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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TEVA PHARMACEUTICAL INDUSTRIES LTD. and TEVA PHARMACEUTICALS USA, INC.,	:	Civil Action No.
Plaintiffs,	:	
v.	:	
CIPLA LTD., AND BYRON CHEMICAL CO., INC.,	:	
Defendants.	:	

COMPLAINT FOR DECLARATORY JUDGMENT

For their Complaint against Defendants Cipla Ltd. ("Cipla") and Byron Chemical Co., Inc. ("Byron"), Plaintiffs Teva Pharmaceutical Industries Ltd. ("Teva Ltd.") and Teva Pharmaceuticals USA, Inc. ("Teva USA") allege as to their own acts, and on information and belief as to the acts of others, as follows:

THE PARTIES

1. Teva Ltd. is a corporation organized under the laws of Israel, and maintains its principal place of business at 5 Basel Street, Petah Tiqva 49131, Israel.

2. Teva USA is a Delaware corporation with its principal place of business located at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090. Teva USA is a wholly-owned subsidiary of Teva Ltd.

3. On information and belief, Cipla is an entity organized and existing under the laws of India, and maintains legal and administrative headquarters at 289 Bellasis Road, Mumbai Central, Mumbai 400 008, India.

4. On information and belief, Cipla has entered into a string of supply contracts with generic drug companies in the United States, and the bulk of Cipla's export sales is derived from the United States.

5. On information and belief, Byron is a New York corporation having a principal place of business at 40-11 23rd Street, Long Island City, NY 11101.

6. On information and belief, Byron operates primarily as an importer of active pharmaceutical ingredients, representing various international manufacturers and distributing their products within the United States.

7. On information and belief, Byron acts as Cipla's United States regulatory and sales agent. Cipla and Byron collectively will be referred to hereafter as "Defendants."

NATURE OF THE ACTION

8. This is an action for patent infringement arising under the Patent Laws of the United States, 35 U.S.C. § 1, et seq., and seeking damages and injunctive relief under 35 U.S.C.

§§ 281-285.

JURISDICTION AND VENUE

9. This court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

10. This Court may declare the rights and other legal relations of the parties pursuant to 28 U.S.C. §§ 2201 and 2202 because this is a case of actual controversy within the Court's jurisdiction.

11. The Court has personal jurisdiction over Cipla because of its continuous and systematic contacts with the United States, including the state of New Jersey, by itself and through its regulatory and sales agent Byron.

12. The Court has personal jurisdiction over Byron because of its continuous and systematic contacts with the state of New Jersey. On information and belief, Byron represents various international manufacturers, imports active pharmaceutical ingredients, and distributes products within the United States, including the state of New Jersey.

13. Venue is proper in this judicial district based on 28 U.S.C. § 1400 (b) and/or 28 U.S.C. § 1391 (b), (c) and (d).

BACKGROUND

The Patents In Suit

14. Teva Ltd. is the owner of all right, title and interest in United States Patent Nos. 6,600,073 ("the '073 patent"), 6,500,987 ("the '987 patent"), 6,495,721 ("the '721 patent"), and 6,897,340 ("the '340 patent"; collectively, "the patents in suit") relating to, *inter alia*, methods for manufacturing certain crystalline forms of a chemical compound known as sertraline

hydrochloride. Two of these crystalline forms of sertraline hydrochloride are known as "Form II" and "Form V."

15. The '073 patent was duly and legally issued by the United States Patent and Trademark Office ("PTO") on July 29, 2003 for an invention entitled "Methods for Preparation of Sertraline Hydrochloride Polymorphs." A copy of the '073 patent is attached as Exhibit A.

16. The '987 patent was duly and legally issued by the PTO on December 31, 2002 for an invention entitled "Sertraline Hydrochloride Polymorphs." A copy of the '987 patent is attached as Exhibit B.

17. Both the '073 patent and the '987 patent claim, *inter alia*, processes for preparation of sertraline hydrochloride Form V.

18. The '721 patent was duly and legally issued by the PTO on December 17, 2002 for an invention entitled "Sertraline Hydrochloride Form II and Methods For the Preparation Thereof." A copy of the '721 patent is attached as Exhibit C.

19. The '340 patent was duly and legally issued by the PTO on May 24, 2005 for an invention entitled "Processes for Preparation of Polymorphic Form II of Sertraline Hydrochloride." A copy of the '340 patent is attached as Exhibit D.

20. The '721 and '340 patents claim, *inter alia*, processes for the preparation of sertraline hydrochloride Form II.

Plaintiffs' Generic Exclusivity

21. Sertraline hydrochloride is a pharmaceutical compound useful in the treatment of depression. It is the active pharmaceutical ingredient ("API") in the product sold by Pfizer Inc. under the trade name ZOLOFT. Teva USA sells generic sertraline hydrochloride tablets in the

United States that are manufactured by Teva Ltd.

22. Pursuant to the Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.* (1994) ("the Act"), Teva USA filed Abbreviated New Drug Application ("ANDA") No. 76-465 with the United States Food & Drug Administration ("FDA") for permission to market its generic sertraline hydrochloride tablets in the United States.

23. Ivax Pharmaceuticals, Inc. ("Ivax"), a separate wholly-owned subsidiary of Teva Ltd., filed ANDA No. 75-719 with the FDA, also seeking permission to market generic sertraline hydrochloride tablets in the United States.

24. Ivax's ANDA was approved on June 30, 2006. Under § 355(j) of the Act, Ivax obtained a limited period of exclusivity from the FDA for its generic sertraline products in the United States. Pursuant to this exclusivity, the FDA will not approve any other ANDA for generic sertraline hydrochloride tablets for a period of 180 days from the date Ivax first commercially marketed a product under its ANDA. This exclusivity period expires on February 6, 2007, *i.e.*, the FDA may grant final approval to other ANDA holders beginning on February 7, 2007.

25. Ivax has selectively waived its exclusivity period with respect to Teva USA's ANDA No. 76-465. Following this selective waiver, the FDA granted final approval to Teva's ANDA on August 11, 2006.

Defendants' Imminent Infringement of the Patents In Suit

26. Under the Act, ANDA holders must provide detailed information to the FDA about how the API to be used in their proposed generic products will be made. Suppliers of API typically are reluctant to disclose confidential information about their manufacturing processes to

their customers. Such API suppliers typically submit this confidential information directly to the FDA in the form of a Drug Master File ("DMF"), which the FDA keeps on file. Customers of the API supplier who file ANDAs may then reference the DMF in their ANDAs. Upon receiving an ANDA referencing a DMF, the FDA will separately review the DMF as part of the ANDA approval process. Accordingly, the act of filing a DMF indicates the present intent of the filer is to supply API to at least one ANDA holder.

27. On information and belief, Cipla has filed three DMFs for sertraline hydrochloride with the FDA, including DMF Nos. 18405, 17317, and 14437.

28. On information and belief, Cipla's DMF No. 18405 is directed to Form I sertraline hydrochloride, DMF No. 17317 is directed to Form II sertraline hydrochloride, and DMF No. 14437 is directed to Form V sertraline hydrochloride.

29. Cipla currently supplies sertraline hydrochloride to Ivax. On information and belief, Defendants plan and intend to supply sertraline hydrochloride API to one or more third party ANDA holders, with the knowledge and intent that the third party ANDA holder(s) will engage in the commercial importation, manufacture, use, sale and/or offer for sale of generic sertraline hydrochloride tablets in the United States. Plaintiffs have made a reasonable effort to determine the identity of the third party ANDA holder(s) that Defendants intend to supply. Currently, Plaintiffs are unable to obtain from a public source any information regarding the entities that Defendants intend to supply.

30. On information and belief, Defendants plan and intend to supply the third party ANDA holder(s) with the knowledge and intent that the third party ANDA holder(s) will engage in the activities described in paragraph 29 immediately upon receiving final approval of the

ANDA(s) by the FDA, and that said approval will occur shortly after Ivax's exclusivity period expires.

31. On information and belief, Defendants plan and intend to supply the third party ANDA holder(s) with the knowledge and intent that the third party ANDA holder(s) will engage in the activities described in paragraph 29 prior to the expiration of the patents in suit.

32. On information and belief, Defendants plan and intend to import sertraline hydrochloride into the United States for sale to third party ANDA holder(s).

33. On information and belief, Defendants' sertraline hydrochloride API is or will be made by a process that infringes one or more of the claims of the patents in suit. Accordingly, Defendants' plans and intentions to import and sell sertraline hydrochloride API in the United States constitute imminent, threatened acts of infringement under 35 U.S.C. § 271(g), which give rise to an actual controversy over which this Court may exercise jurisdiction.

34. On information and belief, Defendants' plans and intentions to supply sertraline hydrochloride API to third party ANDA holder(s) outside of the United States for incorporation into products that they know will be imported and sold in the United States constitute imminent, threatened inducement of infringement under 35 U.S.C. §§ 271(b) and (g), which gives rise to an actual controversy over which this Court may exercise jurisdiction.

35. On information and belief, Defendants' sertraline hydrochloride API is Form II or Form V. On information and belief, sertraline hydrochloride Forms I, II and V are the only crystalline forms for which Cipla has submitted DMFs. On information and belief, Form I is claimed by an unexpired United States patent assigned to Pfizer Inc., and thus it is unlikely that Defendants will attempt to market API containing that polymorph to customers intending to sell

products in the United States.

36. On information and belief, Plaintiffs are not aware of any commercially viable process to manufacture Form V sertraline hydrochloride that is not covered by one or more claims of the '987 patent and/or the '073 patent. Thus, on information and belief, there is a substantial likelihood that Defendants' sertraline hydrochloride API, if Form V, is or will be made by a process that infringes one or more claims of the '987 patent and/or the '073 patent.

37. On information and belief, given the scope of Teva Ltd.'s patent rights to methods of making Form II, there is a substantial likelihood that Defendants' sertraline hydrochloride API, if Form II, is or will be made by a process that infringes one or more claims of the '721 patent and/or the '340 patent.

38. Cipla's international patent publication number WO 2005/047229 A2, dated May 22, 2005, which sets forth proposed methods and examples for making Form V and proposed methods and examples for making Form II, further supports that Defendants' API, whether Form II or Form V, will be made by a process that infringes one or more claims of the patents in suit.

39. Plaintiffs have made a reasonable effort to determine the process by which Defendants' sertraline hydrochloride API is or will be made. Currently, Plaintiffs are unable to obtain from a public source any information regarding the method used to manufacture Defendants' API. On November 22, 2006, Teva Ltd. notified Defendants of the existence of the patents in suit and requested a description of the manufacturing process used to by Defendants to make the API. In order to protect the confidentiality of Defendants' information, Teva Ltd. offered to enter into a confidentiality agreement.

40. Defendants have not responded to Teva Ltd.'s requests for information relating to their manufacturing process despite Teva Ltd.'s offer to review any material subject to a supplied confidentiality agreement.

41. Further, Plaintiffs have been unable to obtain from a public source samples of the API Defendants are selling, or intend to sell, to the third party ANDA holder(s) they are supplying or will supply. However, on information and belief, even if Plaintiffs had been able to obtain samples of Defendants' API from a public source, Plaintiffs are not aware of any analytical technique or combination of techniques that could be used to definitively establish that the API was made by one or more of the methods claimed in the patents in suit. For this reason, Plaintiffs cannot conclusively determine whether Defendants' API infringes the patents in suit unless and until Defendants disclose to Plaintiffs the method by which the API is made.

42. In the absence of a sufficient response from Defendants, Plaintiffs have no choice but to resort to judicial process and the aid of discovery to obtain, under appropriate judicial safeguards, the information required to confirm their beliefs as to infringement and to present to the Court evidence that Defendants will infringe the patents in suit.

43. On information and belief, Defendants' infringement will be willful and deliberate.

44. As a direct and proximate consequence of the planned and intended infringement by Defendants, Plaintiffs will be injured in their business and property rights unless the infringement is enjoined by the Court, and will suffer injury and damages for which they are entitled to relief.

COUNT I
DECLARATORY JUDGMENT OF PATENT INFRINGEMENT

45. The allegations of paragraphs 1 to 44 are incorporated by reference as if fully set forth herein.

46. The importation, sale and/or offer to sell by the Defendants of their sertraline hydrochloride API pursuant to DMF Nos. 18405, 17317, and 14437 will infringe one or more claims of the '073, '987, '721 and/or '340 patents under 35 U.S.C. § 271.

COUNT II
DECLARATORY JUDGMENT OF INDUCEMENT OF Patent Infringement

47. The allegations of paragraphs 1 to 44 are incorporated by reference as if fully set forth herein.

48. The supply of sertraline hydrochloride API pursuant to DMF No. 18405, 17317, and 14437 by the Defendants to third party companies who will engage in the importation, sale and/or offer to sell of products made with that API will induce the infringement of one or more claims of the '073, '987, '721 and/or '340 patents under 35 U.S.C. § 271.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for the entry of a judgment from this Court:

a. Declaring that the '073, '987, '721 and '340 patents are valid and enforceable;

b. Declaring that Defendants will infringe one or more claims of the '073, '987, '721 and/or '340 patents;

c. Declaring that Defendants will induce infringement of one or more claims of the '073, '987, '721 and/or '340 patents;

d. Declaring that Defendants' infringement and inducement will be willful and that this is an exceptional case under 35 U.S.C. § 285;

e. Permanently enjoining Defendants, their respective officers, agents, servants and employees, and those persons in active concert or participation with any of them, from infringing or inducing the infringement of the '073, '987, '721 and '340 patents;

f. Awarding Plaintiffs damages in accord with 35 U.S.C. § 284;

g. Awarding Plaintiffs their attorneys fees, costs and expenses; and

h. Awarding Plaintiffs such other and further relief as this Court may deem to be just and proper.

LITE DEPALMA GREENBERG & RIVAS, LLC

Dated: January 12, 2007

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LOCAL CIVIL RULE 11.2 CERTIFICATION

Plaintiffs, by their attorneys, hereby certify that the matter in controversy is also the subject of the following action:

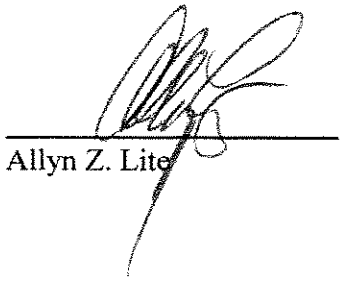
Teva Pharmaceutical Industries Ltd., et al. v. Pliva Inc., Filed on 1/12/07 D.N.J.

The following matters, of which this matter is one, are each being filed in the District of New Jersey on January 12, 2007. Each of the following matters is the subject of the same matter filed as *Teva Pharmaceutical Industries Ltd., et al. v. Pliva Inc.*, and is related to it.

Caption	Docket No.	Court
Teva Pharmaceutical Industries Ltd., et al. v. Sandoz Inc.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Apotex, Inc., et al.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Genpharm Inc.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Invagen Pharmaceuticals Inc.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Zydus-Cadila Healthcare, et al.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Lupin Limited, et al.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Cipla Ltd., et al.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Hetero Drugs Ltd.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Andrx Corp.	Being filed on 1/12/07	D.N.J.

I hereby certify that the following statements made by me are true. I am aware that if any of the foregoing statements made by me are wilfully false, I am subject to punishment.

Dated: January 12, 2007



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Plaintiffs,	:	
v.	:	
CIPLA LTD., AND BYRON CHEMICAL CO., INC.,	:	
Defendants.	:	

RULE 7.1 STATEMENT

Pursuant to Rule 7.1(a) of the Federal Rules of Civil Procedure, Plaintiff Teva Pharmaceuticals USA, Inc. hereby discloses that (1) the parent companies of Teva

Pharmaceuticals USA, Inc. are: Orvet UK Ltd., Teva Pharmaceuticals Europe (Holland) and Teva Pharmaceutical Industries Ltd. (Israel); and (2) Teva Pharmaceutical Industries Ltd. is the only publicly-traded company that owns – through the aforementioned chain – 10% or more of Teva Pharmaceuticals USA, Inc.

Plaintiff Teva Pharmaceutical Industries Ltd. hereby discloses that (1) it has no parent corporation; and (2) no publicly held corporation own 10% or more of its stock.

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Dated: January 12, 2007

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EXHIBIT A

US006600073B1

(12) **United States Patent**
Schwartz et al.

(10) **Patent No.: US 6,600,073 B1**
(45) **Date of Patent: Jul. 29, 2003**

(54) **METHODS FOR PREPARATION OF SERTRALINE HYDROCHLORIDE POLYMORPHS**

(75) Inventors: **Eduard Schwartz**, Rechovot; **Tamar Nidam**, Ychud; **Anita Liberman**, Tel-Aviv; **Marioara Mendelovici**, Rechovot; **Judith Aronhime**, Rehovot; **Claude Singer**, Kfar Saba; **Evgeni Valdman**, Petah Tikva, all of (IL)

(73) Assignee: **Teva Pharmaceutical Industries Ltd.**, Petah Tiqva (IL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/586,842**

(22) Filed: **Jun. 5, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/448,985, filed on Nov. 24, 1999.

(51) **Int. Cl.**[7] **C07C 211/00**
(52) **U.S. Cl.** **564/308**
(58) **Field of Search** 564/308

(56) **References Cited**

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5,082,970	A	1/1992	Braish
5,248,699	A	9/1993	Sysko et al.
5,463,126	A	10/1995	Williams
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6,452,054	B2	9/2002	Aronhime et al.

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J.K. Haleblian and W. McCrone, "*Pharmaceutical Applications of Polymorphism*" *Journal of Pharmaceutical Sciences*, vol. 58, No. 8, pp. 911–929, Aug. 1969.

J.K. Haleblian, "Characterization of Habits and Crystalline Modification of Solids and Their Pharmaceutical Applications", *Journal of Pharmaceutical Sci*ences, vol. 64, No. 8, pp. 1269–1288, Jul. 1975.

Welch, et al., "*Nontriczlic Antidepressant Agents Derived from cis–and trans–1–Amino–4–aryltetralins*", *Journal of Medicinal Chemistry, vol. 27*, No. 11, pp. 1508–1515, Feb. 14, 1984.

Primary Examiner—Samuel Barts
(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon

(57) **ABSTRACT**

Novel methods for the preparation of sertraline hydrochloride Forms III, V, VI, VII, VII, IX and X are disclosed. According to the present invention, sertraline hydrochloride Form III may be produced by heating sertraline hydrochloride Forms V and VI. Sertraline hydrochloride Forms V and VI may be produced from either sertraline hydrochloride or sertraline base by crystallization. Sertraline hydrochloride Form VII may be produced by suspending sertraline chloride polymorph V in water, followed by filtration. Sertraline hydrochloride Forms VIII and IX may be produced by suspending sertraline base in water followed by acidification and filtration. Sertraline hydrochloride Form X may be produced by suspending sertraline hydrochloride in benzyl alcohol with heating, followed by filtration.

