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(54) Title: PROCESS FOR THE PREPARATION OF PURE LEVETIRACETAM

(57) Abstract: The invention relates to processes for the preparation of pure levetiracetam. The invention also relates to pharmaceutical compositions that include the pure levetiracetam.

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# PROCESS FOR THE PREPARATION OF PURE LEVETIRACETAM

## Field of the Invention

The field of the invention relates to processes for the preparation of pure levetiracetam. The invention also relates to pharmaceutical compositions that include the pure levetiracetam.

## Background of the Invention

Chemically, levetiracetam is (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide and is known from U.S. Patent No. 4,943,639. Levetiracetam is used as a protective agent for the treatment and prevention of hypoxic and ischemic type aggressions of the central nervous system. It is also effective in the treatment of epilepsy.

U.S. Patent No. 4,943,639 discloses the preparation of levetiracetam by reacting (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid successively with alkylhaloformate and with ammonia. (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid, in turn was obtained by the chemical resolution of racemic (±)-alpha-ethyl-2-oxo-1-pyrrolidineacetic acid. U.S. Patent Nos. 6,107,492 and 6,124,473 describe the preparation of levetiracetam by optical resolution of the racemic mixture of alpha-ethyl-2-oxo-1-pyrrolidineacetamide through simulated mobile bed chromatography or preparative high performance liquid chromatography. WO 01/64637 discloses the preparation of levetiracetam by asymmetric hydrogenation of (Z) or (E)-2-(2-oxotetrahydro-1H-1-pyrrolyl)-2-butenamide, using a chiral catalyst.

## Summary of the Invention

In one aspect there is provided a process for preparing pure levetiracetam having optical purity more than 99.5%. The process includes obtaining a solution of crude levetiracetam in one or more solvents; removing undissolved material; and recovering the pure levetiracetam having optical purity more than 99.5% from the solution thereof by the removal of the solvent.

The solvent may be one or more of ketone, nitrile, hydrocarbon, chlorinated hydrocarbon, ether, cyclic ether or mixtures thereof. The ketone may include one or more of acetone, methyl ethyl ketone and methyl isobutyl ketone. The nitrile may include acetonitrile. The hydrocarbon may include toluene. The chlorinated hydrocarbon may include one or more of methylene chloride and ethylene dichloride. The ether may include

one or more of diethyl ether and diisopropyl ether. The cyclic ether may include dioxane and tetrahydrofuran. Removing the solvent may include one or more of distillation, distillation under vacuum, filtration, filtration under vacuum, evaporation, decantation and centrifugation.

The process may include further drying of the product obtained.

In another general aspect additional/second solvent may be added to residue obtained after removal of the solvent and it may be cooled before filtration to obtain better yields of the pure levetiracetam.

Examples of additional/second solvent include esters such as ethyl acetate, isobutyl acetate and isopropyl acetate; hydrocarbons such as hexane, cyclohexane, toluene and heptane; lower alkyl ethers such as diethyl ether, diisopropyl ether and mixtures thereof.

The process may produce the pure levetiracetam having optical purity more than 99.5%. In particular, it may produce the pure levetiracetam having optical purity more than 99.8%.

In another aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of pure levetiracetam having optical purity more than 99.5%; and one or more pharmaceutically acceptable carriers, excipients or diluents.

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 pure levetiracetam, by obtaining a solution of crude levetiracetam in one or more solvents; removing undissolved material; and recovering the pure levetiracetam having optical purity more than 99.5% from the solution thereof by the removal of the solvent. The inventors also have developed pharmaceutical compositions that contain the pure levetiracetam having optical purity more than 99.5% for example, more than 99.8%, in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients.

The levetiracetam may be prepared by the methods known in the literature. In particular, it may be prepared using the reactions and techniques described in U.S. Patent No. 4,943,639; PCT patent application WO 01/64637; and British patent GB 2225322.

The term "crude levetiracetam" includes levetiracetam having optical purity of not less than 90%.

