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(54) Title: NOVEL POLYMORPHS OF TENOFOVIR DISOPROXIL FUMARATE

(57) Abstract: The present invention relates to novel polymorphs of tenofovir disoproxil fumarate, to processes for their preparation and to pharmaceutical compositions comprising them.

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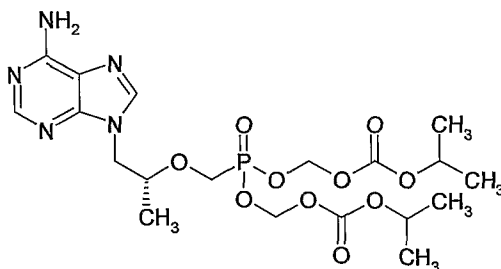
NOVEL POLYMORPHS OF TENOFOVIR DISOPROXIL FUMARATE

FIELD OF THE INVENTION

5 The present invention relates to novel polymorphs of tenofovir disoproxil fumarate, to processes for their preparation and to pharmaceutical compositions comprising them.

BACKGROUND OF THE INVENTION

U.S. Patent No. 5,922,695, which is herein incorporated by reference,
10 disclosed phosphonomethoxy nucleotide analogs, in particular compounds suitable for use in the efficient oral delivery of such analogs and their pharmaceutically acceptable salts. This class of nucleoside analogues possesses broad-spectrum antiviral activity, together with a high level of selectivity in vitro and in vivo. An especially important compound among those
15 disclosed is tenofovir disoproxil, chemically (R)-9-(2-phosphonomethoxypropyl) adenine bis(isopropylloxycarbonyloxymethyl) ester is a highly potent antiviral agent having particular potential for the therapy or prophylaxis of retroviral infections. Tenofovir disoproxil is represented by the following structure:



20 As per the processes described for preparation of tenofovir disoproxil fumarate in U.S. Patent No. 5,922,695 and U.S. Patent No. 5,935,946, tenofovir disoproxil fumarate is obtained as a crystalline form and may be designated as form I (characterized by an x-ray powder diffraction patterns having peaks
25 expressed as 2θ at about 4.9, 10.2, 10.5, 18.2, 20.0, 21.9, 24.0, 25.0, 25.5, 27.8, 30.1 and 30.4 degrees).

 We have discovered two stable novel crystalline forms (designated as Form A, Form B) of tenofovir disoproxil fumarate. The novel forms are at least as stable as the reported form (Form I). The novel crystalline forms are stable

over the time and has good flow properties and so, the novel crystalline forms are suitable for formulating tenofovir disoproxil fumarate.

Amorphous form of tenofovir disoproxil fumarate has not been reported in the prior art. So, there is a need for stable amorphous form of tenofovir
5 disoproxil fumarate for better pharmaceutical preparations.

One object of the present invention is to provide stable novel crystalline forms of tenofovir disoproxil fumarate, process for preparing them and pharmaceutical compositions containing them.

Another object of the present invention is to provide a novel stable
10 amorphous form of tenofovir disoproxil fumarate, process for preparing it and a pharmaceutical composition containing it.

DETAILED DESCRIPTION OF THE INVENTION

According to one aspect of the present invention, there is provided a
15 novel crystalline form of tenofovir disoproxil fumarate, designated as tenofovir disoproxil fumarate form A and typical X-ray powder diffraction spectrum of tenofovir disoproxil fumarate form A is shown in figure 1.

Tenofovir disoproxil fumarate form A is characterized by peaks in the powder X-ray diffraction pattern having 2θ angle positions at about 7.7, 8.0,
20 11.8, 13.6, 14.2, 16.0, 16.6, 17.9, 19.1, 20.3, 21.1, 21.5, 22.4, 22.7, 24.2, 24.6 and 25.2 ± 0.2 degrees.

According to another aspect of the present invention, a process is provided for preparation of crystalline tenofovir disoproxil fumarate form A. Crystalline tenofovir disoproxil fumarate form A is prepared by dissolving
25 tenofovir disoproxil fumarate in isopropyl alcohol and then crystallizing tenofovir disoproxil fumarate form A from the solution.

Crystallization may be initiated by any conventional methods usually known in the art such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution or a combination thereof.

30 Crystallization is preferably initiated by cooling the solution to below about 40°C and more preferably to about $20 - 30^{\circ}\text{C}$.

