

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
3 June 2004 (03.06.2004)

PCT

(10) International Publication Number  
**WO 2004/046084 A1**

(51) International Patent Classification<sup>7</sup>: **C07C 227/42**

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(21) International Application Number:  
PCT/IN2002/000221

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(22) International Filing Date:  
18 November 2002 (18.11.2002)

(25) Filing Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(26) Publication Language: English

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(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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**Published:**

— *with international search report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: IMPROVED PROCESS FOR PREPARATION OF GABAPENTIN

(57) Abstract: A process for producing Gabapentin, (1-(aminomethyl)-1-cyclohexaneacetic acid) from Gabapentin hydrochloride salt. In the process the Gabapentin hydrochloride is converted to Gabapentin using inorganic base such as Barium hydroxide. Gabapentin hydrochloride is converted to Gabapentin sulfate which in turn is converted to free base using Barium hydroxide. The process is directed to improvement in the manufacture of Gabapentin which would be industrially feasible and effective Gabapentin obtained following the process of the invention is suitable as a drug especially in the treatment of cerebral diseases such as epilepsy. The above process involves simple steps and avoid the problems of the known art. In particular the process avoids severe conditions and/or complexities and can be readily adopted for industrial application. The process provides for good yield and does not involve lengthy extended process steps. It is cost-effective and can be carried out involving simple ingredients and steps of manufacture.



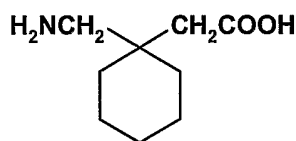
WO 2004/046084 A1

**IMPROVED PROCESS FOR PREPARATION OF GABAPENTIN****FIELD OF THE INVENTION**

The present invention relates to a process for producing Gabapentin, 1-(aminomethyl)-1-cyclohexaneacetic acid from Gabapentin hydrochloride salt. The process is directed to improvement in the manufacture of Gabapentin which would be industrially feasible and facilitate simple and cost-effective manufacture of Gabapentin. Gabapentin obtained following the process of the invention is suitable as a drug especially in the treatment of cerebral diseases such as epilepsy.

**BACKGROUND OF THE INVENTION**

Gabapentin, 1-(aminomethyl)-1-cyclohexaneacetic acid is known to have the chemical structure as hereunder:

**Fig. 1**

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Gabapentin is used in the treatment of cerebral diseases such as epilepsy. There are various methods presently known for preparing Gabapentin from a variety of starting materials. U.S. Patent 4,024,175 describes at least three methods of preparing Gabapentin from cyclohexyl-1,1-diacetic acid. Each of these methods results in the formation of Gabapentin hydrochloride salt, which may be converted to 1-(aminomethyl)-1-cyclohexaneacetic acid by treatment with a basic ion exchanger and then crystallized from a solvent such as ethanol/ether.

U.S. Patent 4,894,476 specifically discloses an improved method for converting the hydrochloride salt into the free amino acid. This involves pouring a deionized water solution of the salt over an ion exchange column, eluting with deionized water, producing a slurry

from the elute, adding an alcohol to the slurry, centrifuging and drying the slurry to obtain the free amino acid.

Alternative methods for preparing Gabapentin have been described that do not proceed via  
5 the hydrochloride or any other mineral acid salt. Such methods include those described in U.S. Patent Nos. 5,132,451, 5,095,148, 5,068,413. Each of these methods involve a cyanic intermediate which is hydrogenated under severe conditions to produce the free amino acid.

These methods are industrially impractical. Those methods comprising ion exchange  
10 columns require the use of large amounts of ion exchanger for lengthy periods of time to lower the level of chloride ions to the desired level. The alternative methods involve further more demanding steps.

WO 98/28255 describes the preparation of Gabapentin from Gabapentin hydrochloride  
15 through optional pre-treatment to remove inorganic salts and then by treating suitable organic amines like triethylamine, tributylamine, tripropylamine, trihexylamine, diethylamine, ethanolamine and benzylamine. Preferably the amine is tributylamine.

### **OBJECTS OF THE INVENTION**

20 It is thus the basic object of the present invention to provide a process of producing Gabapentin which would be simple and avoid the aforesaid problems of the known art.

Another object of the present invention is directed to a process for the manufacture of Gabapentin from Gabapentin hydrochloride salt which would avoid severe conditions and/or  
25 complexities and can be readily adopted for industrial application.

Yet further object of the present invention is directed to provide a method of manufacture of Gabapentin which would have good yield and not involve lengthy extended process steps.

30 Yet another object of the present invention is to provide a method of manufacture of Gabapentin which would be cost-effective and can be carried out involving simple and readily available ingredients starting material.