29 Claims, 16 Drawing Sheets

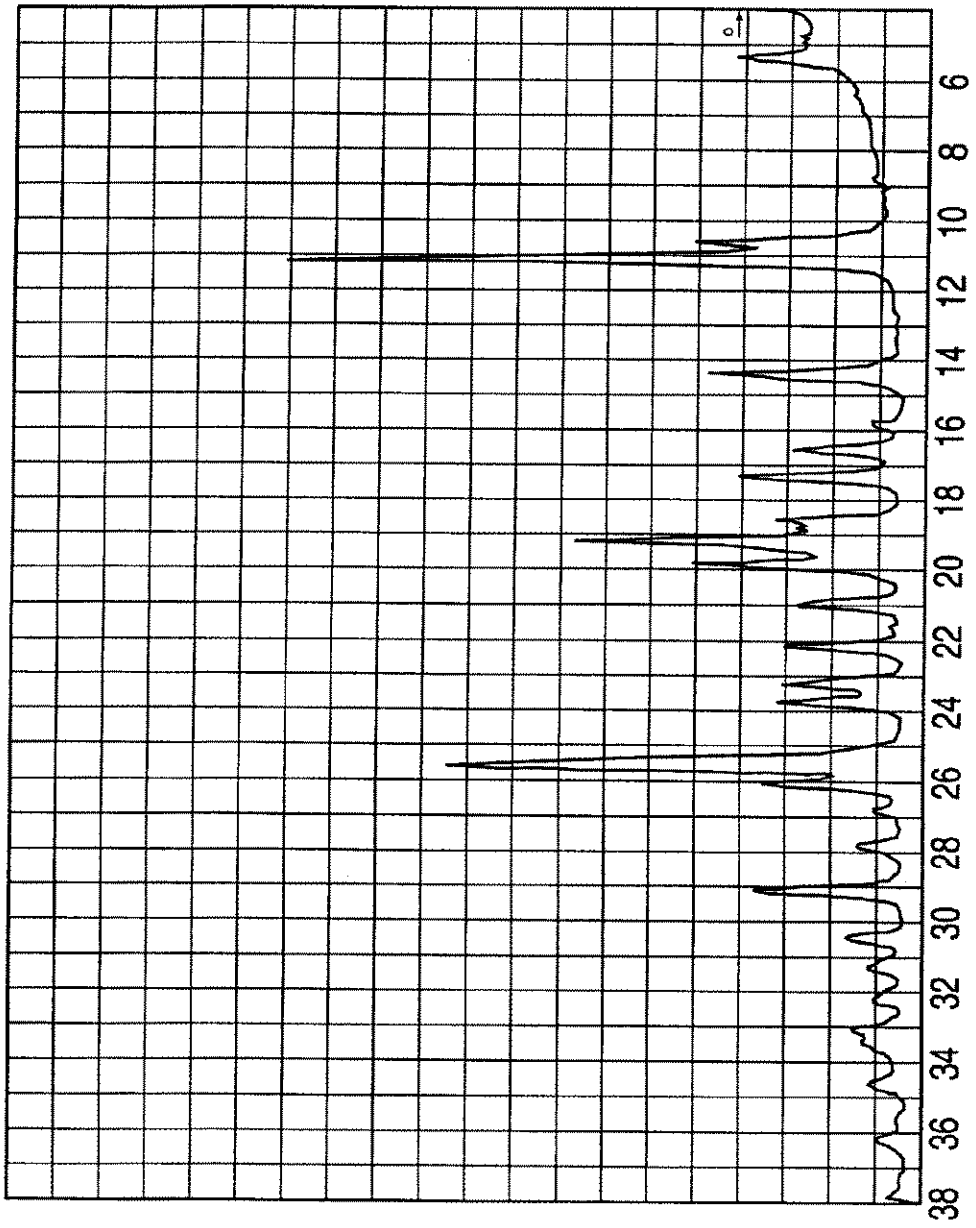

FIG. 1

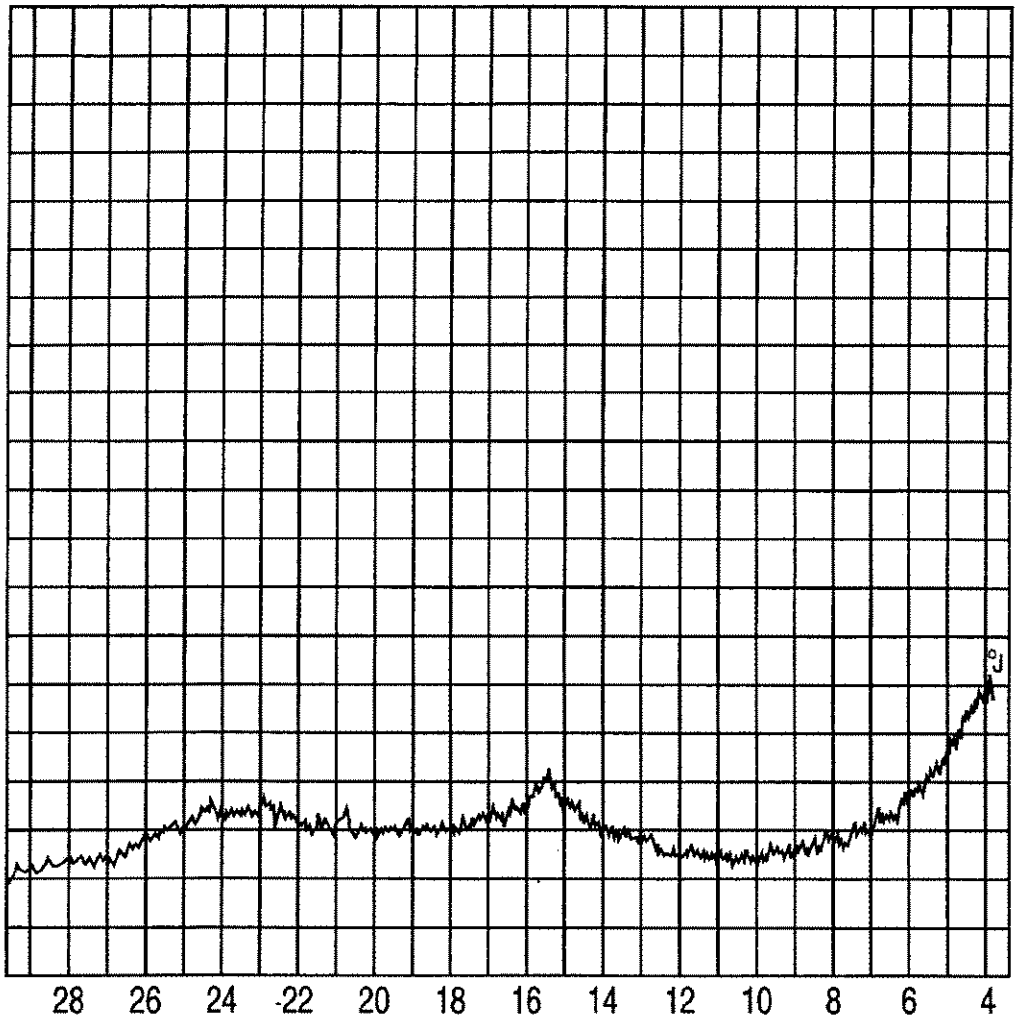

FIG. 2

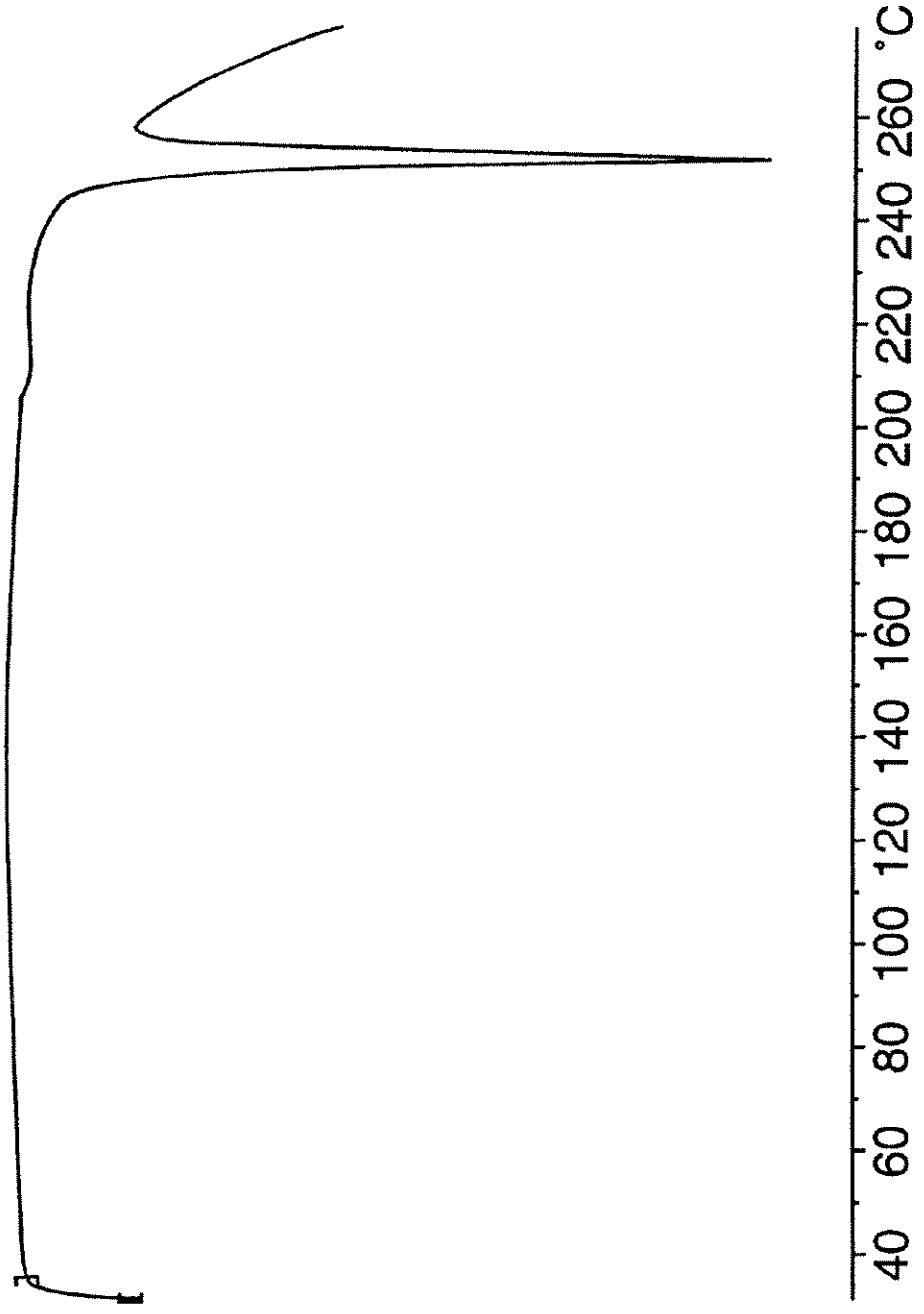

FIG. 3

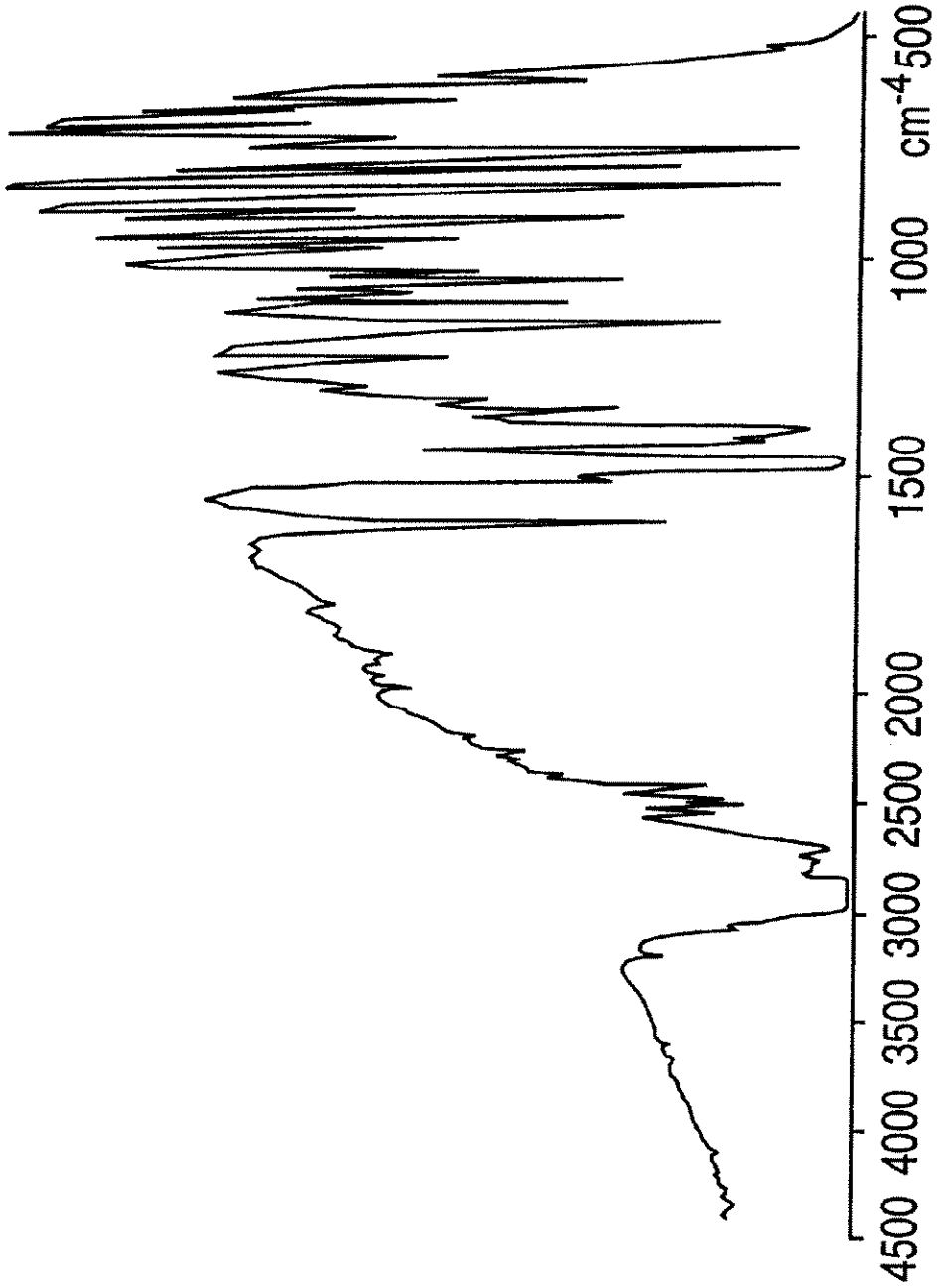

FIG. 4

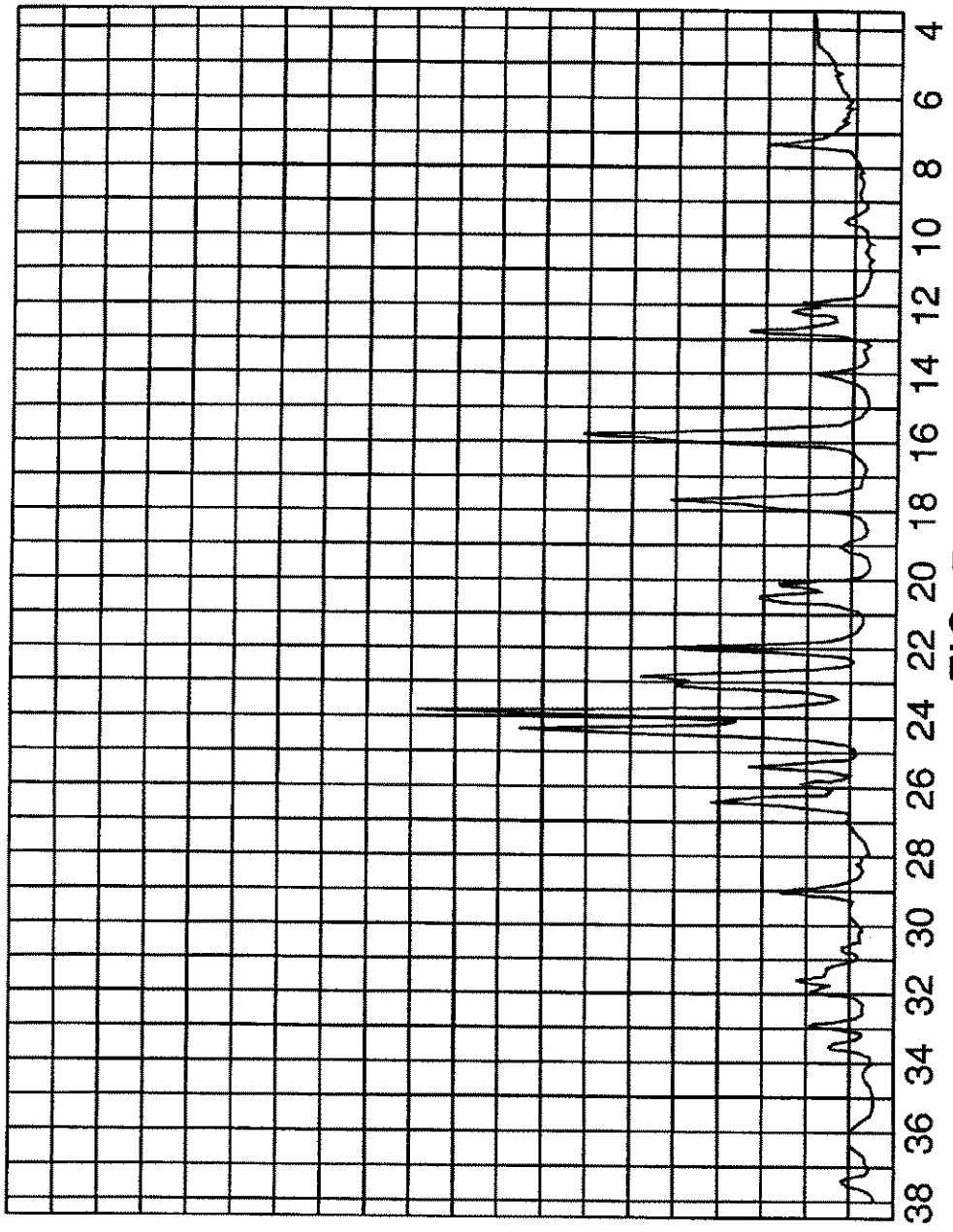

FIG. 5

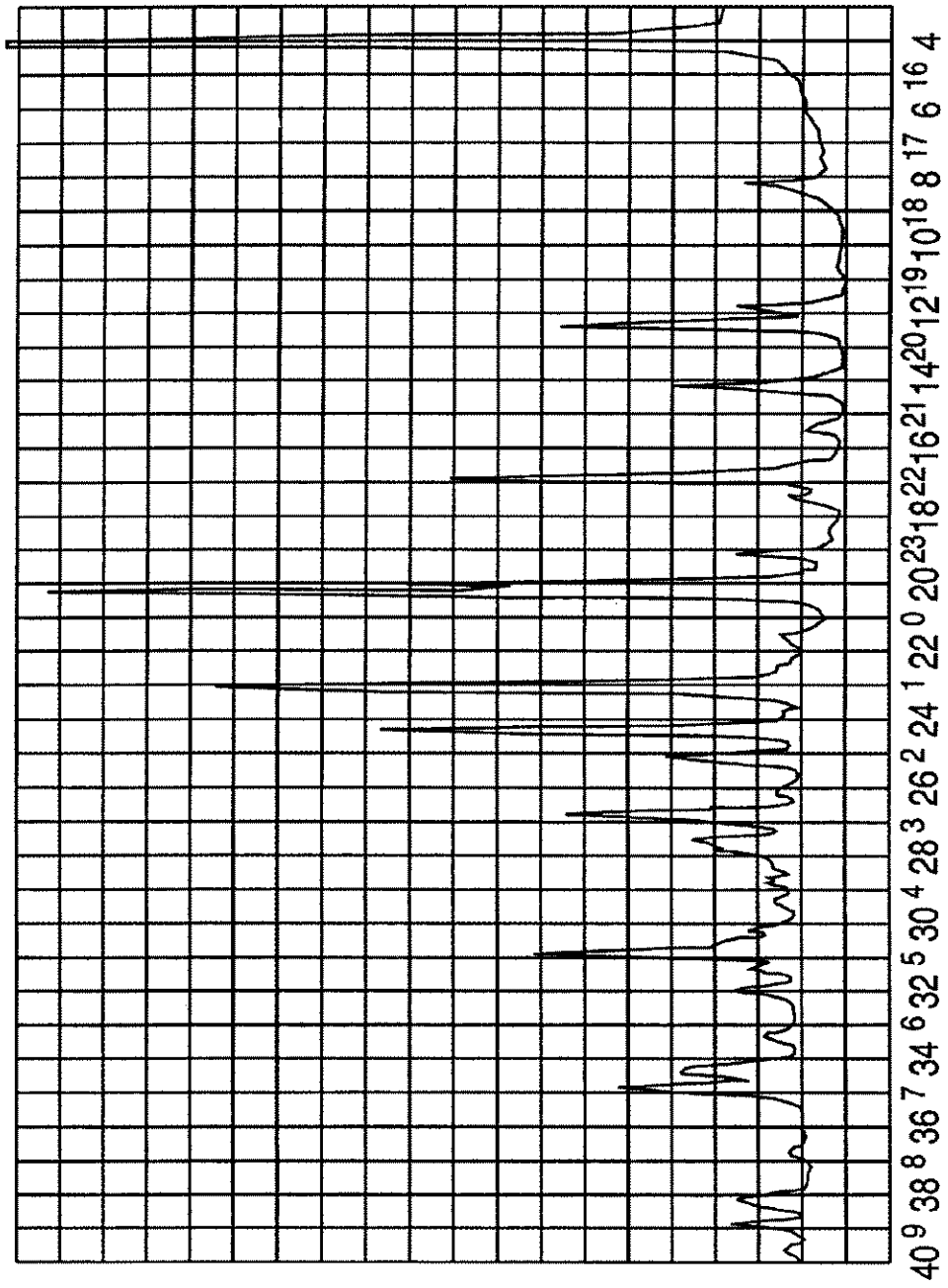
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FIG. 6

