Title: PROCESSES FOR THE PREPARATION OF POLYMORPHS OF EFAVIRENZ

Abstract: The invention relates to processes for the preparation of polymorphic forms of efavirenz. More particularly, it relates to the preparation of Form I and Form II of efavirenz. The invention also relates to pharmaceutical compositions that include the Form I of efavirenz and use of said compositions for treatment of HIV-1 infections in combination with other antiretroviral agents.
PROCESSES FOR THE PREPARATION OF POLYMORPHS OF EFAVIRENZ

Field of the Invention

The field of the invention relates to processes for the preparation of polymorphic forms of efavirenz. More particularly, it relates to the preparation of Form I and Form II of efavirenz. The invention also relates to pharmaceutical compositions that include the Form I of efavirenz and use of said compositions for treatment of HIV-1 infections in combination with other antiretroviral agents.

Background of the Invention

Efavirenz of Formula I is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor. Chemically, efavirenz is (4S)-6-chloro-4-(cyclopropylethynyl)-4-(trifluoromethyl)-1,4-dihydro-2H-3,1-benzoxazin-2-one. It is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{Cl} & \quad \text{F} \\
\text{F} & \quad \text{H}
\end{align*}
\]

FORMULA I

Several processes have been reported for the preparation of efavirenz for example, in U.S. Patent Nos. 5,519,021; 5,698,741; and 5,663,467; International (PCT) Publication Nos. WO 94/03440; 95/20389; and 96/22955; and Tetrahedron Letters, 1995, 36, 937-940.

U.S. Patent Nos. 6,639,071 and 5,965,729 disclose crystalline polymorphic forms of efavirenz designated as Form I, II and III having specific X-Ray diffraction patterns.

U.S. Patent No. 6,639,071 discloses that efavirenz was previously crystallized from a heptane-tetrahydrofuran (THF) solvent system by the crystallization procedure which required the use of high temperatures (about 90°C) to dissolve the final product. Crystals
were formed by nucleation during the cooling process. This crystallization provides minimal purification. The final product slurry was extremely difficult to mix and handle due to its high viscosity and heterogeneous nature. The problem was solved by the addition of an anti-solvent to initiate the crystallization.

The inventors have found that the prior art process for the preparation of Form II of efavirenz is not suitable from a commercial point of view because the process requires milling of the slurry obtained after addition of water to reduce the crystal size. The present inventors have found that this process is very tedious and is not commercially scalable.

U.S. Patent No. 6,673,372 discloses polymorphic forms of efavirenz designated as Form 2 and Form 5.

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

**Description of the Drawings**

Figure 1 is an X-ray powder diffraction pattern of Form II of efavirenz.

Figure 2 is an X-ray powder diffraction pattern of Form I of efavirenz.

**Summary of the Invention**

The form II of efavirenz when made by the process of the present invention is easy to isolate and handle, thus making the process amenable for commercial scale use.

In one general aspect there is provided a process for the preparation of Form II of efavirenz. The process includes obtaining a solution of efavirenz in one or more organic solvents; adding an anti-solvent to the solution; and isolating the Form II of efavirenz by the removal of the solvents.

Removing the solvents may include, for example, one or more of filtration, filtration under vacuum, decantation and centrifugation. The process may include further forming of the product so obtained into a finished dosage form.

The process may include further drying of the product obtained.

In another general aspect there is provided a process for the preparation of Form I of efavirenz. The process includes drying Form II of efavirenz under vacuum at a temperature from about 50°C or more for about 6 hours or more.
In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of the Form I of efavirenz; and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect there is provided a method for treating HIV-1 infections in a warm-blooded animal. The method includes providing a pharmaceutical composition to the warm-blooded animal, the pharmaceutical composition comprising Form I of efavirenz.

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

**Detailed Description of the Invention**

The inventors have developed a process for the preparation of polymorphic forms of efavirenz. More particularly, the inventors have developed a process for the preparation of Form II and conversion of Form II to Form I of efavirenz.

The term “Form II” of efavirenz refers to a polymorph of efavirenz having, for example, an X-Ray Powder Diffraction (XRPD) pattern substantially as depicted in Figure 1. The term “Form I” of efavirenz refers to a polymorph of efavirenz having, for example, an X-Ray Powder Diffraction (XRPD) pattern substantially as depicted in Figure 2.