**SUMMARY OF THE INVENTION**

Thus according to the present invention there is provided a process of producing Gabapentin comprising :

- 5 i) providing an aqueous alkaline solution of Gabapentin Hydrochloride salt and reacting with Sulfuric acid followed by neutralizing with inorganic base;
- ii) filtration of inorganic salts and distillation to obtain a resultant solid ;
- iii) dissolving the said resultant solid of (ii) above in an protic solvent, filtering to remove further inorganic salts followed by distillation of the resulting solvent to obtained a residue ;
- 10 iv) adding another solvent to said residue and isolating Gabapentin therefrom by filtration.

In the above process the inorganic bases can be selected from metal hydroxide or carbonate of IIa of periodic table preferably barium hydroxide.

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The alkali used in the process can be selected from such as Sodium hydroxide, Potassium hydroxide, Calcium hydroxide and alkali metal hydroxides, carbonates.

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The first solvents employed can be selected from Methanol, Acetonitrile, Isopropyl alcohol, acetone.

The 'second' solvent can be selected from Isopropanol, acetone, Methanol, Acetonitrile, Dimethylformamide, Ethyl Acetate, Diisopropylether, Methylene choride.

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The above process of the present invention provide an improved, industrially feasible method for preparing Gabapentin from Gabapentin hydrochloride. The process avoids the disadvantages associated with prior art methods and selectively employs the inorganic bases to convert Gabapentin hydrochloride to Gabapentin. Gabapentin hydrochloride used in the process can be prepared by the method known in prior art such as US Patent No. 4152326

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(1979).

**DETAILED DESCRIPTION OF THE INVENTION :**

In accordance with a preferred aspect the process of the invention comprises:

- (1) mixing aqueous solution of the Gabapentin hydrochloride with alkali ;
- (2) filtration to separate solid and heating with dil. Sulfuric acid followed by pH  
5 adjustment to neutral with inorganic bases at 30 – 80°C.
- (3) filtration of inorganic salts in particular sulfate and concentration of filtrate under vacuum.
- (4) redissolving the resultant solid in protic solvent (first solvent).
- (5) filtration of traces of inorganic salt in particular sulfate salts if any.
- 10 (6) concentration of protic solvent to dryness.
- (7) addition of second solvent and isolation of Gabapentin by filtration.

Thus the initial critical stages of the process of the present invention comprises of mixing of an aqueous solution of Gabapentin hydrochloride with alkali metal hydroxide or carbonate  
15 solutions. Filtration of separated solids and reacting with dil. Sulfuric acid and then adjusting pH to neutral with inorganic base.

The subsequent critical steps of the process is the removal of water by distillation from the filtrate after filtration of corresponding sulfate salt. The water may be distilled off at  
20 atmospheric pressure or under vacuum. The next step involves the addition of protic solvent (first solvent) to dissolve Gabapentin and filtration of traces of, if any, corresponding sulfate salt. In the next step the solvent from the filtrate is removed and addition of 'second' solvent and filtration of Gabapentin. The solvent may be distilled at atmospheric pressure or under vacuum.

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Preferably, the Gabapentin hydrochloride salt is used as a solution in water in concentration ranging from 10 to 40%, more preferably 33%.

The inorganic bases are preferably used as solid and/or as aqueous solution of concentration  
30 5 to 15% more preferably 10%.

The temperature of neutralization is selected from RT 30°C to 80°C preferably 40°C. the final pH of the neutralization is about 5 to 8 preferably 7.

The process of the invention, its objects and advantages are explained hereunder in greater detail by way of the non-limiting exemplary illustrations of the process as discussed hereunder :

**Example 1 :**

Gabapentin hydrochloride (10 g.) was dissolved in water 30 ml. and heated to 40-60°C. To this solution was added Sodium hydroxide to pH 9.0 to 14.0 and the reaction mixture heated at 40-60°C for 3 to 6 hrs. The reaction mass is cooled to 5-10°C and maintained at this temperature for 6 hrs. The separated solid is filtered and added to dil. Sulfuric acid 30 ml. (5 ml. Sulfuric acid diluted to 30 ml. with water).

The reaction mixture heated under reflux for 12 hrs. and then cooled to 30°C. The pH of the solution was adjusted to 7.0 to 7.5 with barium hydroxide suspension in water. The separated barium sulfate is filtered off and wash with water 10 ml. The filtrate is concentrated to dryness under vacuum. Methanol (120 ml.) added to the residue and then clear solution is filtered through Celite. Methanol is recovered under vacuum at below 50°C. The product remained was treated with Iso-propanol (50 ml.), stirred of 30 min. at RT and filtered off. The product obtained is dried till content weight of 6.7 g.