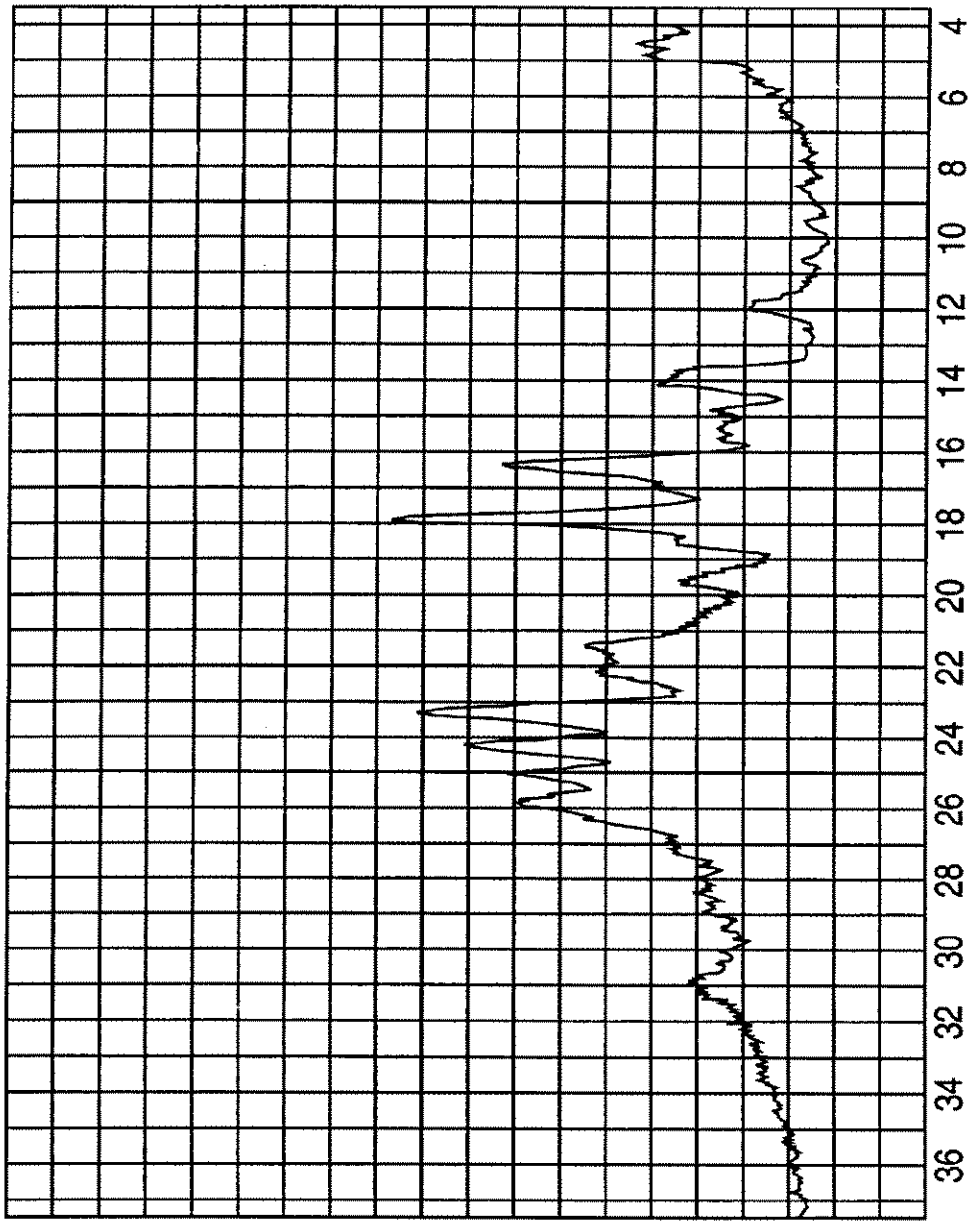


FIG. 7

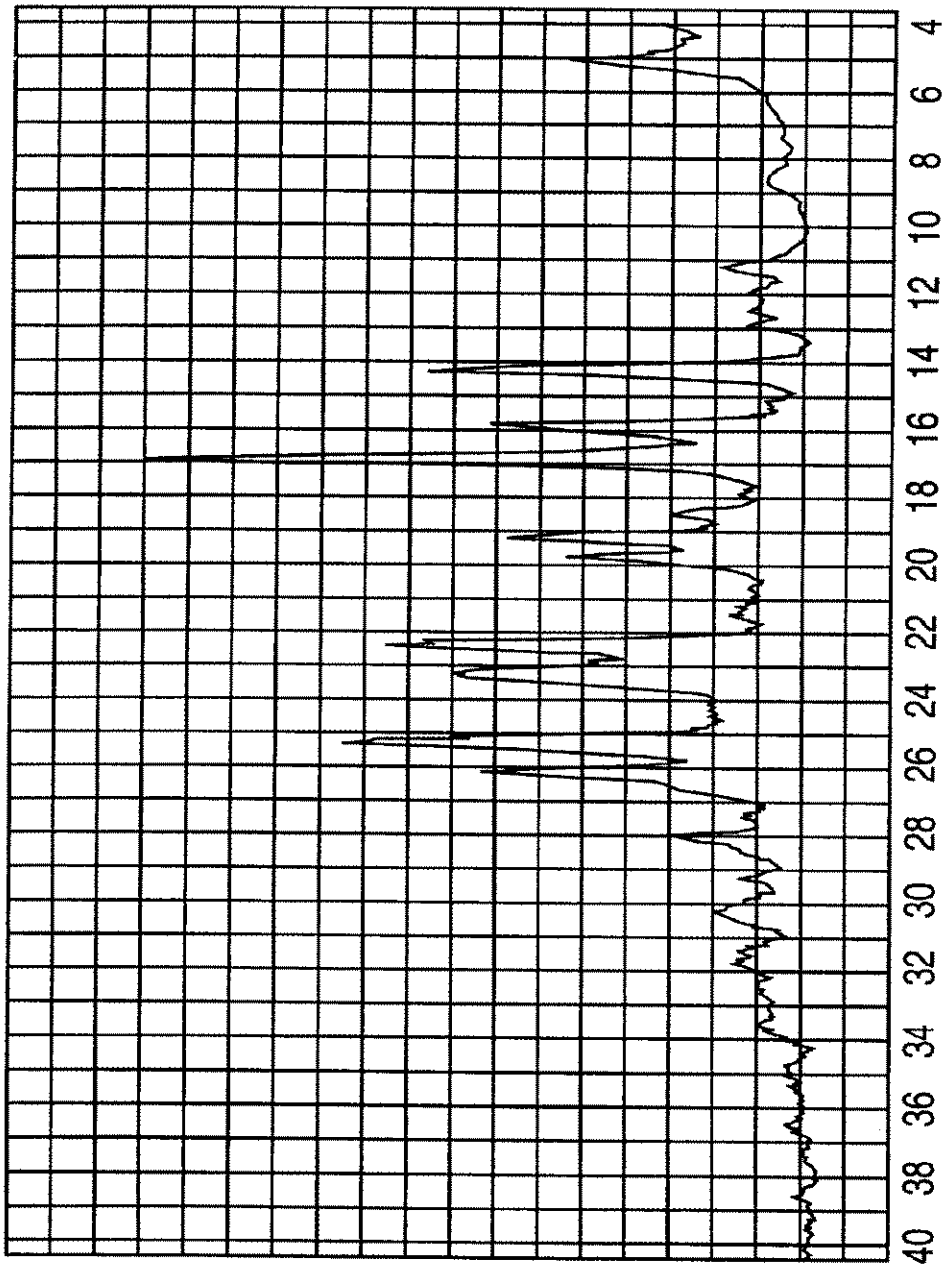


FIG. 8

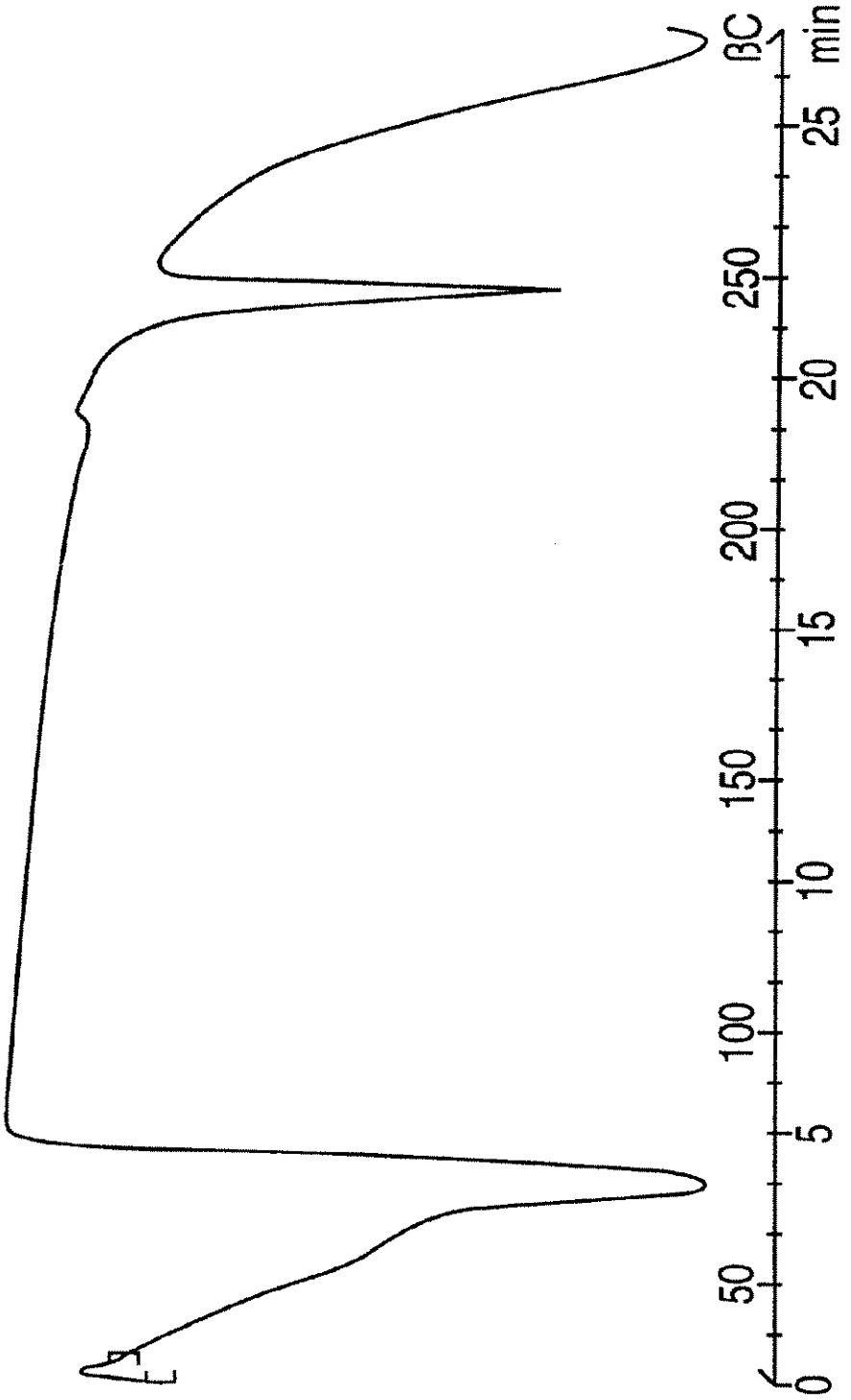


FIG. 9

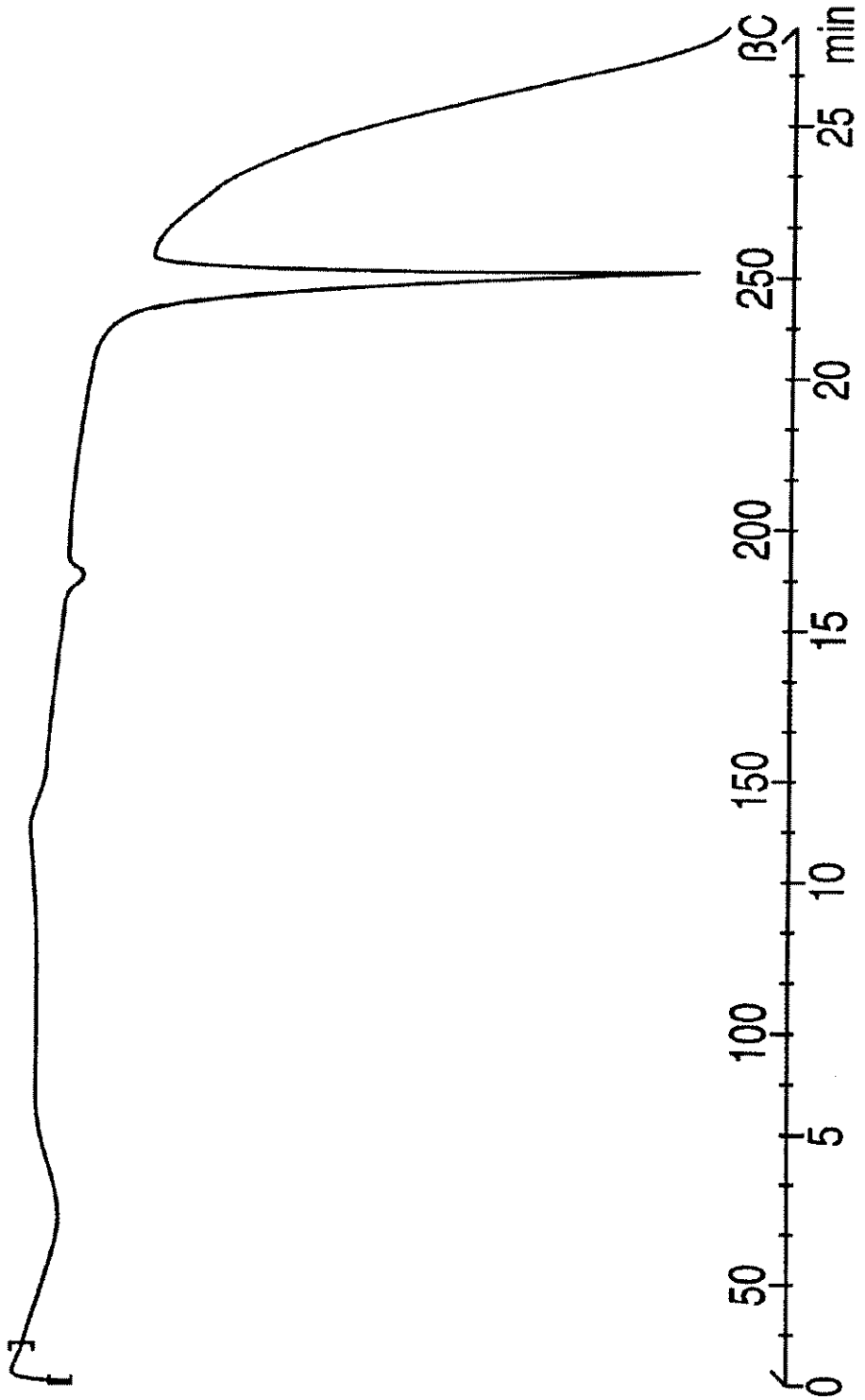


FIG. 10

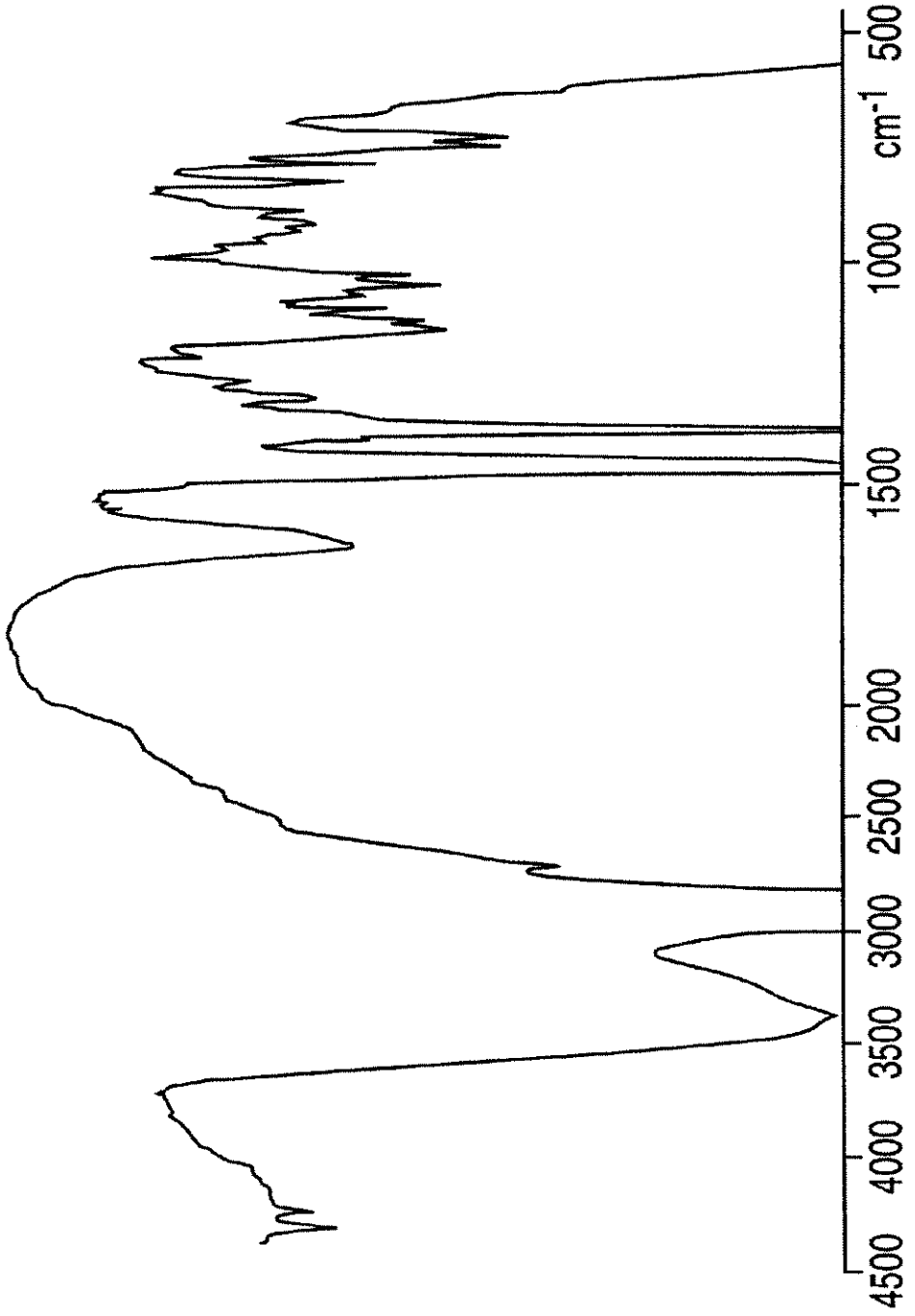


FIG. 11

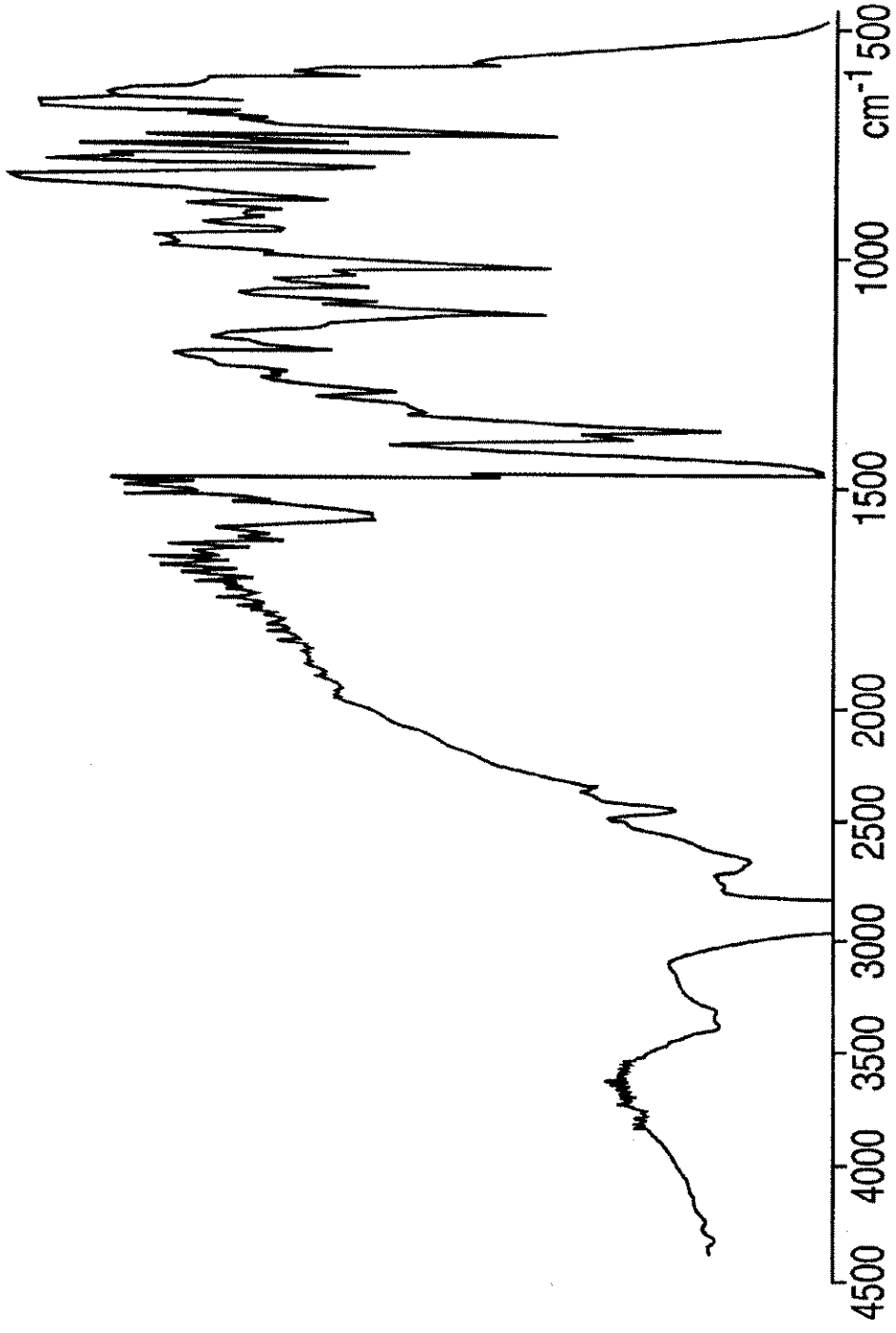
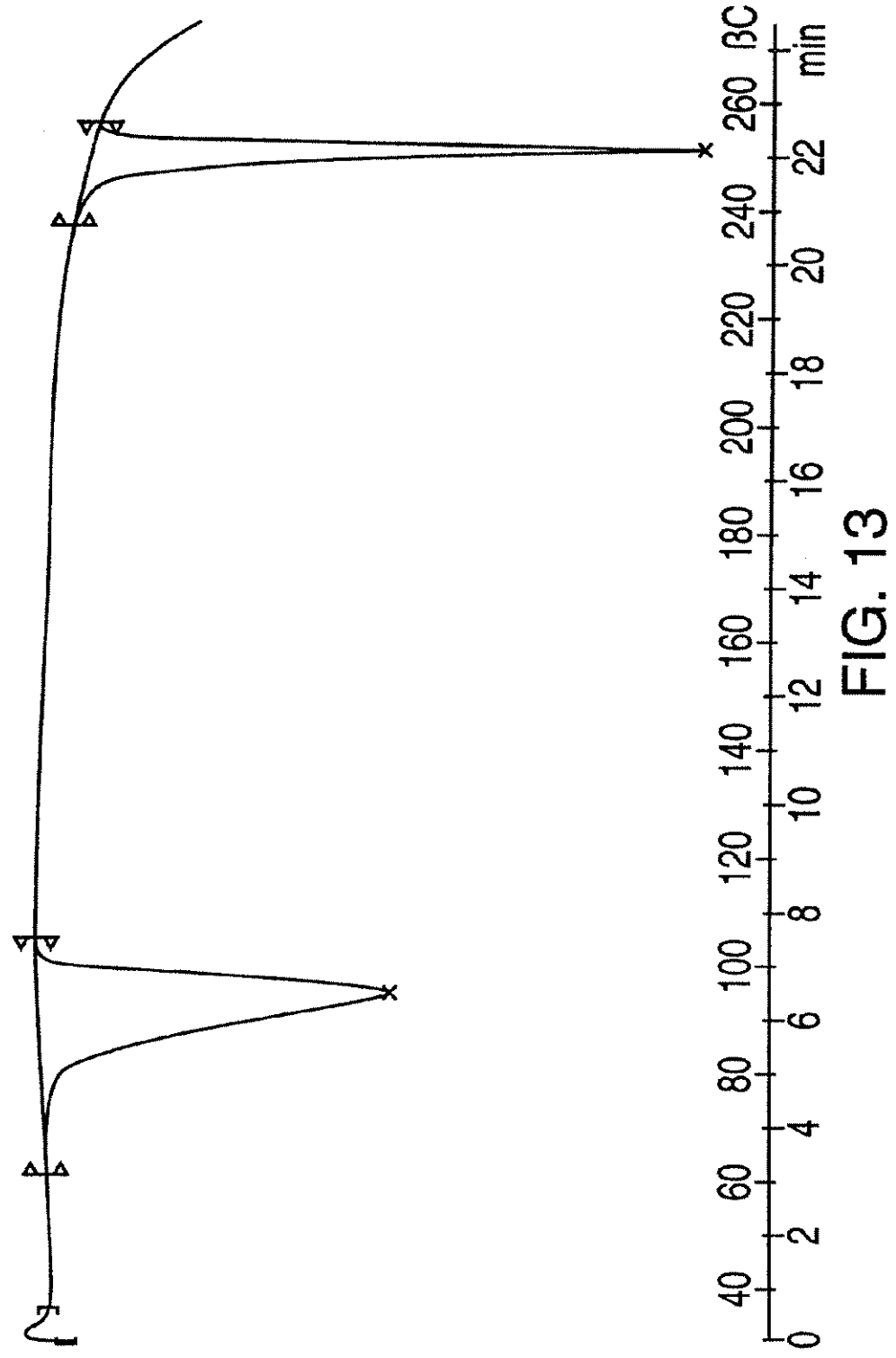