In general, the solution of crude levetiracetam may be obtained by dissolving crude levetiracetam in a suitable solvent. Alternatively, such a solution may be obtained directly from a reaction in which levetiracetam is formed. The solvent containing crude levetiracetam may be heated to obtain a solution. It can be heated from about 30°C to about reflux temperature of the solvent used, for example from about 30°C to about 100°C.

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

The pure levetiracetam may be recovered from the solution by a technique which includes, for example, distillation, distillation under vacuum, filtration, filtration under vacuum, evaporation, decantation, and centrifugation.

The term "suitable solvent" includes any solvent or solvent mixture in which crude levetiracetam is soluble, including, for example, ketone, nitrile, hydrocarbon, chlorinated hydrocarbon and mixtures thereof.

A suitable ketone includes one or more of acetone, methyl ethyl ketone and methyl isobutyl ketone. Examples of nitrile include acetonitrile. Examples of hydrocarbon include toluene and examples of chlorinated hydrocarbons include one or more of methylene chloride and ethylene dichloride. Examples of ethers include solvents such as diethyl ether and diisopropyl ether and cyclic ethers such as dioxane, tetrahydrofuran. Mixtures of all of these solvents are also contemplated.

The undissolved material may be removed by a technique which includes filtration, filtration under vacuum, centrifugation, and decantation.

In general, after removing the undissolved material, the resulting solution may be cooled before recovering the pure levetiracetam. The solution may also be concentrated before cooling. Additional or second solvent may be added to residue

obtained after concentration and it may be cooled before filtration to obtain better yields of the pure levetiracetam.

Examples of additional/second solvent include esters such as ethyl acetate, isobutyl acetate and isopropyl acetate; hydrocarbons such as hexane, cyclohexane, toluene and heptane; lower alkyl ethers such as diethyl ether, diisopropyl ether and mixtures thereof.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. 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 pure levetiracetam

Crude levetiracetam (123g, optical purity ~ 96.00%) was mixed with acetone (2800ml) and stirred at ambient temperature for 60 minutes. The undissolved material was then filtered through hyflo bed and washed with acetone (200ml). The filtrate and washings were combined and concentrated under vacuum at 35 to 40°C to about 240ml of the volume. To the resulting slurry, ethyl acetate (480ml) was charged and stirred for 20 minutes at ambient temperature. The solid so obtained was filtered and washed with ethyl acetate (100ml). It was dried under vacuum at 40 to 45°C till loss on drying was less than 0.5% to give the pure product.

Yield: 108g

Chromatographic purity = 99.99%

Optical purity = 99.95%

Example 2: Preparation of pure levetiracetam

Crude levetiracetam (100g, optical purity ~ 98.48%) was mixed with acetone (2300ml) and stirred at ambient temperature for 60 minutes. The undissolved material was then filtered through hyflo bed and washed with acetone (160ml). The filtrate and washings were combined and concentrated under vacuum at 35 to 40°C to about 200ml. Ethyl acetate (200ml) was then charged into the resulting slurry and stirred for 20 minutes at ambient temperature. The solid so obtained was filtered and washed with ethyl acetate (400ml). The wet solid product was dried under vacuum at 40 to 45°C till loss on drying was less than 0.5% to give the pure product.

Yield: 87g

Chromatographic purity = 99.99%

Optical purity = 99.95%

Example 3: Preparation of pure levetiracetam

Crude levetiracetam (36g, optical purity ~ 96.00%) was mixed with acetone (216ml) and refluxed at 56-57°C. The undissolved material was then filtered through hyflo bed and washed with acetone (200ml). The filtrate and washings were combined and cooled to 25°C. The resulting slurry was further stirred for about 1 hour at the same temperature. The solid so obtained was filtered and washed with acetone (18ml). It was dried under vacuum at 40 to 45°C till loss on drying was less than 0.5% to give the pure product.

Yield: 25.2g

Chromatographic purity = 99.79%

Optical purity = 99.84%

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 included within the scope of the present invention.

We claim:

1. A process for the preparation of pure levetiracetam having optical purity more than 99.5%, the process comprising;

obtaining a solution of crude levetiracetam in one or more solvents;

removing undissolved material; and

recovering the pure levetiracetam from the solution thereof by the removal of the solvent.