According to another aspect of the present invention, there is provided a novel crystalline form of tenofovir disoproxil fumarate, designated as tenofovir

disoproxil fumarate form B and typical X-ray powder diffraction spectrum of tenofovir disoproxil fumarate form B is shown in figure 2.

Tenofovir disoproxil fumarate form B is characterized by peaks in the powder X-ray diffraction pattern having 2θ angle positions at about 5.2, 15.4,
5 20.6, 25.8 and 31.0 ± 0.2 degrees.

According to another aspect of the present invention, a process is provided for preparation of crystalline tenofovir disoproxil fumarate form B. Crystalline tenofovir disoproxil fumarate form B is prepared by dissolving tenofovir disoproxil fumarate in methanol or ethanol and then crystallizing
10 tenofovir disoproxil fumarate form B from the solution.

Crystallization may be initiated by any conventional methods usually known in the art such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution or a combination thereof.

Crystallization is preferably initiated by cooling the solution to below
15 about 40°C and more preferably to about $20 - 30^{\circ}\text{C}$.

According to another aspect of the present invention, there is provided a novel amorphous form of tenofovir disoproxil fumarate. The amorphous tenofovir disoproxil fumarate is characterized by having broad x-ray diffraction spectrum as in figure 3.

According to another aspect of the present invention, a process is provided for preparation of amorphous tenofovir disoproxil fumarate. Amorphous tenofovir disoproxil fumarate is prepared by dissolving tenofovir disoproxil fumarate in a suitable solvent and removing the solvent by freeze-drying.
20

Preferable solvent is selected from alcoholic solvents such as methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, n-butyl alcohol; ketonic solvents such as acetone, diethyl ketone, methyl ethyl ketone, methyl isobutyl ketone and methyl propyl ketone; tetrahydrofuran; dimethylformamide, dimethylsulfoxide; and a mixture thereof. More preferable solvent is selected from methanol, ethanol, isopropyl alcohol, tert-butyl alcohol and n-butyl alcohol. Most preferable
25 solvent is ethanol.
30

Tenofovir disoproxil fumarate used as starting materials may be obtained by processes described in the art, for example by the processes described in U.S. Patent No. 5,922,695, U.S. Patent No. 5,935,946.

The novel crystalline forms can be produced in a consistently reproducible manner by simple procedures. The novel crystalline forms are obtained polymorphically pure with no or less contamination with other crystalline forms.

5 According to another aspect of the present invention there is provided a pharmaceutical composition comprising crystalline tenofovir disoproxil fumarate form A and a pharmaceutically acceptable excipient.

Preferable pharmaceutical composition of tenofovir disoproxil fumarate form A is a solid oral dosage form.

10 According to another aspect of the present invention there is provided a pharmaceutical composition comprising crystalline tenofovir disoproxil fumarate form B and a pharmaceutically acceptable excipient.

Preferable pharmaceutical composition of tenofovir disoproxil fumarate form B is a solid oral dosage form.

15 According to another aspect of the present invention there is provided a pharmaceutical composition comprising amorphous tenofovir disoproxil fumarate and a pharmaceutically acceptable excipient.

Preferable pharmaceutical composition of amorphous tenofovir disoproxil fumarate is a solid oral dosage form.

20

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a X-ray powder diffraction spectrum of crystalline tenofovir disoproxil fumarate form A.

25 Figure 2 is a X-ray powder diffraction spectrum of crystalline tenofovir disoproxil fumarate form B.

Figure 3 is a X-ray powder diffraction spectrum of amorphous tenofovir disoproxil fumarate.

30 X-Ray powder diffraction spectrum was measured on a Bruker axs D8 advance X-ray powder diffractometer having a Copper-K α radiation. Approximately 1 gm of sample was gently flattened on a sample holder and scanned from 2 to 50 degrees two-theta, at 0.03 degrees two-theta per step and a step time of 0.5 seconds. The sample was simply placed on the sample holder. The sample was rotated at 30 rpm at a voltage 40 KV and current 35 mA.

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitations on the scope or spirit of the invention.

5 Example 1

Tenofovir disoproxil fumarate crude (5 gm) is added to isopropyl alcohol (50 ml) at 25 - 30°C and then heated to 45 - 50°C to form a clear solution. The solution is cooled to 25 - 30°C and stirred for 1 hour at 25 - 30°C. Filtered the solid and dried at 45 - 55°C to give 4.6 gm of crystalline tenofovir disoproxil fumarate form A.