FIG. 12


BC
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22
240
20
220
18
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8
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80
4
60
2
40
0

FIG. 13

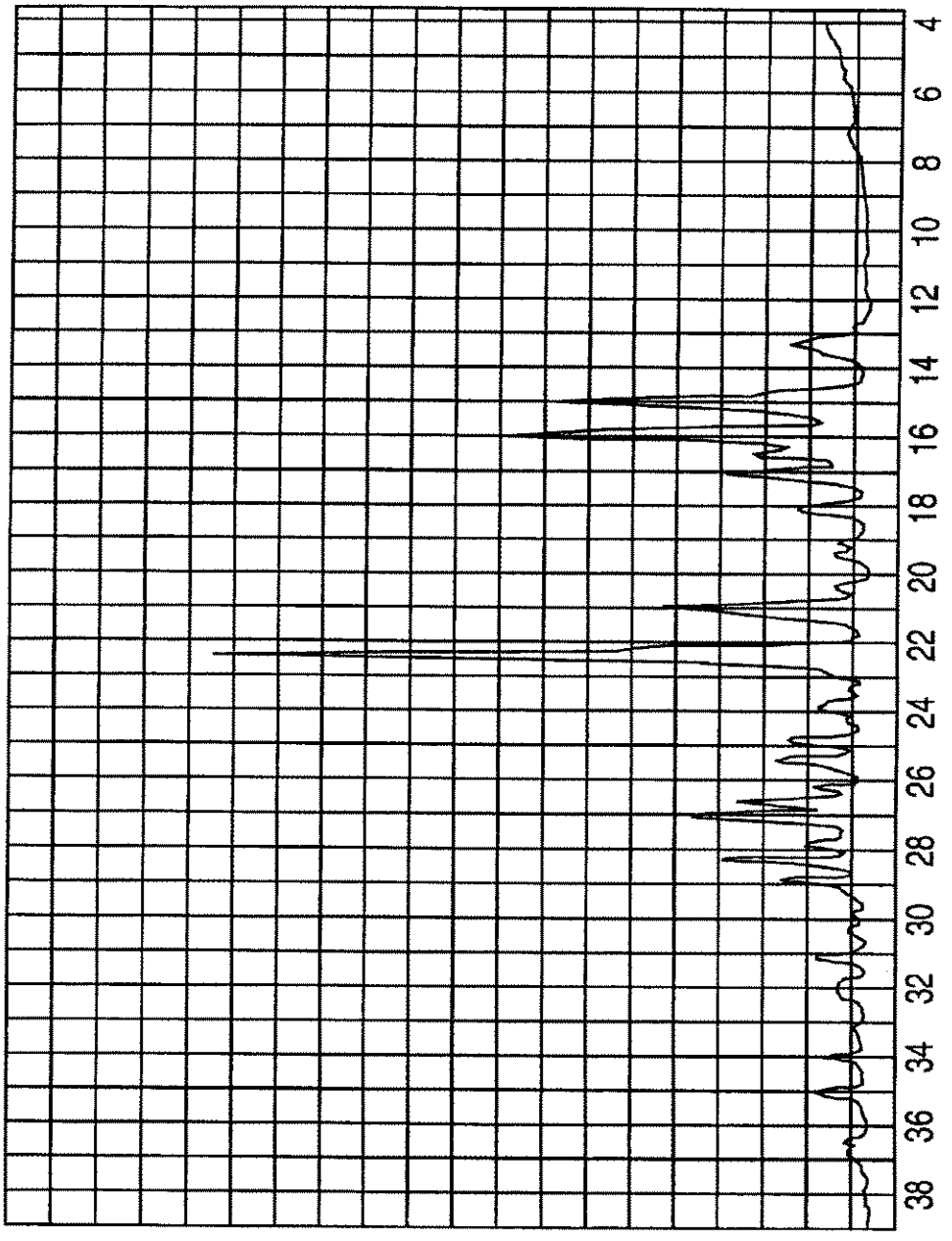


FIG. 14

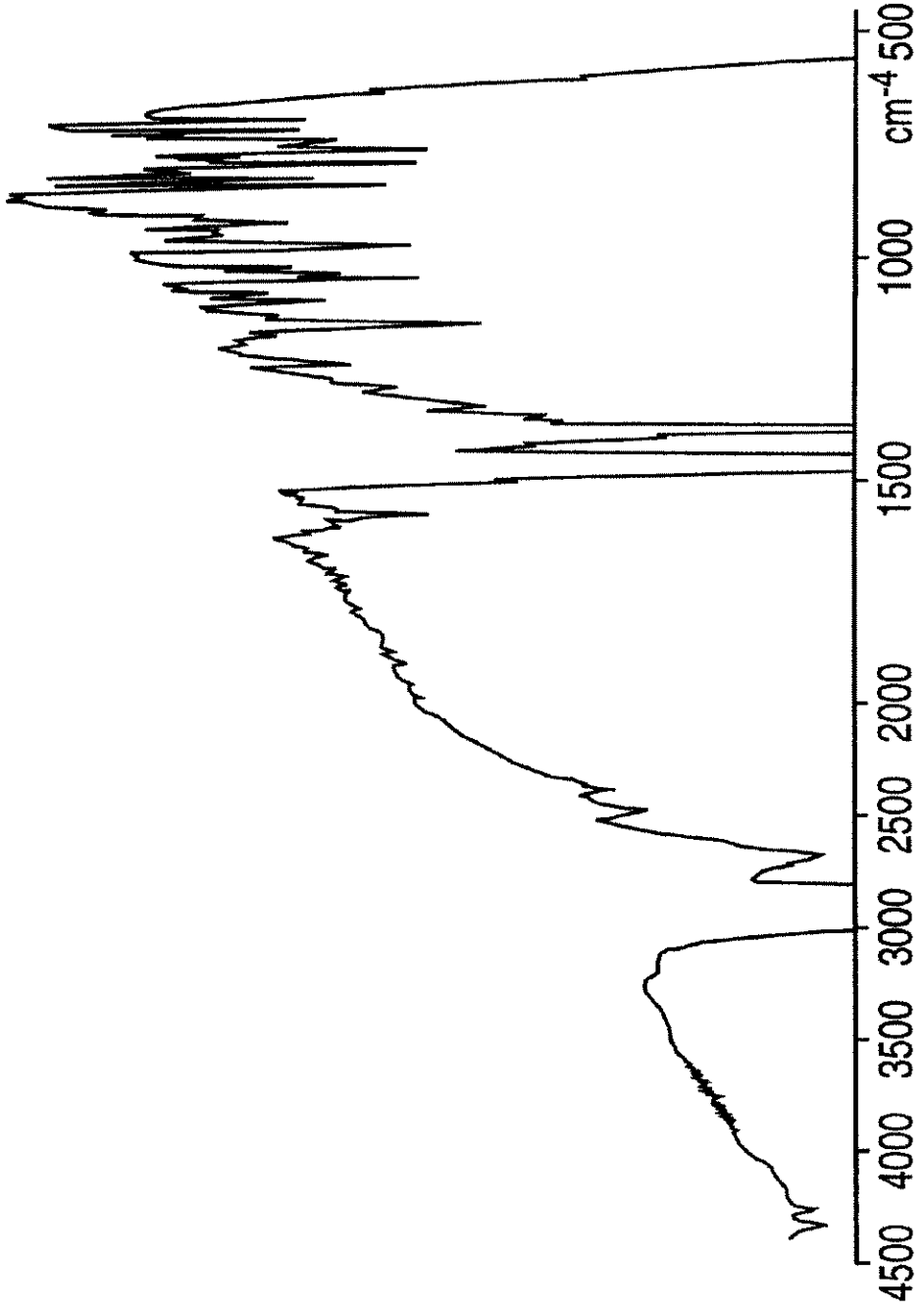
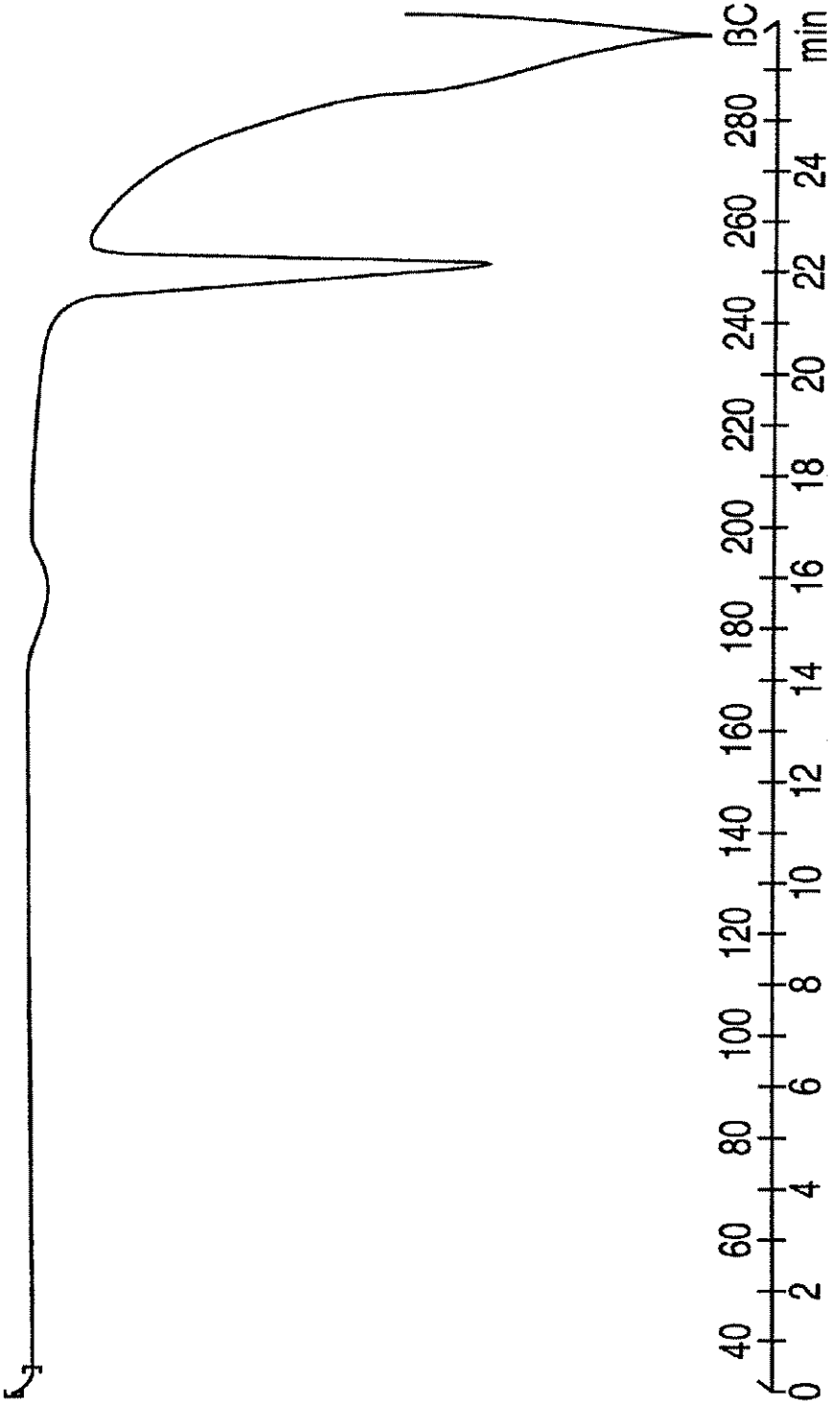


FIG. 15


BC
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18
200
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180
14
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140
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8
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6
80
4
60
2
40
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FIG. 16

METHODS FOR PREPARATION OF SERTRALINE HYDROCHLORIDE POLYMORPHS

CROSS-REFERENCE TO RELATED APPLICATIONS

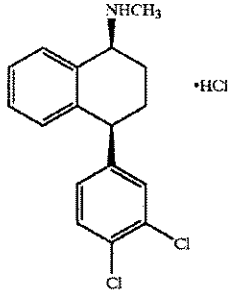
This application is a continuation-in-part of copending application Ser. No. 09/448,985 filed Nov. 24, 1999, the contents of which are incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to novel, reproducible methods for the preparation of crystalline forms of sertraline hydrochloride Forms III and V through X, as well as the preparation of an amorphous form of sertraline hydrochloride.

BACKGROUND OF THE INVENTION

Sertraline hydrochloride, (1S-cis)-4-(3,4 dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride, having the formula



is approved, under the trademark Zoloft®, by the U.S. Food and Drug Administration, for the treatment of depression, obsessive-compulsive disorder and panic disorder.

U.S. Pat. No. 4,536,518 ("the '518 patent") describes the preparation of sertraline hydrochloride with a melting point of 243–245° C., by treating an ethyl acetate/ether solution of the free base with gaseous hydrogen chloride. The solid state properties of the sertraline hydrochloride so produced are not otherwise disclosed.

According to U.S. Pat. No. 5,248,699 ("the '699 patent"), the sertraline hydrochloride produced by the method of the '518 patent has a crystalline form denominated "Form II." The '699 patent discloses four other polymorphs I, III, IV, and V, and characterizes them by single crystal x-ray analysis, powder x-ray diffraction, infra-red spectroscopy, and differential scanning calorimetry. The '699 patent reports that Form II is produced by rapid crystallization of sertraline hydrochloride from an organic solvent, including isopropyl alcohol, ethyl acetate or hexane, and generally describes methods for making sertraline hydrochloride Forms I–V. According to this patent, the preferential formation of Forms I, II or IV in an acidic solution consisting of isopropyl alcohol, hexane, acetone, methyl isobutyl ketone, glacial acetic acid or, preferably, ethyl acetate, depends on the rapidity of crystallization. Form I is described as being made by crystallizing sertraline hydrochloride in an acidic solution using an organic solvent such as those listed above. The crystallization of Form I is carried out at a temperature from about 20° C. to about the solvent reflux temperature, preferably from about 40° to 60° C. The only method described in this patent for making Forms II and IV is by the rapid crystallization of sertraline hydrochloride from an organic solvent such as those listed above. Slow crystallization or granulation of sertraline hydrochloride is said to produce Form I. Form III is described as being formed by heating Forms I, II or IV to temperatures above about 180° C. Granulating either of Forms II, III or IV in any of the solvents listed above at a temperature from about 40° C. to 60° C. is said to cause conversion to Form I. The only method described in this patent for making Form V is by sublimation of sertraline hydrochloride Form I at reduced pressure and at a temperature from about 180–190° C. However, in our hands attempts to repeat this procedure to obtain Form V have been unsuccessful.

SUMMARY OF THE INVENTION

The present invention relates to a process for making sertraline hydrochloride Form V comprising the steps of: dissolving or suspending sertraline hydrochloride in a suitable solvent; removing the solvent; and drying to form sertraline hydrochloride Form V.

The present invention also relates to a process for making sertraline hydrochloride Form V comprising the steps of: dissolving or suspending sertraline base in a solvent; adding hydrogen chloride to the solvent to reduce the pH of the solution or suspension; and isolating sertraline hydrochloride Form V from the solution or suspension.

The present invention also relates to a process for making sertraline hydrochloride Form V comprising the step of drying sertraline hydrochloride Form VII.

The present invention also relates to a process for making sertraline hydrochloride Form V comprising the steps of: dissolving or suspending sertraline hydrochloride in water; adding a sufficient amount of hydrochloric acid or hydrogen chloride to facilitate precipitation of sertraline hydrochloride; removing the water; and isolating sertraline hydrochloride Form V.

The present invention also relates to a process for making sertraline hydrochloride Form VI comprising the steps of: dissolving sertraline base in a solvent; adding hydrochloric acid to the solvent; and isolating sertraline hydrochloride Form VI without further drying.

The present invention also relates to a process for making sertraline hydrochloride Form VI comprising the steps of: dissolving or suspending sertraline hydrochloride in ethanol or methanol; stirring for a time sufficient to induce the transformation of sertraline hydrochloride to sertraline hydrochloride Form VI; and isolating sertraline hydrochloride Form VI.

The present invention also relates to a process for making sertraline hydrochloride Form VIII comprising the steps of: suspending sertraline base in water; adding hydrogen chloride to the water; and filtrating the precipitate so obtained without further drying.

The present invention also relates to a process for making sertraline hydrochloride Form VIII comprising the steps of: suspending or dissolving sertraline hydrochloride ethanolate Form VI or sertraline hydrochloride Form II in water or a mixture of water and isopropyl alcohol; and isolating sertraline hydrochloride Form VIII.

The present invention also relates to a process for making sertraline hydrochloride Form III comprising the steps of: heating sertraline hydrochloride Form V or Form VI to a temperature sufficient, and for a time sufficient, to induce the transformation of sertraline hydrochloride Form V or Form

VI to sertraline hydrochloride Form III; and isolating sertraline hydrochloride Form III.

The present invention also relates to a process for making amorphous sertraline hydrochloride comprising the steps of: suspending or dissolving sertraline base in a non-polar organic solvent; adding gaseous hydrochloric acid; and isolating amorphous sertraline hydrochloride.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form V.

FIG. **2** is a characteristic x-ray powder diffraction spectrum of amorphous sertraline hydrochloride.

FIG. **3** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form V.

FIG. **4** is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form V.

FIG. **5** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form VI.

FIG. **6** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form VII.

FIG. **7** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form VIII.

FIG. **8** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form IX.

FIG. **9** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form VIII.

FIG. **10** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form IX.

FIG. **11** is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form VIII.

FIG. **12** is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form IX.

FIG. **13** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form VI.

FIG. **14** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form X.

FIG. **15** is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form X.

FIG. **16** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form X.

DETAILED DESCRIPTION OF THE INVENTION

Form V

The present invention provides new processes for making sertraline hydrochloride Form V from sertraline hydrochloride, sertraline base or amorphous sertraline hydrochloride. The methods provided in the present invention are more commercially practicable than the sublimation-condensation method of U.S. Pat. No. 5,248,699, which we have not been able to reproduce. It has also surprisingly been found that, by the present method, Form V is formed even at different crystallization rates.

Where the present invention provides methods for the conversion of sertraline hydrochloride to sertraline hydrochloride Form V, in one embodiment sertraline hydrochloride is combined with a solvent. Suitable solvents include methanol, ethanol, 1-methoxy-2-propanol, trichloroethane, water, and mixtures thereof. If a mixture of isopropyl alcohol and water is used, it is preferably an about 6:1 mixture. Preferably the solvent is methanol, ethanol, or mixtures thereof, and most preferably the solvent is ethanol. Sertraline hydrochloride Form V is then isolated by allowing the solution to cool. One preferred method is to rapidly cool the solvent to 5° C. Another preferred method comprises seeding the solution with sertraline hydrochloride Form V crystals, followed by slow cooling to room temperature, followed by filtration and drying.

Alternatively, Form V may be obtained by forming a solution or suspension of sertraline hydrochloride in a suitable solvent and spray drying the solution or suspension. Preferred solvents include water and water/alcohol mixtures.

The present invention also provides methods for the conversion of sertraline hydrochloride to sertraline hydrochloride Form V wherein the solvate sertraline hydrochloride Form VI (described in more detail below) is an intermediate. In this embodiment of the present invention, sertraline hydrochloride is suspended or dissolved in either methanol or ethanol or mixtures thereof thereby forming sertraline hydrochloride Form VI. This intermediate sertraline hydrochloride Form VI is then dried, with or without a separate isolation step, to remove all solvent and sertraline hydrochloride Form V is isolated. Sertraline hydrochloride Form V can also be prepared by suspending or dissolving sertraline hydrochloride solvate Form VI in water.

Sertraline hydrochloride Form V can also be prepared by drying Form VII (described in more detail below). In this embodiment of the present invention, sertraline hydrochloride Form V is dried at 80° C. overnight thereby forming sertraline hydrochloride Form V.

The present invention also provides methods for the conversion of sertraline hydrochloride to sertraline hydrochloride Form V wherein the sertraline hydrochloride Form VIII (described in more detail below) is an intermediate. In this embodiment of the present invention, sertraline hydrochloride Form II is suspended or dissolved in water thereby forming sertraline hydrochloride Form VIII. This intermediate sertraline hydrochloride Form VIII is then dried, with or without a separate isolation step, to remove all solvent and sertraline hydrochloride Form V is isolated. Methods for the preparation of sertraline hydrochloride Form II are disclosed in copending applications serial Nos. 09/448,985 filed Nov. 24, 1999 and attorney docket number 1662/49107, filed May 22, 2000, the contents of which are hereby incorporated by reference.

