32.74, 34.52, 36.92, 38.02 ± 0.2 degrees two-theta values.

The polymorphic Form I of lumefantrine may also be characterized by Differential Scanning Calorimetric (DSC) thermogram as depicted in Figure II having characteristic endothermic absorption between 120°C and 130°C.

The inventors also have developed a process for the preparation of pure lumefantrine. A second aspect of the present invention provides highly pure lumefantrine, wherein the purity is 95% or more by HPLC. More preferably highly pure lumefantrine refers to lumefantrine having purity of 98% or more by HPLC.

Another aspect of the invention provides a process for the preparation of pure lumefantrine wherein the said process comprises of,

a) treating 2-(dibutylamino)-1-(2,7-dichloro-9H-fluoren-4-yl)ethanol with p-chlorobenzaldehyde in the presence of a base and one or more organic solvents;

b) cooling reaction mixture of step a) to 10°C or less;

c) isolating lumefantrine from the reaction mass;

d) obtaining a solution of lumefantrine obtained in step c) in one or more organic solvents;

e) cooling the solution to 25°C or less; and

f) isolating the pure lumefantrine by the removal of the solvents.

The solvent may be, for example, one or more of alkanols, ketones, nitriles, chlorinated hydrocarbons, polar aprotic solvents, esters, ethers, or mixtures thereof.

Examples of base include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium methoxide, potassium methoxide and potassium t-butoxide, and the like. The reaction mixture of step b) may be cooled from about 5°C to about 10°C.

The resulting pure lumefantrine may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. In these cases, the
medicaments can be prepared by conventional methods with conventional pharmaceutical excipients.

The pure lumefantrine has a purity of more than 95% as determined by HPLC. More particularly, the purity of lumefantrine is more than 98%, for example more than 99%.

The pure lumefantrine can be administered for the prevention and treatment of malaria in a warm-blooded animal.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1: Preparation of polymorphic Form I of lumefantrine

a) Preparation of lumefantrine

To a mixture of ethanol (600 ml) and 2-(dibutylamino)-1-(2,7-dichloro-9H-fluoren-4-yl)ethanol (40 g), was added sodium hydroxide (4.74 g) at room temperature. This mixture was stirred for 0.5 hours and p-chlorobenzaldehyde (15.96 g) was added at room temperature followed by further stirring for 60 hours. The reaction mixture was cooled to 5 to 10°C and filtered. The solid so obtained was washed with water (500 ml) and dried first at room temperature and then at 45 to 50°C to obtain crude lumefantrine.

Yield = 31 g

b) Preparation of pure polymorphic Form I of lumefantrine

Crude lumefantrine (30 g) was taken in ethanol (360 ml) and heated to 65-70°C for 30 minutes. The solution was allowed to cool to 25°C and stirred for 2 hours. The product so obtained was filtered, washed with ethanol (15 ml) and dried under vacuum at 45 to 50°C for 6 hours to get pure polymorphic Form I of lumefantrine.
Yield = 18 g
Purity = 99.15% (by HPLC)

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. For example, the compounds described herein can be formulated into dosage forms that are suitable for administering to patients in need of the compound for treating a medical condition for which the compound is indicated, approved, or otherwise beneficial. Specifically, the Form I of lumefantrine can be formulated with one or more pharmaceutically acceptable excipients and/or with one or more active ingredients into a dosage form and administered to treat malaria.
WE CLAIM:

1. A polymorphic Form I of lumefantrine.
3. The polymorphic Form I of lumefantrine of claim 2 having differential scanning calorimetric thermogram of Figure 2.
4. The polymorphic Form I of lumefantrine of claim 2 having differential scanning calorimetric melting exotherms at about 120-130°C.
5. Lumefantrine having a purity of more than 95% by HPLC.
6. The lumefantrine of claim 5 having a purity of more than 98% by HPLC.
7. The pure lumefantrine of claim 6, wherein the lumefantrine has the X-ray diffraction pattern of Figure 1.
8. A process for the preparation of polymorphic form I of lumefantrine, the process comprising:
   a) obtaining a solution of lumefantrine in one or more organic solvents:
   b) cooling the solution to 25°C or less; and
   c) isolating the polymorphic Form I of lumefantrine by the removal of the solvents.
9. The process of claim 8, wherein the organic solvent comprises one or more of alkanols, ketones, nitriles, chlorinated hydrocarbons, polar aprotic solvents, esters, ethers, or mixtures thereof.
10. The process of claim 9, wherein the alkanol comprises one or more of methanol, ethanol, n-propanol, isopropanol, butanol and isobutanol.
11. The process of claim 8, wherein removing the solvent comprises one or more
of filtration, filtration under vacuum, decantation, centrifugation, distillation and
distillation under vacuum.

12. The process of claim 8, further comprising additional drying of the product
obtained.

13. The process of claim 8, wherein the polymorphic Form I of lumefantrine has
the X-ray diffraction pattern of Figure 1.

14. A process for preparation of pure lumefantrine, the process comprising:
a) treating 2-(dibutylamino)-1-(2,7-dichloro-9H-fluoren-4-yl)ethanol with p-
chlorobenzaldehyde in the presence of a base and one or more organic solvents;
b) cooling reaction mixture to 10°C or less;
c) isolating lumefantrine from the reaction mass;
d) obtaining a solution of lumefantrine in one or more organic solvents;
e) cooling the solution to 25°C or less; and
f) isolating the pure lumefantrine by the removal of the solvents.

15. The process of claim 14, wherein the organic solvent comprises one or more
of alkanols, ketones, nitriles, chlorinated hydrocarbons, polar aprotic solvents, esters,
ethers, or mixtures thereof.

16. The process of claim 15, wherein the alkanol comprises one or more of
methanol, ethanol, n-propanol, isopropanol, butanol and isobutanol.

17. A pharmaceutical composition comprising a therapeutically effective amount
of pure lumefantrine having a purity of 95% or more by HPLC, and one or more
pharmacologically acceptable carriers, excipients or diluents.

18. A pharmaceutical composition comprising a therapeutically effective amount
of Form I of lumefantrine, and one or more pharmaceutically acceptable carriers,
exipients or diluents.
19. A method of treating or preventing malaria in a warm blooded animal, the
method comprising providing a dosage form to the warm blooded animal that includes
pure lumefantrine having a purity of 95% or more by HPLC.

20. A method of treating or preventing malaria in a warm blooded animal, the
method comprising providing a dosage form to the warm blooded animal that includes
polymorphic Form I of lumefantrine.
FIGURE 1: X-RAY DIFFRACTION PATTERN OF FORM I OF LUMEFANTRINE
FIGURE 2: DIFFERENTIAL SCANNING CALORIMETRY THERMOGRAM OF FORM I OF LUMEFANTRINE
FIGURE 3: FTIR SPECTRUM OF FORM I OF LUMEFANTRINE
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07C215/38 A61K31/135 A61P33/06

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)

C07C A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, INSPEC

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C.

**See patent family 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
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "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

**Date of the actual completion of the international search**

13 July 2006

**Date of mailing of the International search report**

21 09 2006

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HJ Rijswijk
Tel: (+31-70) 542-2040, Fax (31-70) 540-3016

**Authorized officer**

Pérez Carlón, Raquel
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INTERNATIONAL SEARCH REPORT

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. [x] Claims Nos.: 19, 20
   because they relate to subject matter not required to be searched by this Authority, namely:
   
   Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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. [x] 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.:
   
   1-4, 8-13, 18 and 20

Remark on Protest

[ ] The additional search fees were accompanied by the applicant’s protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4, 8-13, 18 and 20
   Polymorphic form I of lumefantrine, its synthesis, pharmaceutical compositions and therapeutical use.

2. claims: 5-7, 14-17 and 19
   Lumefantrine with more than 95% purity, its synthesis, pharmaceutical compositions and therapeutical uses.
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From PCT/IB/206/00137 (patent family annex) (April 2020)