In one aspect, a process for the preparation of Form II of efavirenz is provided, wherein the process includes the steps of:

a) obtaining a solution of efavirenz in one or more organic solvents;

b) adding an anti-solvent to the solution; and

c) isolating the Form II of efavirenz by the removal of the solvents.

In general, the solution of efavirenz may be obtained by dissolving efavirenz in a suitable solvent. Alternatively, such a solution may be obtained directly from a reaction in which efavirenz is formed. If a suspension is obtained in a solvent, the suspension containing efavirenz may be heated to obtain a solution. It may be heated from about 30 °C to about 150 °C, 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 2-3 hours.

The efavirenz can be prepared by any of the methods known in the art including those described in U.S. Patent Nos. 5,519,021; 5,698,741; 5,663,467; and WO 94/03440; 95/20389; and 96/22955.

The term “efavirenz” includes all polymorphic forms, amorphous form, solvates, hydrates, and mixtures thereof.

The term “suitable solvents” includes any solvent or solvent mixture in which efavirenz can be solubilized, including, for example, aromatic hydrocarbons; lower alkanols; chlorinated hydrocarbons; polar aprotic solvents, or mixtures thereof.

The aromatic hydrocarbon may include one or more of benzene, toluene, and xylene. Examples of alkanol include those primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable lower alkanol solvents include methanol, ethanol, n-propanol, isopropanol and butanol. Examples of chlorinated hydrocarbons include dichloromethane, chloroform, and 1,2-dichloroethane. A suitable polar aprotic solvent includes one or more of N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrroolidone. Mixtures of all of these solvents are also contemplated.

A suitable anti-solvent that may be added to precipitate out Form II of efavirenz includes C₆₋₈ straight or branched chain alkanes, petroleum ether, C₅₋₇ cycloalkanes, C₄₋₁₂ ethers, and mixtures thereof. The reaction mass can be stirred for some time for example, from about 10 minutes to about 6 hours to get Form II of efavirenz. The solvent may be removed from the solution by a technique which includes, for example, filtration, filtration under vacuum, decantation and centrifugation. The product may be washed and dried by conventional methods.

In one aspect, the solution may be cooled before filtration to obtain better yields of the Form II of efavirenz. It may be cooled from about 100 °C to about 0 °C, for example from about 50 °C to about 10 °C.

In a further aspect, a process for the preparation of Form I of efavirenz is provided, wherein the process includes the steps of:
a) obtaining a solution of efavirenz in one or more organic solvents;
b) adding an anti-solvent to the solution;
c) isolating Form II of efavirenz by the removal of the solvents; and
d) drying the isolated Form II under vacuum at a temperature from about
   50°C or more, and obtaining the Form I of efavirenz.

In yet another aspect, a process for the preparation of Form I of efavirenz is
provided, wherein the process includes the step of:

a) drying Form II under vacuum at a temperature from about 50°C or more,
   and obtaining the Form I of efavirenz.

Form II of efavirenz can be converted into Form I of efavirenz by drying under
vacuum at a temperature from about 50°C or more for example, at a temperature from
about 60°C to about 100°C.

The resulting Form I of efavirenz 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 compositions include dosage forms suitable for oral, buccal, rectal, and
parenteral (including subcutaneous, intramuscular, and ophthalmic) administration. The
oral dosage forms may include solid dosage forms, like powder, tablets, capsules,
suppositories, sachets, troches and lozenges as well as liquid suspensions, emulsions,
pastes and elixirs. Parenteral dosage forms may include intravenous infusions, sterile
solutions for intramuscular, subcutaneous or intravenous administration, dry powders to be
reconstituted with sterile water for parenteral administration, and the like.

The Form I of efavirenz can be administered for the treatment of HIV-1 infections
in combination with other antiretroviral agents, 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 Form II of efavirenz

Efavirenz (5 gm) was dissolved in toluene (5 ml) by heating to 70°C. Hexane (75 ml) was added to this solution and the resultant mass was cooled to ambient temperature and further stirred for 30 minutes. The product obtained was filtered, washed with a mixture of toluene and hexane (1:15) and finally dried at 35-40°C under vacuum.