The present invention also provides methods for the conversion of sertraline base to sertraline hydrochloride Form V. In one such embodiment, sertraline base is added to at least one solvent, and hydrogen chloride gas is bubbled through the solution. Suitable solvents include methanol, ethanol, water, ethyl acetate, isopropyl alcohol, ether, hexane, and toluene, and mixtures thereof. Alternatively, an appropriate amount of hydrogen chloride gas dissolved in a suitable solvent and then combined with the sertraline base solution. As used herein, "hydrogen chloride" includes both gaseous hydrogen chloride and aqueous hydrogen chloride (i.e. hydrochloric acid). Sertraline hydrochloride Form V is isolated by allowing precipitation to occur from about 0° C. to about 60° C. followed by filtration and drying. Preferred solvents include methanol, ethanol, hexane, isopropyl alcohol, or mixtures thereof. In a variation of this method, sertraline base is added to a suitable solvent and the resulting solution is added to a hydrochloric acid solution of pH 0–4; preferably the pH of the solution is about 1.

Alternatively, sertraline base is added to a solvent. The solution is heated and concentrated hydrochloric acid is added. Water may also be added. The solvent may be partially removed by distillation. Sertraline hydrochloride Form V is isolated by allowing the mixture to cool to room temperature and remain at room temperature overnight,

followed by filtration and drying. Suitable solvents for use in this method include methanol, ethanol, water, hexane, isopropyl alcohol, and ethyl acetate, and mixtures thereof.

Alternatively, sertraline base may be combined with a solvent selected from the group consisting of methanol, ethanol and a mixture thereof. A saturated solution of hydrogen chloride gas in isopropyl alcohol is added to induce formation of sertraline hydrochloride Form V. Sertraline hydrochloride Form V is isolated by allowing the solution to stand at room temperature overnight, followed by filtration and drying of the precipitate.

Form V may also be obtained by forming a suspension of sertraline base and hydrochloric acid in water or a water/ethanol mixture and spray drying the suspension. In this embodiment of the present invention, the solution or suspension of sertraline base and hydrochloric acid is sprayed into a heated chamber. The temperature of the chamber is such that the solvent is removed thus forming sertraline hydrochloride Form V.

Sertraline base for use in the processes of the present invention may be produced by dissolving sertraline mandelate in ethyl acetate followed by neutralization of the sertraline mandelate with aqueous sodium hydroxide. The organic phase is separated from the aqueous phase and dried using magnesium sulfate. The solvent is removed under reduced pressure to produce sertraline base as an oil. Methods for making sertraline base are set forth in U.S. Pat. Nos. 4,536,518 and 5,248,699, the contents of which are incorporated herein by reference.

Where the present invention provides methods for the conversion of amorphous sertraline hydrochloride to sertraline hydrochloride Form V, amorphous sertraline hydrochloride is kept in a closed container, such as a bag, and warmed to about 40° C. to about 80° C. or is stored at room temperature for a period between a few hours and several days depending on the temperature.

The sertraline hydrochloride Form V that results from practicing the invention as exemplified herein can be characterized by its powder X-ray diffraction pattern. FIG. **1** is a representative pattern of sertraline hydrochloride Form V. The principal peaks observed are at about 5.2°±0.2, 10.4°±0.2, 11.0°±0.2, 14.3°±0.2, 16.5°±0.2, 17.3°±0.2, 18.4°±0.2, 19.1°±0.2, 19.7°±0.2, 20.9°±0.2, 22.0°±0.2, 23.2°±0.2, 23.6°±0.2, 25.5°±0.2, 26.0°±0.2, and 29.1°±0.2 degrees 2 theta.

Three experiments were performed in order to repeat the procedure described in U.S. Pat. No. 5,248,699 for preparing Form V by sublimation. Two experiments were performed by sublimating a sample of Form I under 30 mm Hg vacuum and temperature between 170–190° C. A third experiment was performed by sublimating a sample of Form I under high vacuum (0.1 mm Hg) and temperature between 180–195° C.

The three samples of sertraline hydrochloride prepared by sublimation were analyzed by powder x-ray diffraction. In all cases, the typical broad featureless pattern without sharp peaks typical of amorphous materials was obtained. FIG. **2** is one such pattern.

In conclusion, sertraline hydrochloride could not be obtained by following the procedure set forth in U.S. Pat. No. 5,248,699 for preparing Form V by sublimation of Form I.

The IR spectrum of sertraline hydrochloride Form V produced by the present process is characterized by the following bands: 773 cm^{-1}, 822 cm^{-1}, 1012 cm^{-1}, 1032 cm^{-1}, 1054 cm^{-1}, 1133 cm^{-1}, 1328 cm^{-1}, 1562 cm^{-1}, and 1590 cm^{-1}, as shown in FIG. **4**.

The sertraline hydrochloride Form V of the present process is further characterized by the DSC thermogram data, for example, as disclosed in FIG. **3**. The DSC thermogram is characterized by a small endotherm (~3 Joule per gram) at about 210° C., believed to be a solid-solid transformation (based upon observation under a hot stage microscope) to Form III, and a melting peak 251° C.

Form VI

Sertraline hydrochloride Form VI is a solvated crystal form of sertraline hydrochloride. Sertraline hydrochloride Form VI may be an ethanolate, wherein ethanol is incorporated into the crystal structure of Form VI. Alternatively, sertraline hydrochloride Form VI may be a methanolate, wherein methanol is incorporated into the crystal structure of sertraline hydrochloride Form VI. All sertraline hydrochloride Form VI solvates have identical powder x-ray diffraction patterns. Therefore, when referring to sertraline hydrochloride Form VI all sertraline hydrochloride Form VI solvates, such as sertraline hydrochloride Form VI ethanolate and sertraline hydrochloride Form VI methanolate, are necessarily included.

To form the novel crystalline form sertraline hydrochloride Form VI, sertraline base is added to the appropriate solvent. Which solvent is appropriate will depend on which solvate is to be formed, e.g. ethanol (to form the ethanolate) and methanol (to form the methanolate). Hydrogen chloride gas is then bubbled through the solution. Sertraline hydrochloride Form VI is isolated by allowing precipitation to occur, followed by filtration. The DSC thermogram of Form VI crystallized from ethanol displays a desolvation peak at 95° C. (see FIG. **13**) and loses 11.2% weight (by TGA); Form VI crystallized from methanol loses 8.3 % weight (by TGA) upon desolvation. Form VI crystallized from ethanol is an ethanolate, and more specifically is a monoethanolate. Form VI crystallized from methanol is a methanolate, and more specifically is a monomethanolate.

The present invention also provides new processes for making sertraline hydrochloride solvate Form VI by reslurry of other sertraline hydrochloride crystalline forms. In the conversion of sertraline hydrochloride to sertraline hydrochloride ethanolate Form VI, sertraline hydrochloride is dissolved in the appropriate solvent and stirred for about 18–36 hours; 24 hours is preferred. Sertraline hydrochloride solvate Form VI is isolated by a suitable method, such as filtration. Sertraline hydrochloride Forms I, II, III IV, V and X are suitable for use as starting materials in this process.

The sertraline hydrochloride Form VI so isolated is a solvate and exhibits the powder x-ray diffraction pattern of FIG. **5**, comprising peaks at 7.3°±0.2, 12.1°±0.2, 12.7°±0.2, 14.0°±0.2, 15.6°±0.2, 17.6°±0.2, 20.1°±0.2, 20.6°±0.2, 21.9°±0.2, 22.7°±0.2, 23.0°±0.2, 23.8°±0.2, 24.3°±0.2, 25.4°±0.2, and 26.3°±0.2 degrees two-theta. Drying of the precipitated sertraline hydrochloride Form VI at 50–60° C. overnight yields sertraline hydrochloride Form V.

Form VII

It has also been discovered that a new crystalline form of sertraline hydrochloride, designated Form VII, may be obtained by suspending or dissolving Form V in water, and filtrating the suspension after one day without further drying.

In another embodiment of the invention, sertraline hydrochloride Form VII is made from sertraline hydrochloride Form VI. Sertraline hydrochloride Form VI is dispersed in water and the mixture is heated to facilitate the dissolution of sertraline hydrochloride Form VI. The solution may be heated to between about 30° C. and about 90° C., preferably to about 80° C. The pH is then lowered, preferably to about

pH 1, and the mixture is allowed to cool to room temperature and stirred until the reaction is complete. Preferably the reaction is stirred for two hours at room temperature. Sertraline hydrochloride Form VII is isolated by filtration and washing with water.

As shown in FIG. 6, sertraline hydrochloride Form VII is characterized by two unique strong x-ray powder diffraction peaks at 4.0°±0.2, and 20.0 degrees two-theta and medium intensity peaks at 8.0°±0.2, 11.6°±0.2, 12.0°±0.2, 13.8°±0.2, 16.5°±0.2, 22.8°±0.2, 24.1°±0.2, 25.0°±0.2, 26.6°±0.2, 30.7°±0.2, 34.7°±0.2 2 two-theta. The TGA curve shows a loss on drying of about 45%.

Forms VIII and IX

Additional new crystalline forms of sertraline hydrochloride, Forms VIII and IX, have also been discovered. Sertraline hydrochloride hydrate Form VIII may be produced by suspending sertraline base in water and heating, followed by acidification and filtration. Form IX is obtained by drying of Form VIII. Preferably the sertraline base is suspended in water, the suspension heated to a temperature between about 30° C. and about 80° C. Hydrogen chloride is added to reduce the pH, preferably to between about 1 to about 4, and the resulting solution is cooled to room temperature.

The present invention also provides new processes for making sertraline hydrochloride Form VIII from sertraline hydrochloride ethanolate Form VI. In one embodiment of the present invention, a slurry of sertraline hydrochloride ethanolate Form VI in water or a mixture of water and isopropyl alcohol is stirred, preferably for about one hour. The slurry is then filtered and washed with water and sertraline hydrochloride hydrate Form VIII is isolated.

The present invention also provides precesses of making sertraline hydrochloride Form VIII from sertraline hydrochloride Form II. In the conversion of sertraline hydrochloride Form II to sertraline hydrochloride Form VIII, sertraline hydrochloride Form II is suspended in water or a mixture of water and isopropyl alcohol and stirred, preferably overnight, and sertraline hydrochloride hydrate Form VIII is isolated by filtration.

Sertraline hydrochloride Form VIII is characterized by x-ray powder diffraction peaks at 4.7°±0.2, 11.8°±0.2, 16.3°±0.2, 17.8°±0.2, 19.6°±0.2, 23.2°±0.2, 24.2°±0.2, 25.1°±0.2, and 26.0°±0.2 two-theta, as described in FIG. 7.

The DSC thermogram for Form VIII is characterized by a strong endotherm below 100° C., small endothermic and exothermic events at about 220° C. and a melting peak at 247° C. as described in FIG. 9.

The TGA curve shows a loss on drying step of about 20% below 100° C.

The IR spectrum of Form VIII is characterized by the following bands: 740 cm^{-1}, 779 cm^{-1}, 822 cm^{-1}, 887 cm^{-1}, 915 cm^{-1}, 1031 cm^{-1}, 1053 cm^{-1}, 1110 cm^{-1}, 1134 cm^{-1}, 1153 cm^{-1}, 1217 cm^{-1}, 1307 cm^{-1}, and 1377 cm^{-1}, as described in FIG. 11.

Sertraline hydrochloride Form IX is characterized by x-ray powder diffraction peaks at 5.1°±0.2, 14.2°±0.2, 15.8°±0.2, 16.8°±0.2, 19.2°±0.2, 19.7°±0.2, 22.4°±0.2, 23.2°±0.2, 25.3°±0.2 and 26.1°±0.2 two-theta, as described in FIG. 8.

The IR spectrum of Form IX is characterized by the following bands: 701 cm^{-1}, 715 cm^{-1}, 741 cm^{-1}, 758 cm^{-1}, 780 cm^{-1}, 816 cm^{-1}, 823 cm^{-1}, 1030 cm^{-1}, 1053 cm^{-1}, 1078 cm^{-1}, 1110 cm^{-1}, 1204 cm^{-1}, 1217 cm^{-1}, 1307 cm^{-1}, and 1350 cm^{-1}, as described in FIG. 12.

Form X

It has further been discovered that another crystalline form of sertraline hydrochloride, denominated Form X may be obtained by suspending sertraline hydrochloride in benzyl alcohol, and heating to facilitate dissolution. The solution is cooled and the precipitate filtered, washed with benzyl alcohol and dried, to yield sertraline hydrochloride Form X.

The Form X produced in this manner is characterized by a powder x-ray diffraction pattern having its principal peaks at 15.0°±0.2, 16.0° 16.5°±0.2 17.0°±0.2, 18.1°±0.2, 21.0°±0.2, 22.4°±0.2, 24.9°±0.2, 25.4°±0.2, 26.2°±0.2, 27.1°±0.2, 28.4°±0.2, and 29.0°±0.2 degrees two-theta as described in FIG. 14.

The IR spectrum of Form X is characterized by the following bands: 742 cm^{-1}, 776 cm^{-1}, 806 cm^{-1}, 824 cm^{-1}, 1002 cm^{-1}, 1017 cm^{-1}, 1028 cm^{-1}, 1060 cm^{-1}, 1079 cm^{-1}, 1135 cm^{-1}, 1218 cm^{-1}, 1314 cm^{-1}, 1336 cm^{-1}, and 1560 cm^{-1} as described in FIG. 15.

The DSC of Form X shows a small endotherm at about 190° C. followed by a melting endotherm at about 250° C. (see FIG. 16).

Form III

The present invention provides new processes for making sertraline hydrochloride Form III from sertraline hydrochloride Forms V and VI. In the conversion of sertraline hydrochloride Form V to sertraline hydrochloride Form III, Form V is heated to a temperature between about 150° C. and about 180° C. for about 3 hours to about 2 days to induce the formation of sertraline hydrochloride Form III. Heating for 24 hours is preferred. The reaction may be stirred. The method of the present invention has the advantage of using no solvent.

Amorphous Sertraline Hydrochloride

In an embodiment of the present invention, amorphous sertraline is made by dissolving sertraline hydrochloride in water or a water/alcohol mixture and drying the solution by the spray dryer technique. Amorphous sertraline hydrochloride may also be made by sublimation of sertraline hydrochloride.

The amorphous sertraline hydrochloride produced by methods of the present invention is characterized by a powder x-ray diffraction pattern having the typical broad featureless pattern without sharp peaks typical of amorphous materials. FIG. 2 is one such pattern.

Pharmaceutical Compositions Containing Sertraline Hydrochloride Polymorphs

In accordance with the present invention, these new crystalline forms of sertraline hydrochloride and known forms of sertraline hydrochloride prepared by the new methods disclosed herein may be prepared as pharmaceutical compositions that are particularly useful for the treatment of depression, obsessive-compulsive disorder and panic disorder. Such compositions comprise one of the new crystalline forms of sertraline hydrochloride with pharmaceutically acceptable carriers and/or excipients known to one of skill in the art.

For example, these compositions may be prepared as medicaments to be administered orally, parenterally, rectally, transdermally, bucally, or nasally. Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or gelatin capsules, sub-lingual tablets, syrups and suspensions. Suitable forms of parenteral administration include an aqueous or non-aqueous solution or emulsion, while for rectal administration suitable forms for administration include suppositories with hydrophilic or hydrophobic vehicle. For topical administration the invention provides suitable transdermal delivery systems known in the art, and for nasal delivery there are provided suitable aerosol delivery systems known in the art.

Experimental

The powder X-ray diffraction patterns were obtained by methods known in the art using a Philips X-ray powder diffractometer, Goniometer model 1050/70 at a scanning speed of 2° per minute, with a Cu radiation of λ=1.5418 §.

The differential scanning calorimeter thermograms were obtained by methods known in the art using a DSC Mettler 821 Star°. The weight of the samples was less than 5 mg. The temperature range of scans was 30° C.–300° C. at a rate of 10° C./min. Samples were purged with nitrogen gas at a flow rate of 40 mL/min. Standard 40 μm aluminum crucibles were used having lids with three small holes.

The infrared spectra were obtained by methods known in the art using a Perkin Elmer FT-IR Paragon 1000 spectrometer. Samples were analyzed in Nujol mulls. Spectra were obtained at 4 cm^{-1} resolution and 16 scans each.

EXAMPLES

The present invention will now be further explained in the following examples. However, the present invention should not be construed as limited thereby. One of ordinary skill in the art will understand how to vary the exemplified preparations to obtain the desired results.

Example 1

Preparation of Sertraline Base

Sertraline mandelate (5 g) was stirred at room temperature with 50 mL ethyl acetate. Aqueous sodium hydroxide was added dropwise until the sertraline mandelate was completely neutralized. The phases were separated and the organic phase was dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure resulting sertraline base as an oil (3.2 g).

Example 2

Preparation of Sertraline Hydrochloride Form VI and Form V

Sertraline base (25 g) was dissolved in methanol (125 mL) at room temperature. The solution was acidified with hydrogen chloride gas until pH 1.5 was reached. (Precipitation occurred during acidification.) The temperature rose to approximately 40° C. The slurry was allowed to cool to room temperature and stirred for about 2 hours. The solid was separated by filtration to give sertraline hydrochloride methanolate Form VI. Drying the product overnight gave sertraline hydrochloride Form V.

Example 3

Preparation of Sertraline Hydrochloride Form VI and Form V

Sertraline base (3.2 g) was dissolved in absolute ethanol (32 mL) at room temperature and then hydrogen chloride gas was bubbled in until pH 0.5 was reached. The temperature rose to 40° C. The slurry was allowed to cool to room temperature and stirred for about 16 hours. The solid was separated by filtration, and washed with ethanol (3×2 mL). FIG. 5 sets forth the X-ray diffraction pattern of the product (sertraline hydrochloride ethanolate Form VI) so obtained. Drying overnight at 50–60° C. of that product yielded 2.95 g (82%) of sertraline hydrochloride Form V.

Example 4

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was dissolved in absolute ethanol (15 mL) at room temperature. A saturated solution of hydrogen chloride in isopropyl alcohol was added dropwise to reach a pH of 1.3. The resulting slurry was stirred at room temperature overnight. The solid was separated by filtration and dried overnight at 50–60° C. yielding 2.75 g (81. 8%) sertraline hydrochloride Form V.

Example 5

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was dissolved in absolute ethanol (15.5 mL) at room temperature and then the solution was cooled to approximately 0° C. Hydrogen chloride gas was bubbled until pH 0.5 was reached. The temperature rose to approximately 7° C. Precipitation occurred and the slurry was stirred at about 10° C. for 2 hours. The solid was isolated by filtration, washed with ethanol and dried at approximately 50° C. The dried material (2.87 g, yield 82.7%) was sertraline hydrochloride Form V.

Example 6

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was stirred with 35 mL water. The slurry was heated at ~70° C. and, while maintaining this temperature, concentrated hydrochloric acid was added until pH 1 was reached. During acidification, almost complete dissolution was observed followed by precipitation. The mixture was cooled to room temperature and stirred for 2 hours. The solid was isolated by filtration, washed with water and dried overnight at 50–60° C., yielding 3.23 g (96%) sertraline hydrochloride Form V.

Example 7

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was dissolved in 10 mL absolute ethanol at 40° C. The solution was heated to 50–60° C. and concentrated hydrochloric acid 32% (1.2 mL) was added until pH ~1.3 was reached. Water (12 mL) was added. The resulting clear solution was concentrated to half its volume and was allowed to cool naturally to room temperature. The solid was isolated by filtration, washed with water and dried overnight at 50–60° C., yielding 3.18 g (94.65%) sertraline hydrochloride Form V.

Example 8

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3.7 g) was dissolved in 18.5 mL absolute ethanol and the solution was heated to 60° C. Hydrogen chloride gas was bubbled through the ethanol solution until pH ~0.5 was reached. The mixture was cooled to room temperature and the stirring was continued for 2 hours. The solid obtained after filtration, washing with ethanol and drying at 50° C. was sertraline hydrochloride Form V (3.16 g, yield 76%).

Example 9

Preparation of Sertraline Hydrochloride Form V

Sertraline free base was dissolved in ethanol absolute and the solution was acidified with hydrogen chloride gas to about pH 3. Precipitation occurs and the slurry was stirred at room temperature for 2 hours. The resulting solid was filtered, washed with ethanol and dried to yield sertraline hydrochloride Form V.

Example 10

Preparation of Sertraline Hydrochloride Form V

Sertraline free base (13.3 g) was dissolved in absolute ethanol (60 mL) and was added dropwise over one hour to ethanol (20 mL) containing hydrogen chloride (17.5 g) at 35° C. with precipitation. After 2 hours, the solid was filtrated, washed with ethanol and dried at about 80° C. to yield sertraline hydrochloride Form V (12.9 g, yield 87%).

Example 11

Preparation of Sertraline Hydrochloride Form V

Anhydrous sertraline hydrochloride (2 g) was stirred with 14 mL absolute ethanol and heated to reflux to obtain a clear solution. The solution was seeded with sertraline hydrochloride Form V and cooled naturally to room temperature. Massive precipitation was observed at about 50° C. The slurry was stirred at room temperature during 2 hours. The solid was filtered, washed with ethanol (3 mL) and dried overnight at 50–60° C. yielding 1.71 g (85.5%) of sertraline hydrochloride Form V.

Example 12

Preparation of Sertraline Hydrochloride Form V

Sertraline hydrochloride ethanolate (Form VI) (40 g) in 400 mL water was heated to 80° C. and complete dissolution was obtained. The pH was adjusted to approximately one with hydrochloric acid and the solution was naturally cooled to room temperature and stirred for 2 hours. The solid was filtered and dried at 50° C. for approximately 16 hours, yielding sertraline hydrochloride Form V.

Example 13

Preparation of Sertraline Hydrochloride Form V

Sertraline hydrochloride ethanolate (Form VI) (2 g) was mechanically stirred with ethanol (0.5 mL) at room temperature for 40 hours. The resulting solid was sertraline hydrochloride Form V.

Table 1 sets forth a summary of additional experiments conducted generally following procedures described above.