2. The process of claim 1, wherein the solvent comprises one or more of ketone,nitrile, hydrocarbon, chlorinated hydrocarbon, ether, cyclic ether or mixtures thereof.

3. The process of claim 2, wherein the ketone comprises one or more of acetone, methyl ethyl ketone and methyl isobutyl ketone.

4. The process of claim 2, wherein the nitrile is acetonitrile.

5. The process of claim 2, wherein the hydrocarbon is toluene.

6. The process of claim 2, wherein the chlorinated hydrocarbon comprises one or more of methylene chloride and ethylene dichloride.

7. The process of claim 2, wherein the ether comprises one or more of diethyl ether and diisopropyl ether.

8. The process of claim 2, wherein the cyclic ether comprises one or more of dioxane and tetrahydrofuran.

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

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

11. The process of claim 10, wherein removing the solvent comprises one or more of distillation and distillation under vacuum.

12. The process of claim 11 further comprising adding second solvent after removing the solvent.

13. The process of claim 12, wherein the second solvent comprises one or more of esters, hydrocarbons, ethers and mixtures thereof.

14. The process of claim 13, wherein the ester comprises one or more of ethyl acetate, isobutyl acetate and isopropyl acetate.

15. The process of claim 13, wherein the hydrocarbon comprises one or more of hexane, cyclohexane, toluene, heptane, and octane.

16. The process of claim 13, wherein the ether comprises one or more of diethyl ether, diisopropyl ether.

17. The process of claim 10, wherein removing the solvent comprises one or more of filtration, filtration under vacuum and centrifugation.

18. The process of claim 17 further comprising cooling before removing the solvent.

19. The process of claim 1 further comprising additional drying of the product obtained.

20. The process of claim 1 further comprising forming the product obtained into a finished dosage form.

21. Pure levetiracetam having optical purity more than 99.5% prepared by the process of claim 1.

22. Pure levetiracetam having optical purity 99.8% or more prepared by the process of claim 1.

23. A pharmaceutical composition comprising a therapeutically effective amount of the pure levetiracetam obtained by the process of claim 1; and one or more pharmaceutically acceptable carriers, excipients or diluents.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/27 A61K31/4015 A61P25/08

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 C07D

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, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 03/014080 A (CAVOY EMILE ; ATES CELAL (BE); SURTEES JOHN (BE); UCB SA (BE); BURTEAU) 20 February 2003 (2003-02-20) page 17, line 12 - line 16; example 7 page 1, line 5 - line 10 | 1-23 |
| X | WO 01/64637 A (DIFFERDING EDMOND ; SURTEES JOHN (BE); UCB FARCHIM S A AG LTD (CH); ZI) 7 September 2001 (2001-09-07) cited in the application page 23, line 14 - line 28 | 1-23 |
| X | US 4 943 639 A (GOBERT JEAN ET AL) 24 July 1990 (1990-07-24) cited in the application examples 1c,2b,3b,4 | 1-23 |

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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

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 25 November 2004 | 10/12/2004 |

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| 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 | Seymour, L |

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# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/002850

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | WO 2004/069796 A (TEVA PHARMA ; DOLITYZKY BEN-ZION (IL); TEVA PHARMA (US)) 19 August 2004 (2004-08-19) page 3, line 32 - page 4, line 22; examples 3,8,9 | 1-23 |