Example 2

Tenofovir disoproxil fumarate crude (2 gm) is added to methanol (20 ml) at 25 - 30°C and then heated to 50 - 55°C to form a clear solution. The solution is cooled to 25 - 30°C and stirred for 1 hour at 25 - 30°C. Filtered the solid and dried at 50 - 60°C to give 1.6 gm of crystalline tenofovir disoproxil fumarate form B.

Example 3

Tenofovir disoproxil fumarate (2 gm) is added to ethanol (20 ml) at 25 - 30°C and then heated to 55 - 60°C to form a clear solution. The solution is cooled to 25 - 30°C and stirred for 1 hour 30 minutes at 25 - 30°C. Filtered the solid and dried at 45 - 55°C to give 1.8 gm of crystalline tenofovir disoproxil fumarate form B.

Example 4

Example 1 is repeated using tenofovir disoproxil fumarate form B instead
25 of tenofovir disoproxil fumarate crude to give 4.7 gm of tenofovir disoproxil
fumarate form A.

Example 5

Example 2 is repeated using tenofovir disoproxil fumarate form A instead of tenofovir disoproxil fumarate crude to give 1.6 gm of tenofovir disoproxil fumarate form B.

Example 6

Tenofovir disoproxil fumarate (5 gm) is dissolved in a mixture of ethanol (75 ml) and water (20 ml) and then filtered the solution on hi-flow bed. The

solution is subjected to freeze drying to give 4.6 gm of amorphous tenofovir disoproxil fumarate.

Example 7

Example 6 is repeated using tenofovir disoproxil fumarate form A instead
5 of tenofovir disoproxil fumarate to give 4.7 gm of amorphous tenofovir disoproxil fumarate.

We claim:

1. A crystalline tenofovir disoproxil fumarate form A, characterized by an X-ray powder diffraction spectrum having peaks expressed as 2θ angle positions at about 7.7, 8.0, 11.8, 13.6, 14.2, 16.0, 16.6, 17.9, 19.1, 20.3, 21.1, 21.5, 22.4, 22.7, 24.2, 24.6 and 25.2 ± 0.2 degrees.
2. A process for preparation of crystalline tenofovir disoproxil fumarate form A as defined in claim 1, which comprises:
 - a) dissolving tenofovir disoproxil fumarate in isopropyl alcohol; and
 - b) crystallizing tenofovir disoproxil fumarate form A from the solution.
3. The process as claimed in claim 2, wherein the crystallization is initiated by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution or a combination thereof.
4. The process as claimed in claim 3, wherein the crystallization is initiated by cooling the solution.
5. The process as claimed in claim 4, wherein the solution is cooled to below about 40°C .
6. The process as claimed in claim 5, wherein the solution is cooling to about $20 - 30^{\circ}\text{C}$.
7. A crystalline tenofovir disoproxil fumarate form B, characterized by an X-ray powder diffraction spectrum having peaks expressed as 2θ angle positions at about 5.2, 15.4, 20.6, 25.8 and 31.0 ± 0.2 degrees.
8. A process for preparation of crystalline tenofovir disoproxil fumarate form B as defined in claim 7, which comprises:
 - a) dissolving tenofovir disoproxil fumarate in methanol or ethanol; and
 - c) crystallizing tenofovir disoproxil fumarate form B from the solution.
9. The process as claimed in claim 8, wherein the crystallization is initiated by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution or a combination thereof.
10. The process as claimed in claim 9, wherein the crystallization is initiated by cooling the solution.
11. The process as claimed in claim 10, wherein the solution is cooling to below about 40°C .