TABLE 1

PREPARATION OF SERTRALINE HCL - FORM V

Exp't	Method of Crystallization	XRD	Yield (%)
	SERTRALINE BASE AS STARTING MATERIAL		
A	Methanol/HCl gas	V	78.7
B	Methanol/HCl gas	V	69
C	Methanol/HCl aqueous	V	87.8
D	Ethanol/HCl gas	V	80.9
E	Water/HCl aqueous	V	96
F	Hexane/Isopropyl alcohol/HCl gas	V	89.9
G	Methanol/HCl aqueous/water	V	89
H	Isopropyl alcohol/HCl aqueous/water	V	78
I	Ethanol/HCl aqueous/evaporation of ethanol	V	96.1
J	Ethyl acetate/HCl aqueous/water/evaporation of ethyl acetate	V	96.1
K	Ethanol/isopropyl alcohol/HCl gas	V	81.8
L	Methanol/isopropyl alcohol/HCl gas	V	82.4

TABLE 1-continued

PREPARATION OF SERTRALINE HCL - FORM V

Exp't	Method of Crystallization	XRD	Yield (%)
	SERTRALINE HCl AS STARTING MATERIAL		
M	Methanol (Form I and amorphous)	V	60
N	Ethanol (Form V)	V	85.5
O	Isopropyl alcohol/water (Form V)	V	28

PXRD = powder x-ray diffraction.

Example 14

Preparation of Sertraline Hydrochloride Form VII

1.003 g Sertraline hydrochloride Form V was stirred for 24 hours at room temperature in 20 mL water (HPLC grade). At the end of the stirring the mixture looked like a jelly suspension. The suspension was filtrated and the compound obtained was kept at cold conditions (4° C.) until analyzed by x-ray diffraction.

Example 15

Preparation of Sertraline Hydrochloride Form VII from Sertraline Hydrochloride Form VI

A solution of sertraline hydrochloride ethanolate (Form VI) (40 g) in water (400 mL) was heated at 80° C. and complete dissolution of sertraline hydrochloride ethanolate (Form VI) was obtained. The pH was adjusted to about 1 and the solution was allowed to cool to room temperature and then stirred for 2 additional hours. The solid was isolated by filtration and washed with water to yield sertraline hydrochloride Form VII.

Sertraline hydrochloride Form VII dried overnight at 80° C. forms sertraline hydrochloride Form V.

Example 16

Preparation of Sertraline Hydrochloride Forms VIII and IX from Sertraline Base

Sertraline base (2.7 g) was suspended in 27 mL of water. This mixture was heated to 80° C. and treated with hydrochloric acid until about pH 1 was reached. A clear solution was obtained, which on cooling gave a precipitate. After 2 hours stirring at room temperature the solid was isolated by filtration. This solid was characterized by powder x-ray diffraction (see FIG. **3**, Form VIII). Drying for 24 hours at ~50° C. yielded 2.32 g (76.8%) of sertraline hydrochloride Form IX, characterized by powder x-ray diffraction, infrared absorption, differential scanning calorimetry, and thermal gravimetric analysis as set forth above and depicted in FIGS. **8**, **10**, and **12**.

Example 17

Preparation of Sertraline Hydrochloride Form VIII

Sertraline hydrochloride ethanolate (Form VI) (40 g) was stirred with water (80 mL) for 1 hour at room temperature. The slurry was filtrated and washed with water to yield sertraline hydrochloride hydrate Form VIII.

Example 18

Preparation of Sertraline Hydrochloride Form VIII from Sertraline Hydrochloride Form II

Sertraline hydrochloride Form II (0.4 g) and water (8 mL) were stirred at room temperature over night. The solid was filtrated to yield sertraline hydrochloride hydrate Form VIII.

Example 19

Preparation of Sertraline Hydrochloride Form X

In a 0.1 liter three-necked bottom round flask equipped with a mechanical stirrer, a condenser and a thermometer, 30 mL benzyl alcohol is added to 10 g sertraline hydrochloride. The suspension is heated to 100° C. when a clear solution is obtained. The solution is cooled 2 hours to 25° C. and the precipitate is filtered and washed with benzyl alcohol. After drying under vacuum at 80° C. for 24 hours, 6.2 g of sertraline hydrochloride Form X is obtained (yield 62%). The sertraline hydrochloride Form X was characterized by powder x-ray diffraction and infrared absorption analysis as set forth above and in FIG. **14** and FIG. **15**.

Example 20

Preparation of Sertraline Hydrochloride Ethanolate Form VI by Reslurry of Form I

Sertraline hydrochloride Form I (1 g) and absolute ethanol (20 mL) were stirred at room temperature for 24 hours. Filtration of the mixture yielded sertraline hydrochloride ethanolate-Form VI.

Example 21

Preparation of Sertraline Hydrochloride Ethanolate Form VI by Reslurry of Form II

Sertraline hydrochloride Form II (1 g) and absolute ethanol (20 mL) were stirred at room temperature for 24 hours. Filtration of the mixture yielded sertraline hydrochloride ethanolate Form VI.

Example 22

Preparation of Sertraline Hydrochloride Ethanolate Form VI by Reslurry of Form V

Sertraline hydrochloride Form V (1 g) and ethanol absolute (20 mL) were stirred at room temperature for 24 hrs. Filtration of the mixture yielded sertraline hydrochloride ethanolate Form VI.

Example 23

Preparation of Amorphous Sertraline Hydrochloride

Sertraline free base (10 g) was dissolved in ethyl acetate (690 mL). At room temperature, ether (690 mL) was added to the sertraline ethyl acetate solution and the solution was acidified with HCl gas to about pH 0.5. The resulting gelatinous suspension was stirred at room temperature over night. Filtration and air drying of the suspension yielded amorphous sertraline hydrochloride (9.39 g, yield 83.8%).

Example 24

Preparation of Sertraline Hydrochloride Form III from Form V

Sertraline hydrochloride Form V was heated at 150° C. in a reactor under mechanical stirring for 24 hrs. The resulting material obtained was sertraline hydrochloride Form III.

Example 25

Preparation of Sertraline Hydrochloride Form III from Form VI

Sertraline hydrochloride form VI was heated to 180° C. for 24 hours. The dried material is sertraline hydrochloride Form III.

Example 26

Preparation of Sertraline Hydrochloride Form III from Form V

Sertraline hydrochloride Form V was heated at a temperature >180° C. for 24 hours. The resulting material was sertraline hydrochloride Form III.

Example 27

Preparation of Amorphous Sertraline Hydrochloride

Sertraline hydrochloride Form V (10 g) was dissolved in water (2L) and this solution was dried by the spray dryer technique. The material obtained in this way is Sertraline hydrochloride amorphous.

Example 28

Preparation of Amorphous Sertraline Hydrochloride by Sublimation

Sertraline hydrochloride Form I was sublimated at 190–200° C., at a vacuum of 30–0.1 mm Hg, using a laboratory-type sublimator. The resulting material was amorphous sertraline hydrochloride.

A similar procedure starting from Form V also gave amorphous sertraline hydrochloride.

Example 29

Preparation of Sertraline Hydrochloride Form V from Amorphous Sertraline Hydrochloride

Sertraline hydrochloride amorphous was heated to 80° C. for 24 hours. The resulting product was sertraline hydrochloride Form V.

It should be understood that some modification, alteration and substitution is anticipated and expected from those skilled in the art without departing from the teachings of the invention. Accordingly, it is appropriate that the following claims be construed broadly and in a manner consistent with the scope and spirit of the invention.

What is claimed is:

1. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) dissolving or suspending sertraline hydrochloride in a suitable solvent;

(b) removing the solvent; and

(c) drying to form sertraline hydrochloride Form V.

2. The process of claim **1**, wherein the solvent is selected from the group consisting of methanol, ethanol, water, 1-methoxy-2-propanol, trichloroethane, and isopropyl alcohol, and mixtures thereof.

3. The process of claim **2**, wherein the solvent is water.

4. The process of claim **3**, wherein the step of drying to form sertraline hydrochloride Form V is achieved by spray drying.

5. The process of claim **1**, further comprising the step of seeding the solution with sertraline hydrochloride Form V.

6. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) dissolving or suspending sertraline base in a solvent;

(b) adding hydrogen chloride gas to the solvent to reduce the pH of the solution or suspension; and

(c) isolating sertraline hydrochloride Form V from the solution or suspension.

7. The process of claim 6 wherein the pH of the solution or suspension of sertraline base and hydrogen chloride is about 0 to about 4.

8. The process of claim 6 wherein the solvent is selected from the group consisting of methanol, ethanol, water, ethyl acetate, isopropyl alcohol, ether, hexane, and toluene, and mixtures thereof.

9. The process of claim 8 wherein the solvent is ether.

10. The process of claim 8 wherein the solvent is water.

11. The process of claim 10 wherein the step of isolating sertraline hydrochloride Form V is done by spray drying the solution or suspension.

12. A process for making sertraline hydrochloride Form V comprising the step of drying sertraline hydrochloride Form VII at about 80° C.

13. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) dissolving or suspending sertraline hydrochloride in water;

(b) adding a sufficient amount of hydrogen chloride to facilitate precipitation of sertraline hydrochloride;

(c) removing the water; and

(d) isolating sertraline hydrochloride Form V.

14. A process for making sertraline hydrochloride Form VI comprising the steps of:

(a) dissolving sertraline base in a solvent;

(b) adding hydrogen chloride to the solvent; and

(c) isolating sertraline hydrochloride Form VI without further drying.

15. The process of claim 14 wherein the isolation step comprises precipitation of sertraline hydrochloride Form VI followed by filtration.

16. The process of claim 14 wherein the solvent is at least one solvent selected from the group consisting of ethanol, methanol, or mixtures of methanol or ethanol with water.

17. A process for making sertraline hydrochloride Form VI comprising the steps of:

(a) suspending sertraline hydrochloride Form I, II or V in ethanol or methanol;

(b) stirring for a time sufficient to induce the transformation of sertraline hydrochloride to sertraline hydrochloride Form VI; and

(c) isolating sertraline hydrochloride Form VI.

18. A process for making sertraline hydrochloride Form VIII comprising the steps of:

(a) suspending sertraline base in water;

(b) adding hydrogen chloride to the water; and

(c) filtrating the precipitate so obtained without further drying.

19. A process for making sertraline hydrochloride Form VIII comprising the steps of:

(a) suspending or dissolving sertraline hydrochloride ethanolate Form VI or sertraline hydrochloride Form II in water or a mixture of water and isopropyl alcohol; and

(b) isolating sertraline hydrochloride Form VIII.

20. A process for making sertraline hydrochloride Form III comprising the steps of:

(a) heating sertraline hydrochloride Form V or Form VI to a temperature sufficient, and for a time sufficient, to induce the transformation of sertraline hydrochloride Form V or Form VI to sertraline hydrochloride Form III; and

(b) isolating sertraline hydrochloride Form III.

21. The process of claim 20 wherein the temperature is between about 150° C. and about 180° C.

22. A process for making amorphous sertraline hydrochloride comprising the steps of:

(a) suspending or dissolving sertraline base in a solvent selected from the group consisting of ether, toluene and t-butyl-methyl ether, and mixtures thereof;

(b) adding hydrogen chloride gas; and

(c) isolating amorphous sertraline hydrochloride.

23. The process of claim 2, wherein the solvent is 1-methoxy-2-propanol.

24. A process for making sertraline hydrochloride Form V comprising the steps of :

(a) dissolving or suspending sertraline base in a solvent;

(b) adding hydrochloric acid to the solvent to reduce the pH of the solution or suspension; and

(c) isolating sertraline hydrochloride Form V form the solution or suspension.

25. The process of claim 24, wherein the pH of the solution or suspension of sertraline base and hydrogen chloride is about 0 to about 4.

26. The process of claim 24 wherein the solvent is selected from the group consisting of methanol, ethanol, water, ethyl acetate, isopropyl alcohol, ether, hexane, and toluene, and mixtures thereof.

27. The process of claim 26 wherein the solvent is ether.

28. The process of claim 26 wherein the solvent is water.

29. The process of claim 28 wherein the step of isolating sertraline hydrocloride Form V is done by spray drying the solution or suspension.

* * * * *

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TEVA PHARMACEUTICAL INDUSTRIES LTD. and TEVA PHARMACEUTICALS USA, INC.,	:	Civil Action No.
Plaintiffs,	:	
v.	:	**CERTIFICATE OF NON-ARBITRABILITY**
CIPLA LTD., AND BYRON CHEMICAL CO., INC.,	:	
Defendants.	:	

Allyn Z. Lite, of full age, certifies that pursuant to L. Civ. R. 201.1 the within matter is not arbitrable, being that the Complaint seeks damages that are in an excess of $150,000 and injunctive relief.

Dated: January 12, 2007

Allyn Z. Lite

EXHIBIT B

US006500987B1

(12) **United States Patent**
Schwartz et al.

(10) **Patent No.: US 6,500,987 B1**
(45) **Date of Patent: Dec. 31, 2002**

(54) **SERTRALINE HYDROCHLORIDE POLYMORPHS**

(75) Inventors: **Eduard Schwartz**, Rechovot; **Tamar Nidam**, Yehud; **Anita Liberman**, Tel-Aviv; **Marioara Mendelovici**; **Judith Aronhime**, both of Rehovot; **Claude Singer**, Kfar Saba; **Evgeni Valdman**, Petah Tikva, all of (IL)

(73) Assignee: **Teva Pharmaceutical Industries Ltd.**, Petah Tiqva (IL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/448,985**

(22) Filed: **Nov. 24, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/110,113, filed on Nov. 27, 1998, provisional application No. 60/125,172, filed on Mar. 19, 1999, provisional application No. 60/133,117, filed on May 7, 1999, and provisional application No. 60/147,888, filed on Aug. 9, 1999.

(51) **Int. Cl.**[7] **C07C 211/00**
(52) **U.S. Cl.** **564/308**; 514/647
(58) **Field of Search** 514/647; 564/308

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Primary Examiner—Samuel Barts
(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon

(57) **ABSTRACT**

The present invention is directed to forms II, III, V, VI, VII, VIII, IX and X of sertraline hydrochloride and novel methods for their preparation. According to the present invention, sertraline hydrochloride polymorph II may be produced by slurrying sertraline hydrochloride polymorph VI in aprotic organic solvent. Sertraline hydrochloride polymorphic form III may be produced by heating sertraline hydrochloride polymorphs V and VI. Sertraline hydrochloride forms V and VI may be produced from either sertraline hydrochloride or sertraline base by crystallization. Sertraline hydrochloride Form VII may be produced by suspending sertraline chloride polymorph V in water, followed by filtration. Sertraline hydrochloride Forms VIII and IX may be produced by suspending sertraline base in water followed by acidification and filtration. Sertraline hydrochloride Form X may be produced by suspending sertraline hydrochloride in benzyl alcohol with heating, followed by filtration.

89 Claims, 16 Drawing Sheets

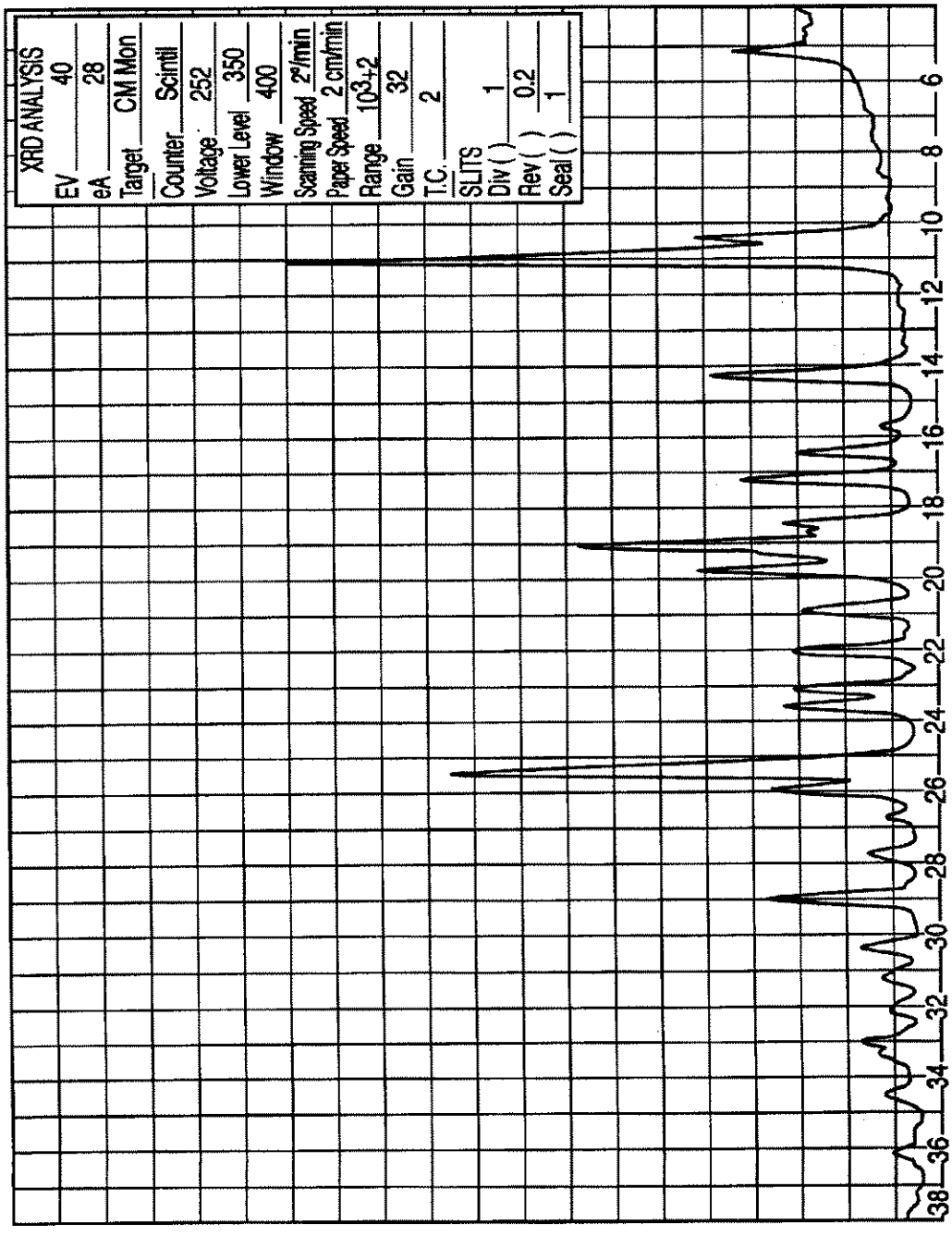
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FIG. 1