**Examples 2-9 :**

The method of Example 1 was followed using different solvents shown in Table1 alongwith percentage yield (w/w)

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**TABLE - 1**

Example No.	First Solvent	Second Solvent	Yield (w/w) %
2	Methanol	Methanol	55
3	Methanol	IPA	67
4	Methanol	Acetone	65
5	Methanol	Acetonitrile	52
6	Acetonitrile	Methanol	53
7	Acetonitrile	IPA	64
8	Acetonitrile	Acetone	65
9	Acetonitrile	Acetonitrile	51

Importantly, the various options of the first and second solvents tried as above in accordance with the process of the invention have demonstrated good yield by way of a simple and cost effective process. The above exemplary illustrations also demonstrate the simplicity on the process and the possible avoiding of complexity involved in manufacture of Gabapentin  
5 from Gabapentin hydrochloride salt. The process is industrially viable and should serve in wide-scale manufacture of Gabapentin especially for its drug/medicinal applications/end uses.

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CLAIMS

1. A process of producing Gabapentin comprising :
  - 5 i) providing an aqueous alkaline solution of Gabapentin Hydrochloride salt and reacting with Sulfuric acid followed by neutralizing with inorganic bases;
  - ii) filtration of inorganic salts and distillation to obtain a resultant solid ;
  - iii) dissolving the said resultant solid of (ii) above in an protic solvent, filtering to removing traces of inorganic salts followed by distillation of the resulting solvent to  
10 obtained a residue ;
  - iv) adding another solvent to said residue and isolating Gabapentin therefrom by filtration.
  
2. A process as claimed in claim 1 comprising of :
  - 15 (1) mixing aqueous solution of the Gabapentin hydrochloride with alkali,
  - (2) filtration to separate solid and heating with dil. Sulfuric acid followed by pH adjustment to neutral with inorganic bases at 30 – 80°C.
  - (3) filtration of inorganic salts in particular sulfate and concentration of filtrate under vacuum.
  - 20 (4) redissolving the resultant solid in protic solvent.
  - (5) filtration of traces of inorganic salt in particular sulfate salt if any.
  - (6) concentration of protic solvent to dryness.
  - (7) addition of second solvent and isolation of Gabapentin by filtration.
  
- 25 3. A process as claimed in anyone of claims 1 or 2 wherein said alkali used is selected from such as Sodium hydroxide, Potassium hydroxide, Calcium hydroxide and alkali metal hydroxides, carbonates.
  
- 30 4. A process as claimed in anyone of claims 1 to 3 wherein the inorganic bases are selected from metal hydroxide or carbonate of IIa of periodic table.

5. A process as claimed in anyone of claims 1 to 4 wherein the Gabapentin salts are used as a solution in water in concentration ranging from 10 to 40%.
6. A process as claimed in claim 5 wherein the concentration of the aq. solution is 33%.
- 5 7. The process as claimed in anyone of claims 1 to 6 wherein the inorganic base used is preferably barium hydroxide.
8. The process as claimed in anyone of claims 1 to 7 wherein the inorganic bases are used  
10 as solid and/or as aq. solutions of concentration 5 to 15%.
9. The process as claimed in claim 8 wherein the inorganic bases are used as solid and/or as aq. solution of concentration of the solution of inorganic base is 10%.
- 15 10. The process as claimed in anyone of claims 1 to 9 wherein the temperature of neutralization is maintained from RT (30<sup>0</sup>C) to 80<sup>0</sup>C.
11. The process as claimed in claim 10 wherein the temperature of neutralisation is maintained at 40<sup>0</sup>C.
- 20 12. The process as claimed in anyone of claims 1 to 11 wherein the final pH of the neutralisation is 5 to 8.
13. The process as claimed in claim 12 wherein the final pH of the neutralisation is 7.
- 25 14. The process as claimed in anyone of claims 1 to 13 wherein the 'first' solvent is selected from the group consisting of Methanol, Acetonitrile, Isopropyl alcohol, acetone.
15. The process as claimed in claim 14 wherein the 'first' solvent is preferably Methanol.
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16. The process as claimed in anyone of claims 1 to 15, wherein the 'second' solvent is selected from the group consisting of Isopropanol, Acetone, Methanol, Acetonitrile, Dimethylformamide, Ethyl Acetate, Diisopropylether, Methylene chloride.
- 5 17. The process of claim 16, wherein the 'second' solvent is preferably Isopropanol.
18. A process of producing Gabapentin substantially as herein described and illustrated with reference to the accompanying examples.

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# INTERNATIONAL SEARCH REPORT

Inte      Application No  
PCT/IN 02/00221

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7    C07C227/42

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)  
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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of box C.       Patent family members are listed in annex.

° Special categories of cited documents :

<p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*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)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p>	<p>*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</p> <p>*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</p> <p>*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.</p> <p>*&amp;* document member of the same patent family</p>
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Date of the actual completion of the international search  <b>4 August 2003</b>	Date of mailing of the international search report  <b>13/08/2003</b>
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Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  <b>Rufet, J</b>
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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