12. The process as claimed in claim 11, wherein the solution is cooling to about 20 - 30°C.
13. Amorphous form of tenofovir disoproxil fumarate.
14. A process for preparation of amorphous tenofovir disoproxil fumarate as
5 defined in claim 13, which comprises:
a) dissolving tenofovir disoproxil fumarate in a suitable solvent; and
b) removing the solvent from the solution formed in step (a) by freeze drying.
15. The process as claimed in claim 14, wherein solvent is selected from
10 alcoholic solvents such as methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, n-butyl alcohol; ketonic solvents such as acetone, diethyl ketone, methyl ethyl ketone, methyl isobutyl ketone and methyl propyl ketone; tetrahydrofuran; dimethylformamide, dimethylsulfoxide; and a mixture thereof.
- 15 16. The process as claimed in claim 15, wherein solvent is selected from methanol, ethanol, isopropyl alcohol, tert-butyl alcohol and n-butyl alcohol.
17. The process as claimed in claim 15, wherein solvent is ethanol.
18. A pharmaceutical composition comprising crystalline tenofovir disoproxil fumarate form A of claim 1 and a pharmaceutically acceptable excipient.
- 20 19. The pharmaceutical composition as claimed in claim 18, wherein the pharmaceutical composition of tenofovir disoproxil fumarate form A is a solid oral dosage form.
20. A pharmaceutical composition comprising crystalline tenofovir disoproxil fumarate form B of claim 7 and a pharmaceutically acceptable excipient.
- 25 21. The pharmaceutical composition as claimed in claim 20, wherein the pharmaceutical composition of tenofovir disoproxil fumarate form B is a solid oral dosage form.
22. A pharmaceutical composition comprising amorphous tenofovir disoproxil fumarate of claim 13 and a pharmaceutically acceptable excipient.
- 30 23. The pharmaceutical composition as claimed in claim 22, wherein the pharmaceutical composition of amorphous tenofovir disoproxil fumarate is a solid oral dosage form.