Yield: 4.15 gm

Example 2: Preparation of Form I of efavirenz

Form II of efavirenz (4.15 g) prepared by example 1 was dried under vacuum at 50-60 °C for 12 hours. The solid obtained was subsequently dried at 75-80 °C for about 6-12 hours to obtain the title compound.

Yield: 4.15 g

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, it is understood that the various polymorphic forms of efavirenz can be incorporated in dosage forms for treating conditions for which efavirenz is useful.
We Claim:

1. A process for the preparation of Form II of efavirenz, the process comprising:
   a) obtaining a solution of efavirenz in one or more organic solvents;
   b) adding an anti-solvent to the solution; and
   c) isolating the Form II of efavirenz by the removal of the solvents.

2. The process of claim 1, wherein the organic solvent comprises one or more of aromatic hydrocarbons, lower alkanols, chlorinated hydrocarbons, polar aprotic solvents, or mixtures thereof.

3. The process of claim 2, wherein the aromatic hydrocarbon comprises one or more of benzene, toluene and xylene.

4. The process of claim 3, wherein the aromatic hydrocarbon is toluene.

5. The process of claim 2, wherein the lower alkanol comprises one or more of methanol, ethanol, n-propanol, isopropanol, butanol and isobutanol.

6. The process of claim 2, wherein the chlorinated hydrocarbon comprises one or more of dichloromethane, chloroform and 1,2-dichloroethane.

7. The process of claim 2, wherein the polar aprotic solvent comprises one or more of N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

8. The process of claim 1, wherein the anti-solvent comprises one or more of C_{5-8} straight or branched chain alkanes, petroleum ether, C_{5-7} cycloalkanes, C_{4-12} ethers, or mixtures thereof.

9. The process of claim 8, wherein the anti-solvent is a C_{6-8} straight or branched chain alkane.

10. The process of claim 1, wherein removing the solvents comprises one or more of filtration, filtration under vacuum, decantation and centrifugation.

11. The process of claim 1, further comprising additional drying of the product obtained.
12. The process of claim 1, wherein the Form II of efavirenz has the X-ray diffraction
   pattern of Figure 1.

13. A process for the preparation of Form I of efavirenz, the process comprising:
   a) obtaining a solution of efavirenz in one or more organic solvents;
   b) adding an anti-solvent to the solution;
   c) isolating Form II of efavirenz by the removal of the solvents; and
   d) drying the isolated Form II under vacuum at a temperature from about
   50°C or more, and obtaining the Form I of efavirenz.

14. The process of claim 13, wherein the organic solvent comprises one or more of
   aromatic hydrocarbons, lower alkanols, chlorinated hydrocarbons, polar aprotic
   solvents, or mixtures thereof.

15. The process of claim 13, wherein the anti-solvent comprises one or more of C₆-₈
   straight or branched chain alkanes, petroleum ether, C₅-₇ cycloalkanes, C₄-₁₂ ethers,
   or mixtures thereof.

16. The process of claim 13, wherein removing the solvents comprises one or more of
   filtration, filtration under vacuum, decantation and centrifugation.

17. The process of claim 13, wherein the Form II is dried at a temperature from about
   60°C to about 100°C.

18. The process of claim 13, wherein the Form I of efavirenz has the X-ray diffraction
   pattern of Figure 2.

19. The process of claim 13, further comprising forming the product into a finished
   dosage form.

20. A method of treating HIV-1 infections in a warm-blooded animal, the method
   comprising providing a pharmaceutical composition to the warm-blooded animal
   that includes Form I of efavirenz prepared by the process of claim 13.

21. A process for the preparation of Form I of efavirenz, the process comprising:
   a) drying Form II under vacuum at a temperature from about
   50°C or more, and obtaining Form I of efavirenz.
FIGURE 1: XRD OF FORM II OF EFAVIRENZ
FIGURE 2 – XRD OF FORM I OF EFAVIRENZ
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

C07D265/18 A61K31/535 A61P31/18

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)

C07D 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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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

9 December 2005

**Date of mailing of the international search report**

24/01/2006

**Name and mailing address of the ISA**

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**Authorized officer**

Bakboord, J
INTERNATIONAL SEARCH REPORT

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.: 20 because they relate to subject matter not required to be searched by this Authority, namely:
   Although claim 20 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

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).

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:

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.
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