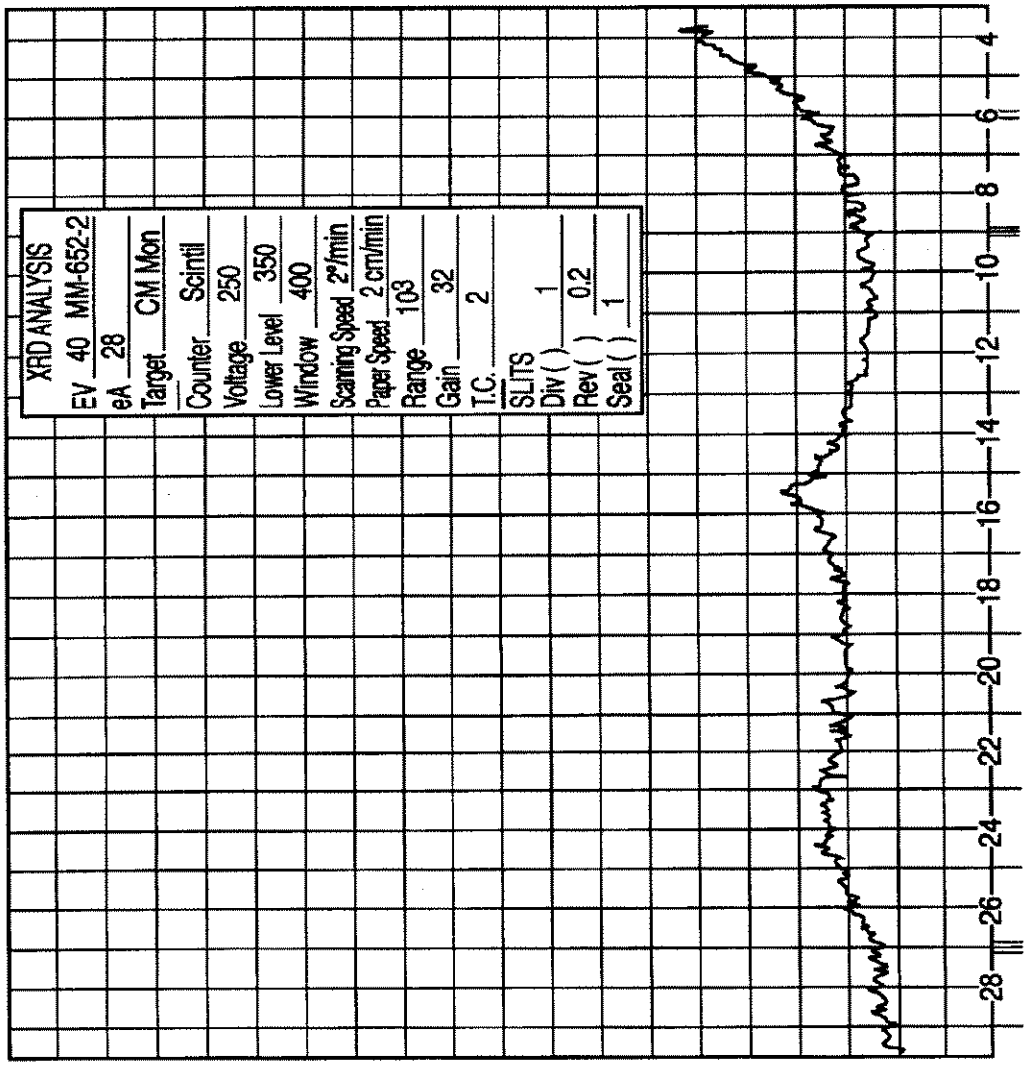
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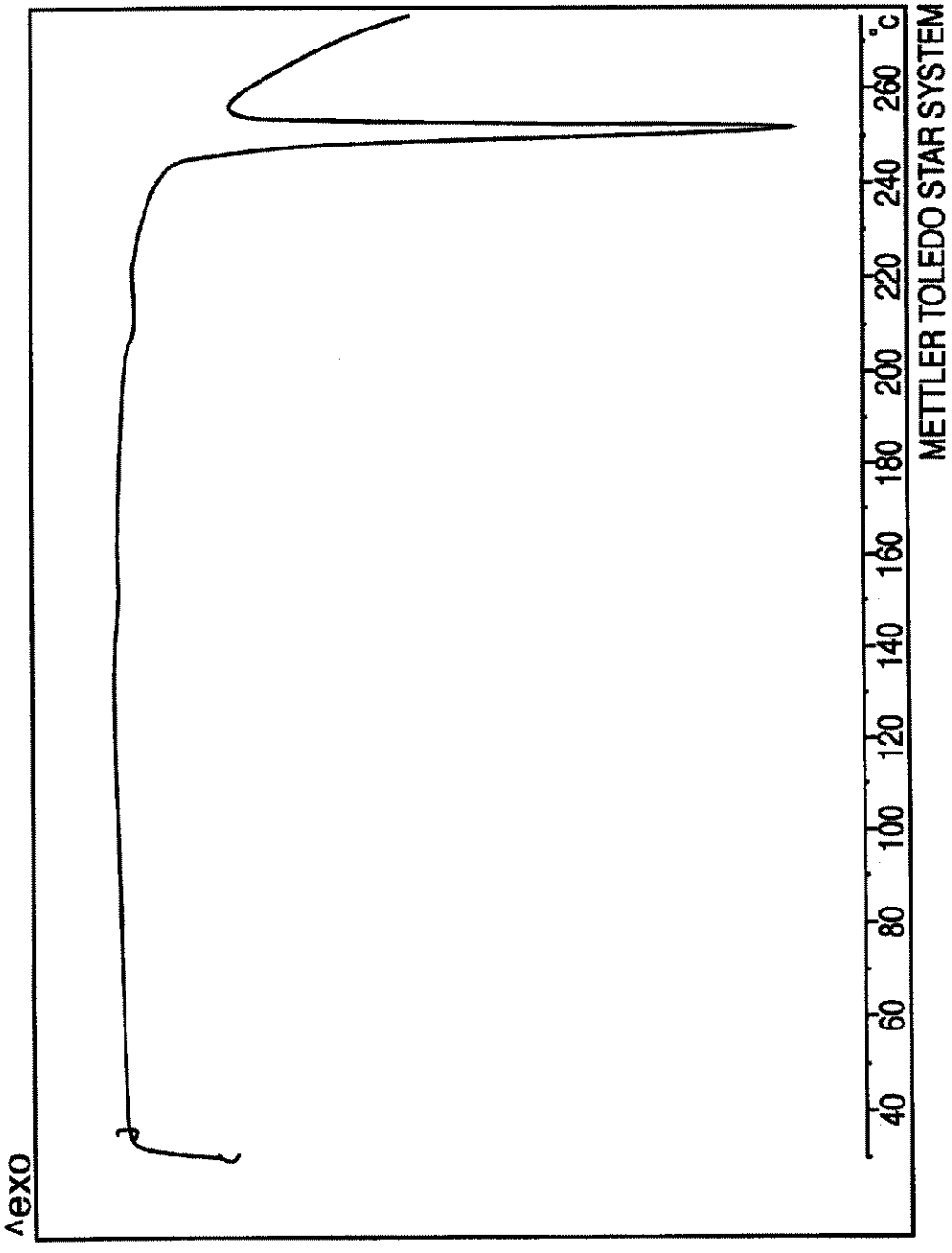
FIG. 2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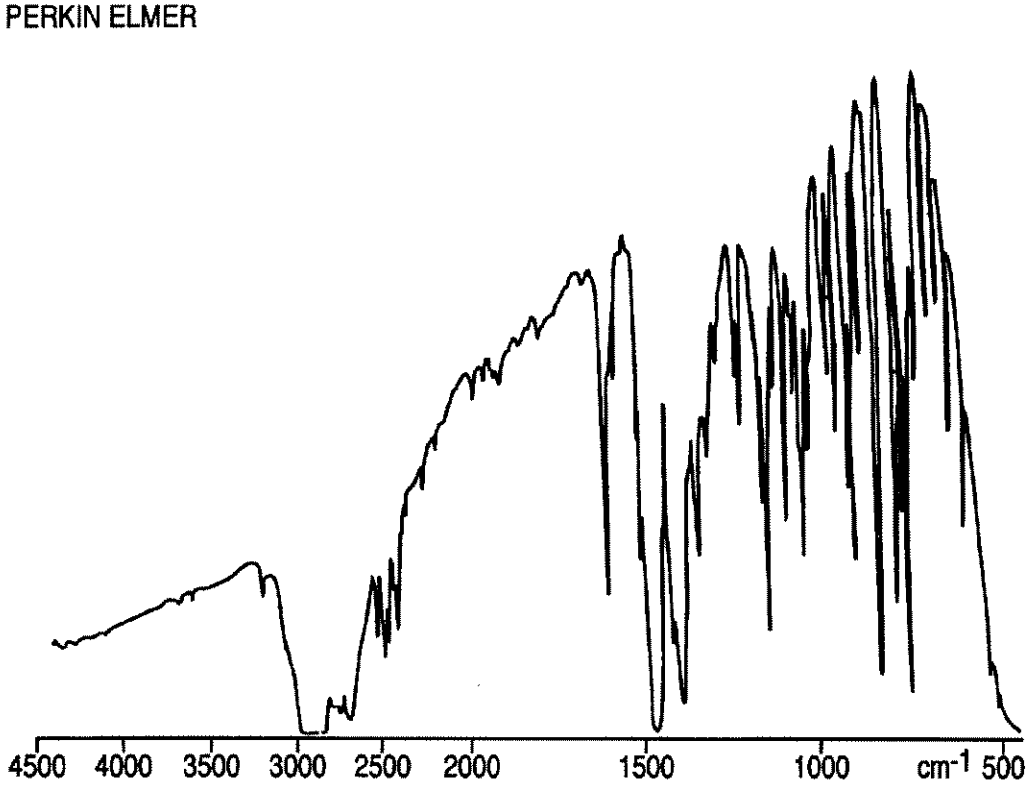
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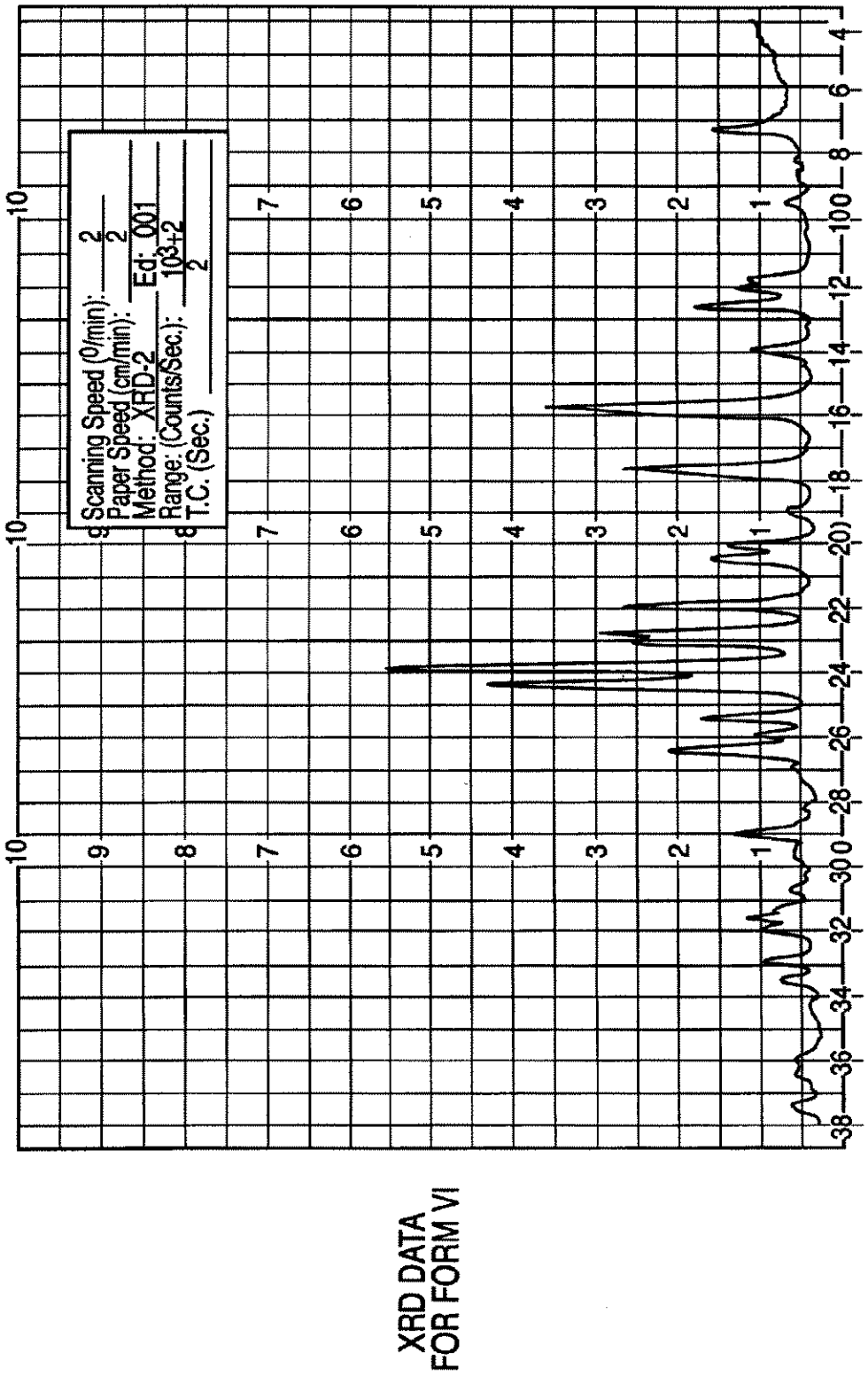

XRD DATA
FOR FORM VI

FIG. 5

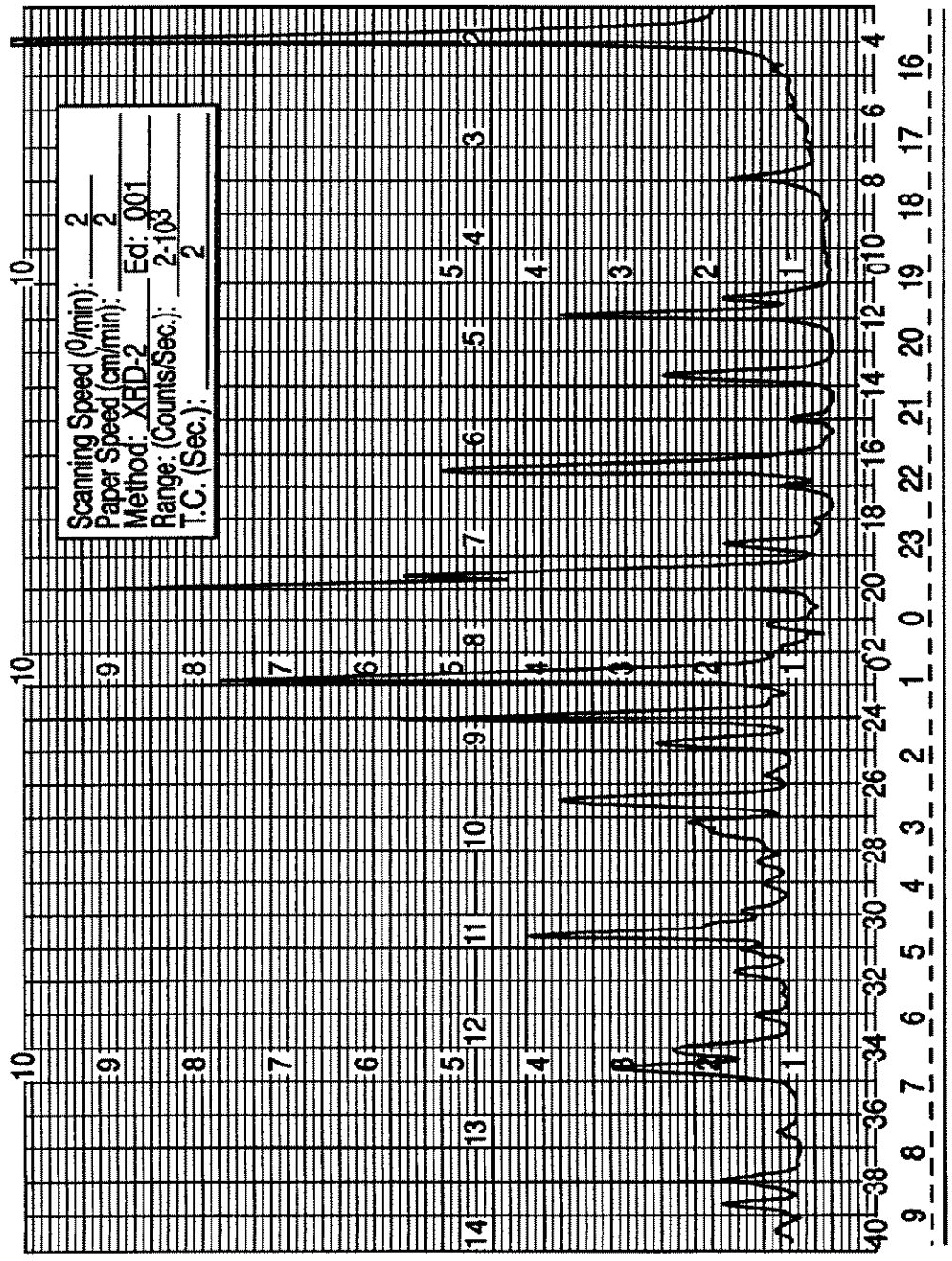
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FIG. 6

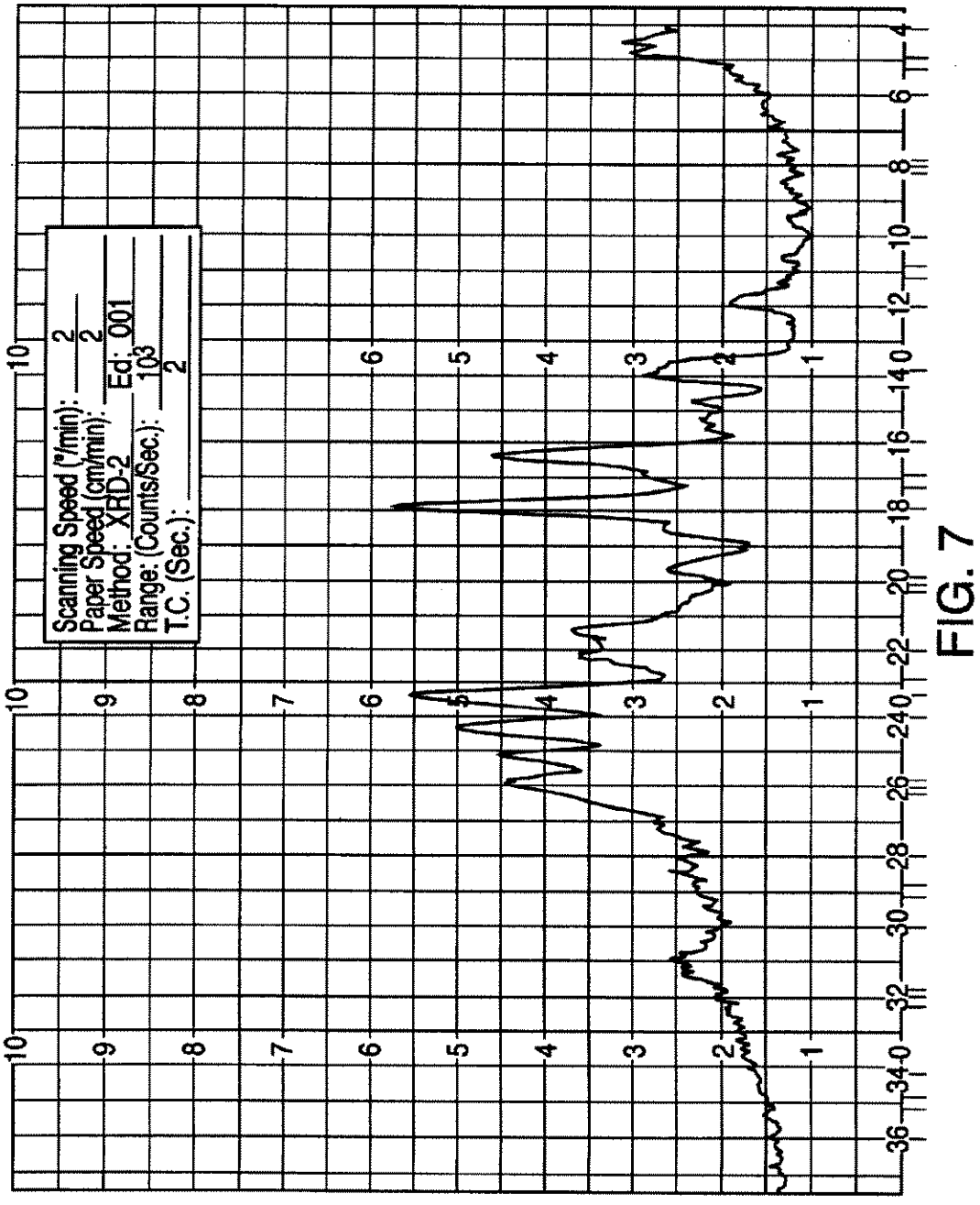
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FIG. 7

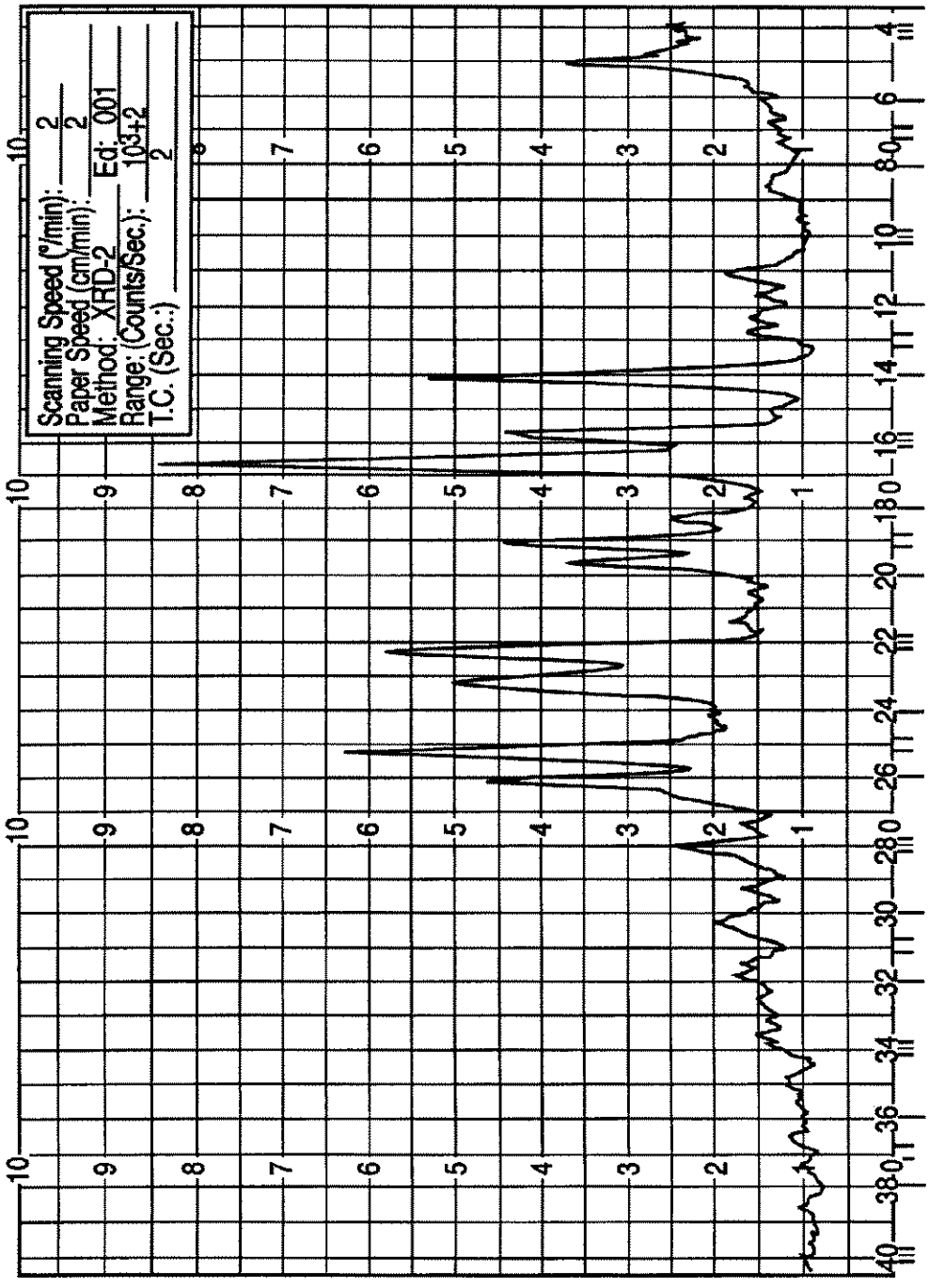
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FIG. 8