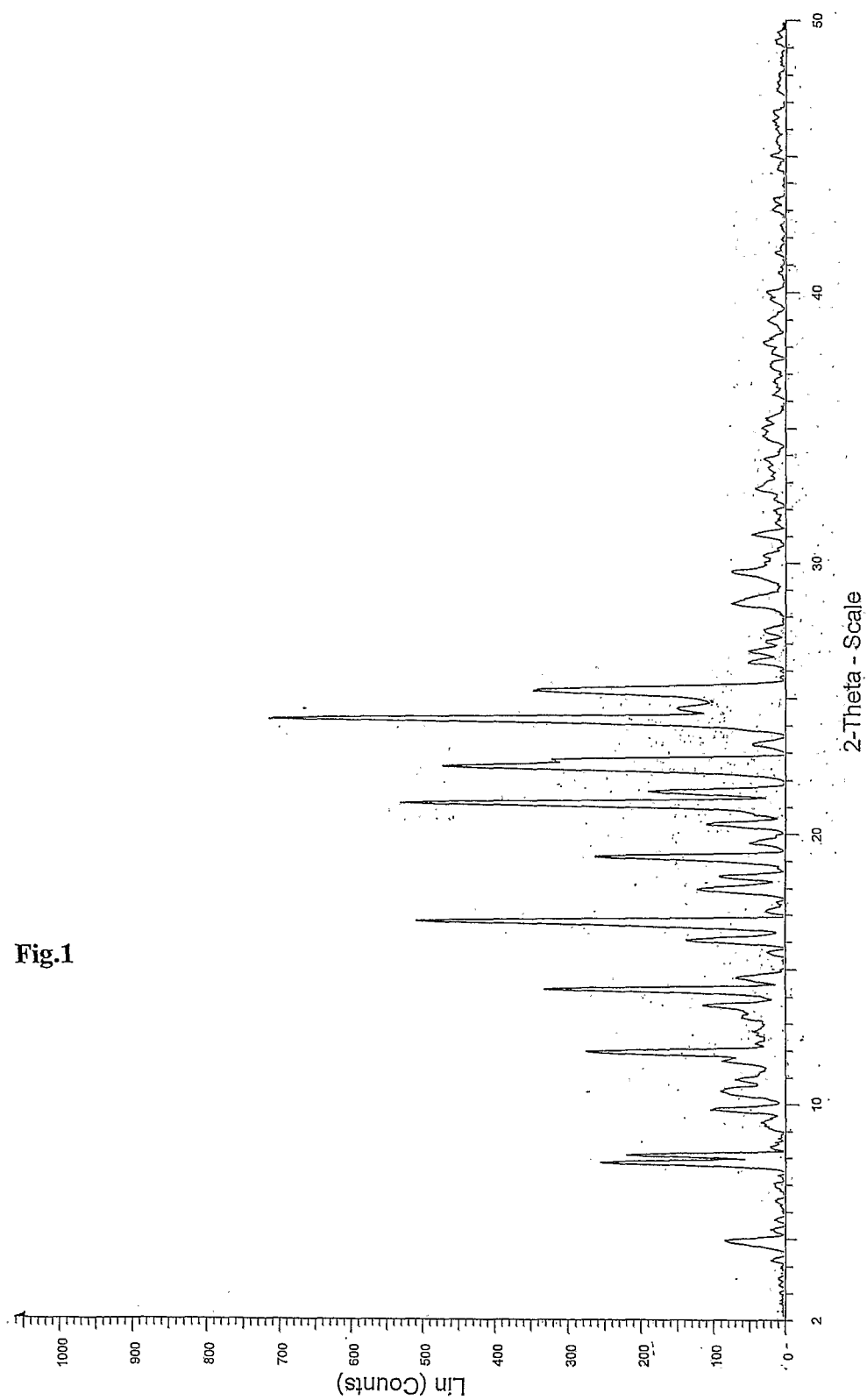


Fig.2

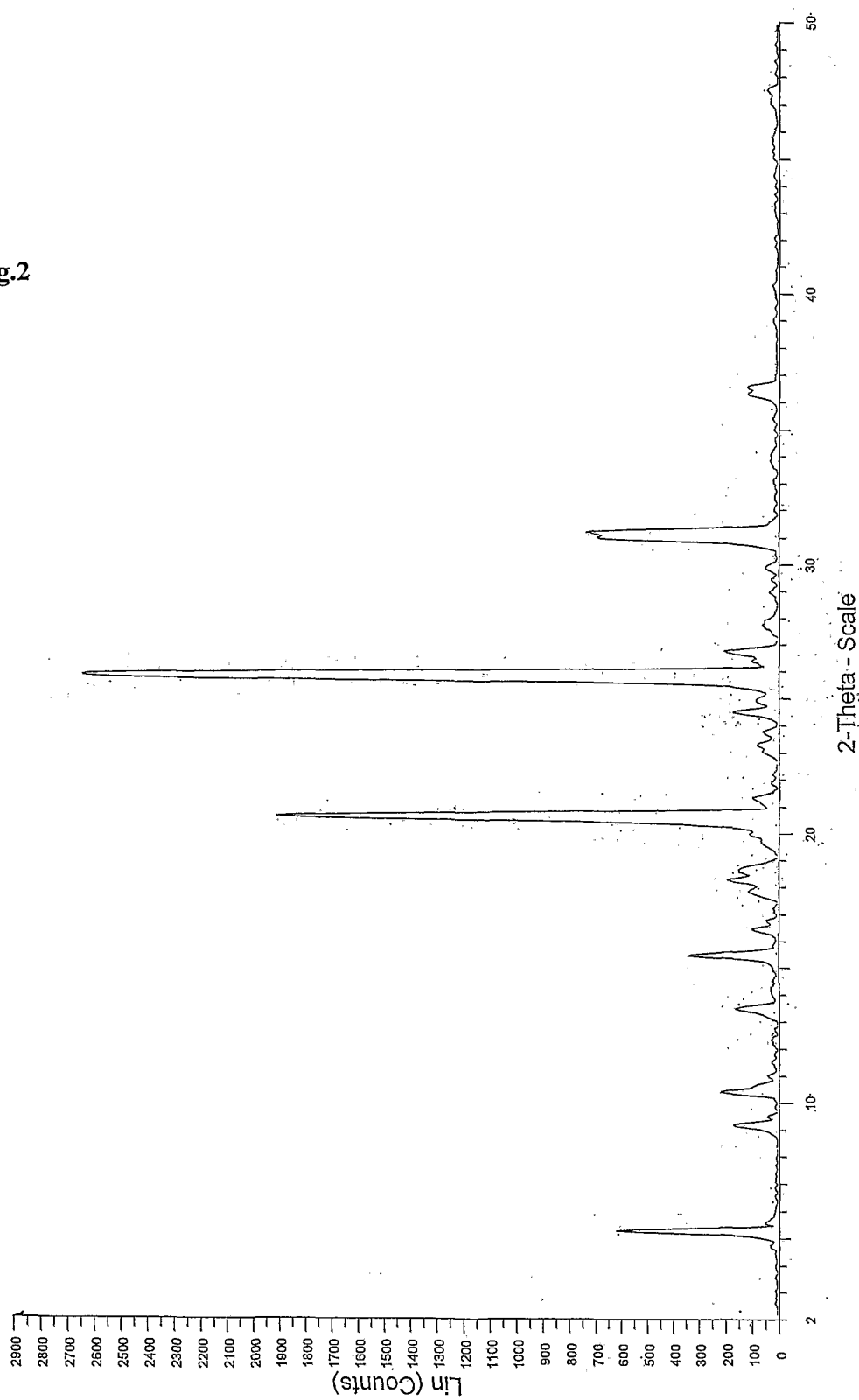
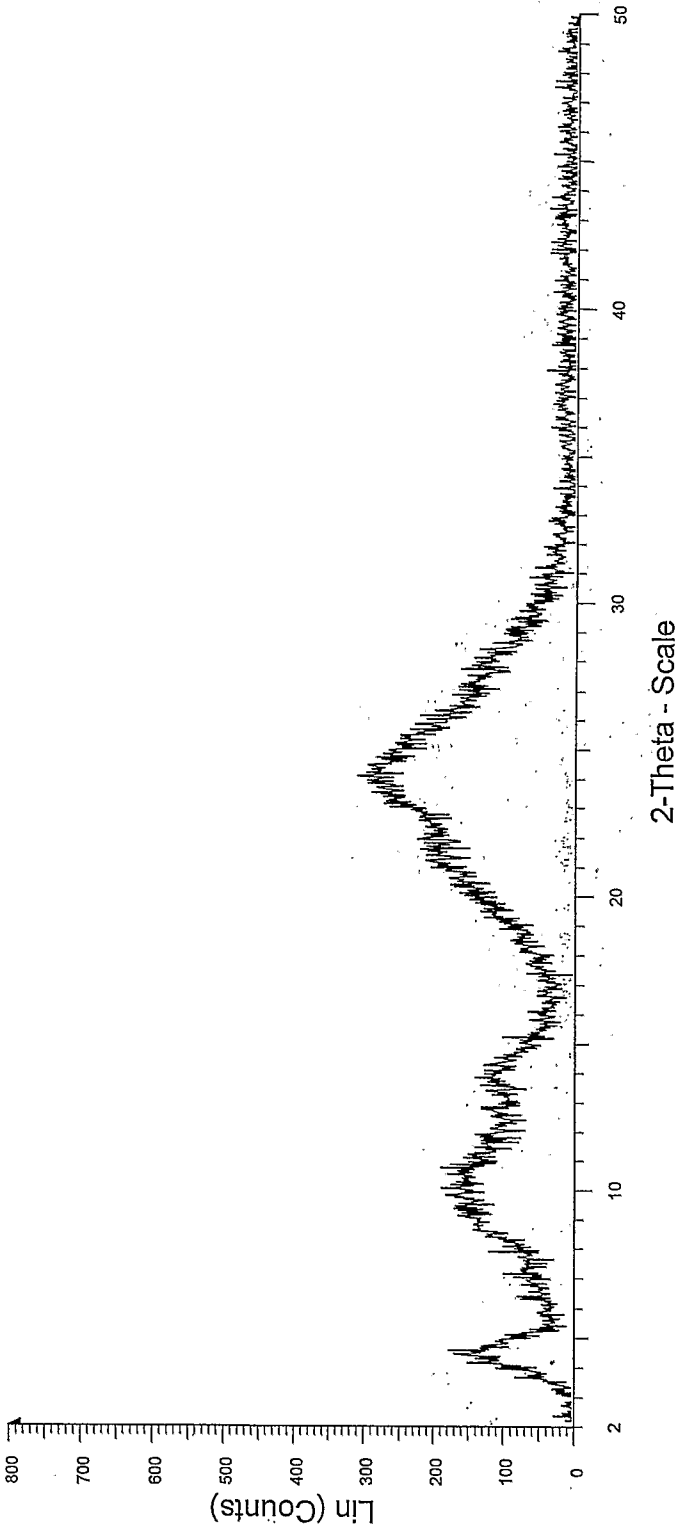


Fig.3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2005/000248

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁸: **C07F 9/6561** (01.2006); **C07D 473/34** (01.2006)

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)

IPC⁸: C07F

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 practicable, search terms used)

EPOQUE: EPODOC, WPI, EMBASE, XPESP; CAS-databases

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5922695 A (ARIMILLI et al.) 13 July 1999 (13.07.1999) <i>example 1 step 7</i> --	1-23
X	US 5935946 A (MUNGER, Jr. et al.) 10 August 1999 (10.08.1999) <i>column 15 line 18 - column 18, line 52, figures 1-3</i> ----	1-23

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search
24 April 2006 (24.04.2006)Date of mailing of the international search report
10 May 2006 (10.05.2006)Name and mailing address of the ISA/ AT
Austrian Patent Office
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 2005/000248

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