1

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/002850

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 03014080 A | 20-02-2003 | CA 2455155 A1 | 20-02-2003 |
| | | WO 03014080 A2 | 20-02-2003 |
| | | EP 1419144 A2 | 19-05-2004 |
| | | US 2004204476 A1 | 14-10-2004 |
| WO 0164637 A | 07-09-2001 | AU 5214401 A | 03-09-2001 |
| | | AU 7389601 A | 12-09-2001 |
| | | BG 107004 A | 30-04-2003 |
| | | BG 107016 A | 30-04-2003 |
| | | BR 0108657 A | 29-04-2003 |
| | | BR 0108664 A | 29-04-2003 |
| | | CA 2401033 A1 | 30-08-2001 |
| | | CA 2401048 A1 | 07-09-2001 |
| | | CN 1404469 T | 19-03-2003 |
| | | CN 1404470 T | 19-03-2003 |
| | | CZ 20022849 A3 | 12-02-2003 |
| | | CZ 20022850 A3 | 12-02-2003 |
| | | WO 0164637 A1 | 07-09-2001 |
| | | WO 0162726 A2 | 30-08-2001 |
| | | EP 1265862 A2 | 18-12-2002 |
| | | EP 1263727 A1 | 11-12-2002 |
| | | EP 1447399 A1 | 18-08-2004 |
| | | EP 1452524 A1 | 01-09-2004 |
| | | EP 1477478 A2 | 17-11-2004 |
| | | HU 0204526 A2 | 28-04-2003 |
| | | HU 0300196 A2 | 28-06-2003 |
| | | JP 2003523996 T | 12-08-2003 |
| | | JP 2003528828 T | 30-09-2003 |
| | | NO 20023995 A | 21-10-2002 |
| | | NO 20023997 A | 22-10-2002 |
| | | NZ 520448 A | 26-03-2004 |
| | | PL 359388 A1 | 23-08-2004 |
| | | US 2003120080 A1 | 26-06-2003 |
| | | US 2003040631 A1 | 27-02-2003 |
| | | US 2004092576 A1 | 13-05-2004 |
| | | US 2004116507 A1 | 17-06-2004 |
| | | US 2004087646 A1 | 06-05-2004 |
| | | US 2004192757 A1 | 30-09-2004 |
| | | ZA 200205671 A | 10-11-2003 |
| | | ZA 200205837 A | 04-11-2003 |
| US 4943639 A | 24-07-1990 | AT 45567 T | 15-09-1989 |
| | | AU 574465 B2 | 07-07-1988 |
| | | AU 4253085 A | 20-11-1986 |
| | | BG 47497 A3 | 16-07-1990 |
| | | BG 50156 A3 | 15-05-1992 |
| | | CA 1235129 A1 | 12-04-1988 |
| | | CN 85105301 A ,B | 14-01-1987 |
| | | CY 1567 A | 20-12-1991 |
| | | DE 3572348 D1 | 21-09-1989 |
| | | DE 10075021 I1 | 19-10-2000 |
| | | DE 10199005 I1 | 12-07-2001 |
| | | DK 212985 A ,B, | 16-11-1985 |
| | | EP 0162036 A1 | 21-11-1985 |
| | | ES 8608485 A1 | 01-12-1986 |
| | | ES 8704893 A1 | 01-07-1987 |
| | | FI 851875 A ,B, | 16-11-1985 |
| | | GR 851155 A1 | 25-11-1985 |

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/002850

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 4943639 A | | HK 52391 A | 19-07-1991 |
| | | IE 59950 B1 | 04-05-1994 |
| | | IL 75179 A | 31-05-1988 |
| | | JP 1901367 C | 27-01-1995 |
| | | JP 6029186 B | 20-04-1994 |
| | | JP 60252461 A | 13-12-1985 |
| | | KR 9203818 B1 | 15-05-1992 |
| | | LT 2584 R3 | 25-03-1994 |
| | | LU 90615 A9 | 02-10-2000 |
| | | LU 90682 A9 | 30-01-2001 |
| | | LV 5233 A3 | 10-10-1993 |
| | | NL 300028 I1 | 01-02-2001 |
| | | NO 851933 A ,B, | 18-11-1985 |
| | | PL 253374 A1 | 06-05-1986 |
| | | PL 257385 A1 | 07-10-1986 |
| | | PT 80460 A ,B | 01-06-1985 |
| | | SG 80090 G | 23-11-1990 |
| | | SU 1402260 A3 | 07-06-1988 |
| | | SU 1430392 A1 | 15-10-1988 |
| | | SU 1428195 A3 | 30-09-1988 |
| | | US 4837223 A | 06-06-1989 |
| | | US 4696943 A | 29-09-1987 |
| | | ZA 8503635 A | 24-12-1985 |
| WO 2004069796 A | 19-08-2004 | WO 2004069796 A2 | 19-08-2004 |