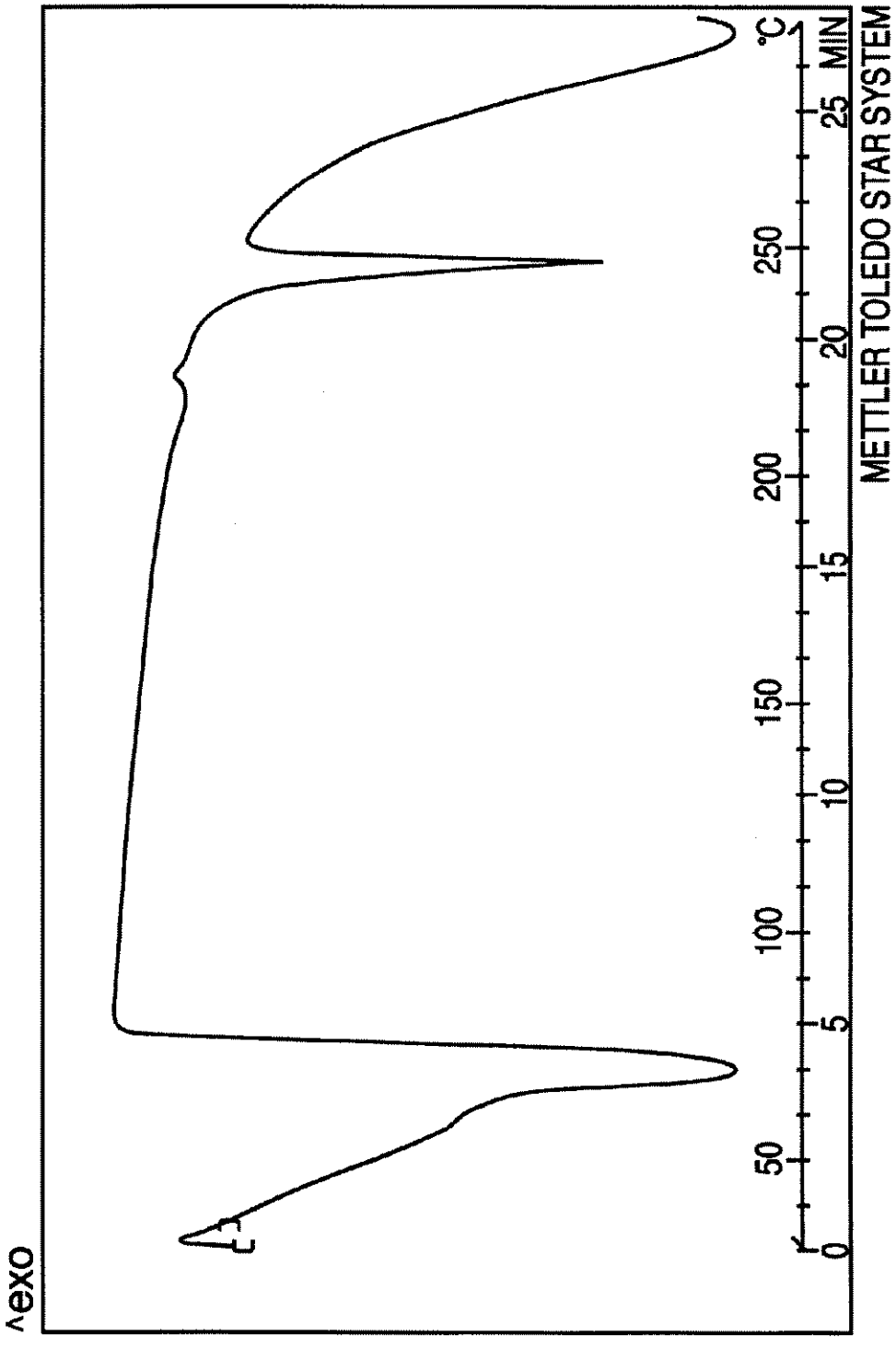
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FIG. 9

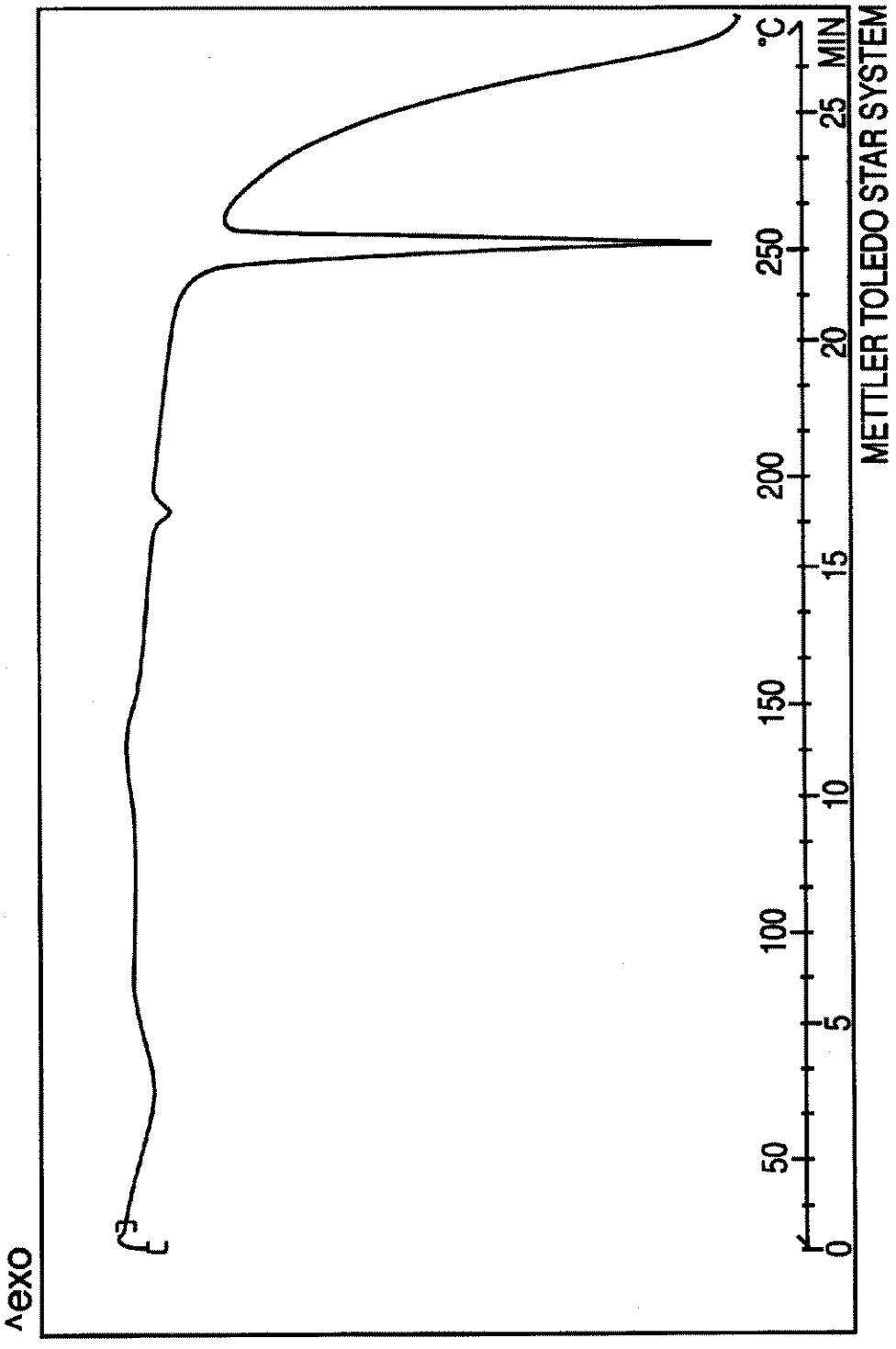
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FIG. 10

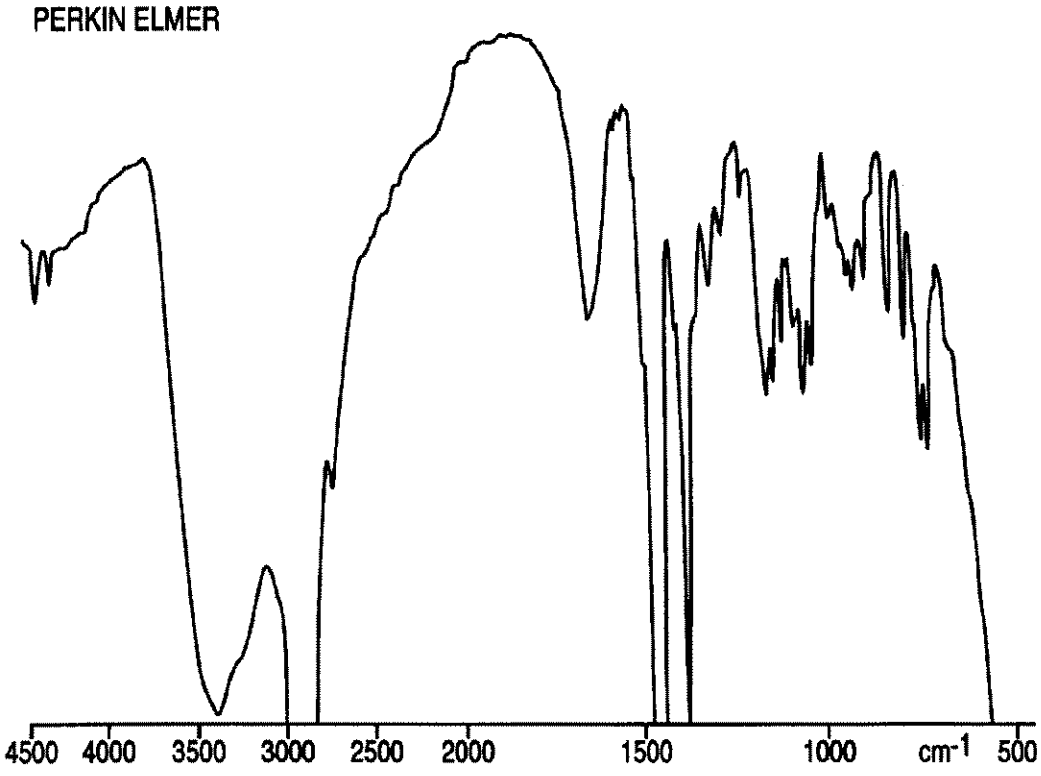

PERKIN ELMER
4500 4000 3500 3000 2500 2000 1500 1000 cm-1 500
16 SCANS, 4.0cm-1
SRT HCL mm-686-1 NUJOL

FIG. 11

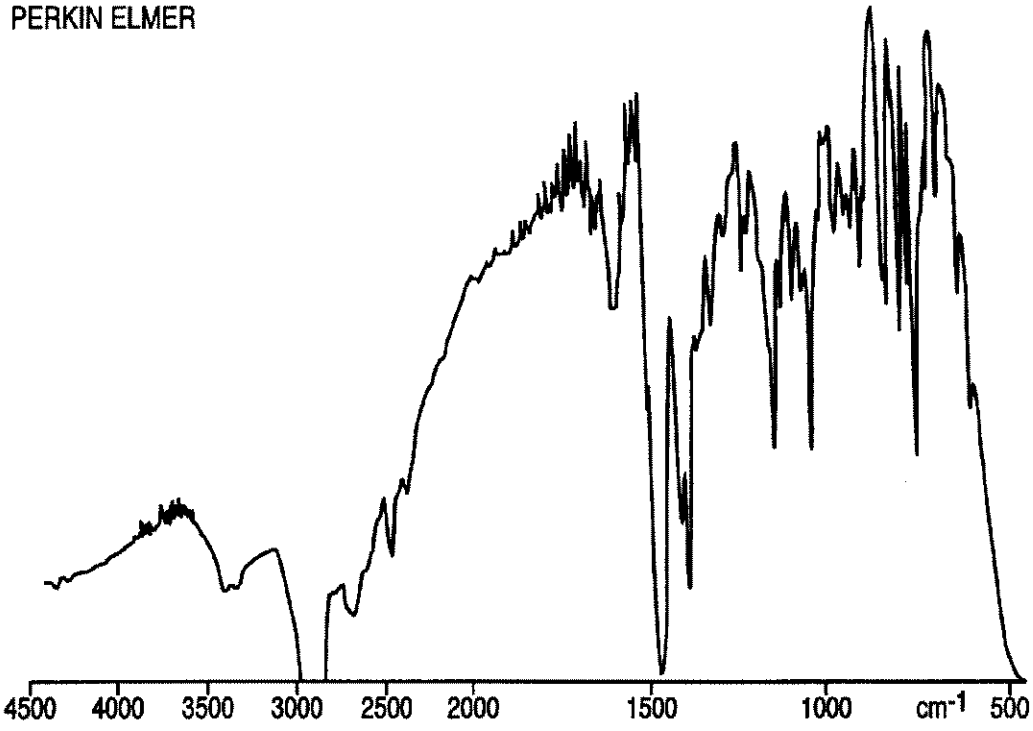
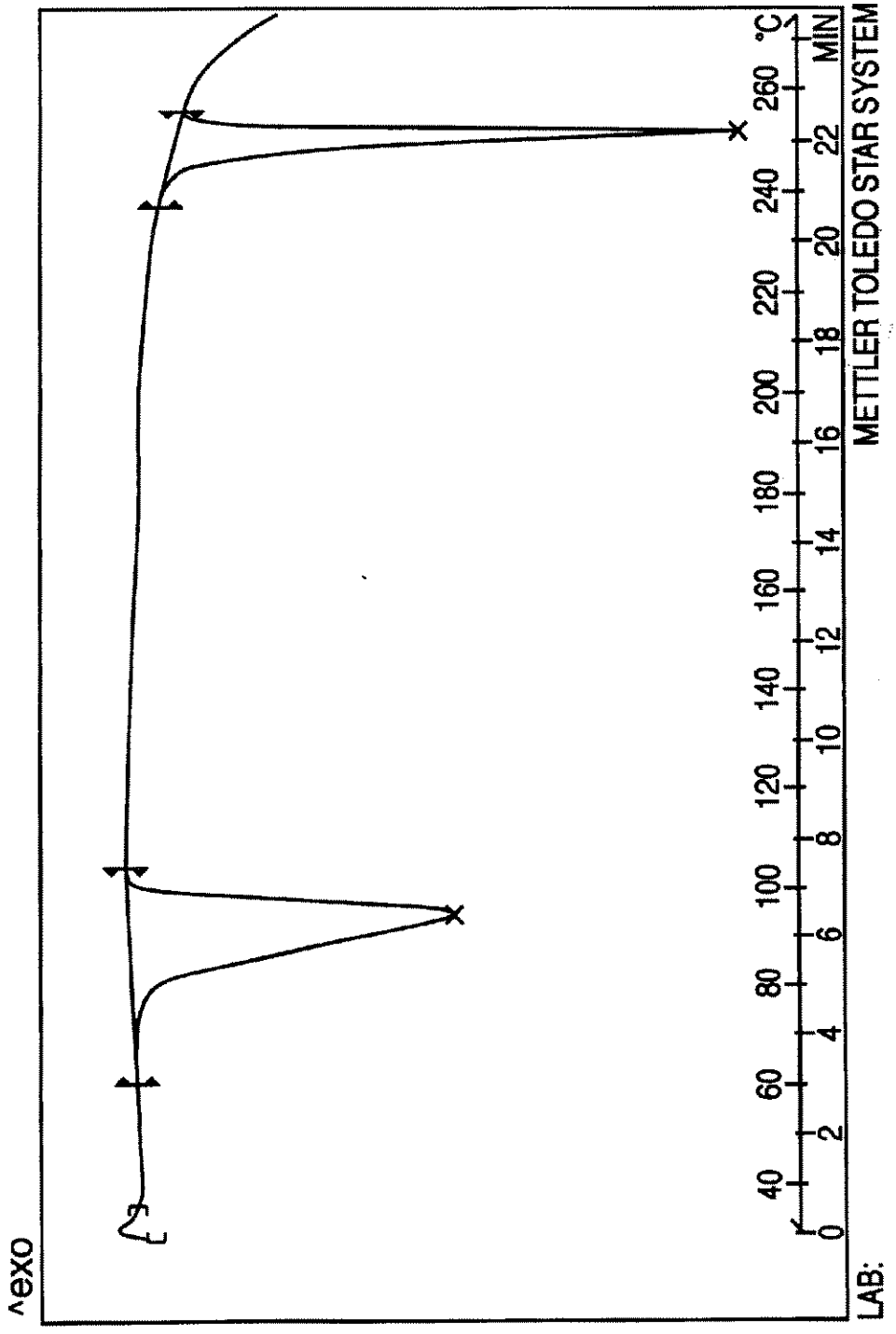

PERKIN ELMER
4500
4000
3500
3000
2500
2000
1500
1000
cm-1
500
16 SCANS, 4.0cm-1
SRT HCL TN 1641-1 NUJOL

FIG. 12



DSC OF FORM VI ETHANOLATE

FIG. 13

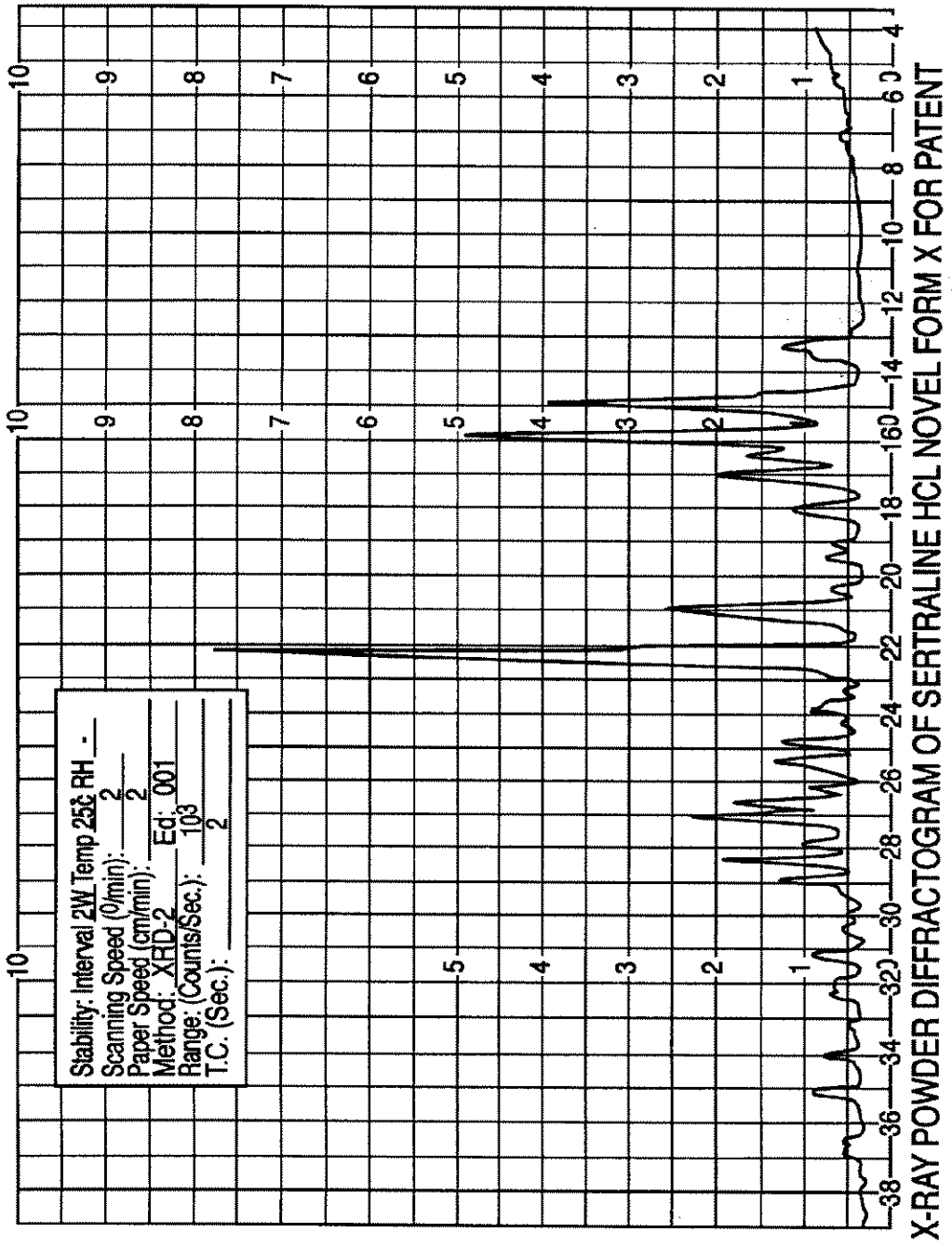
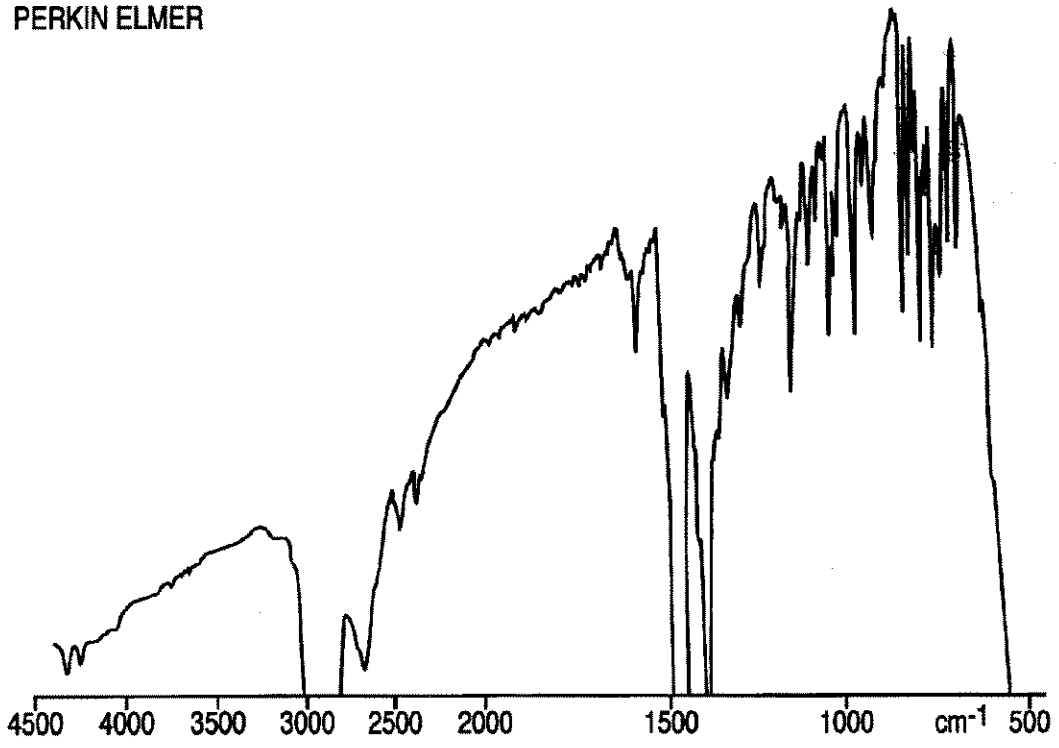
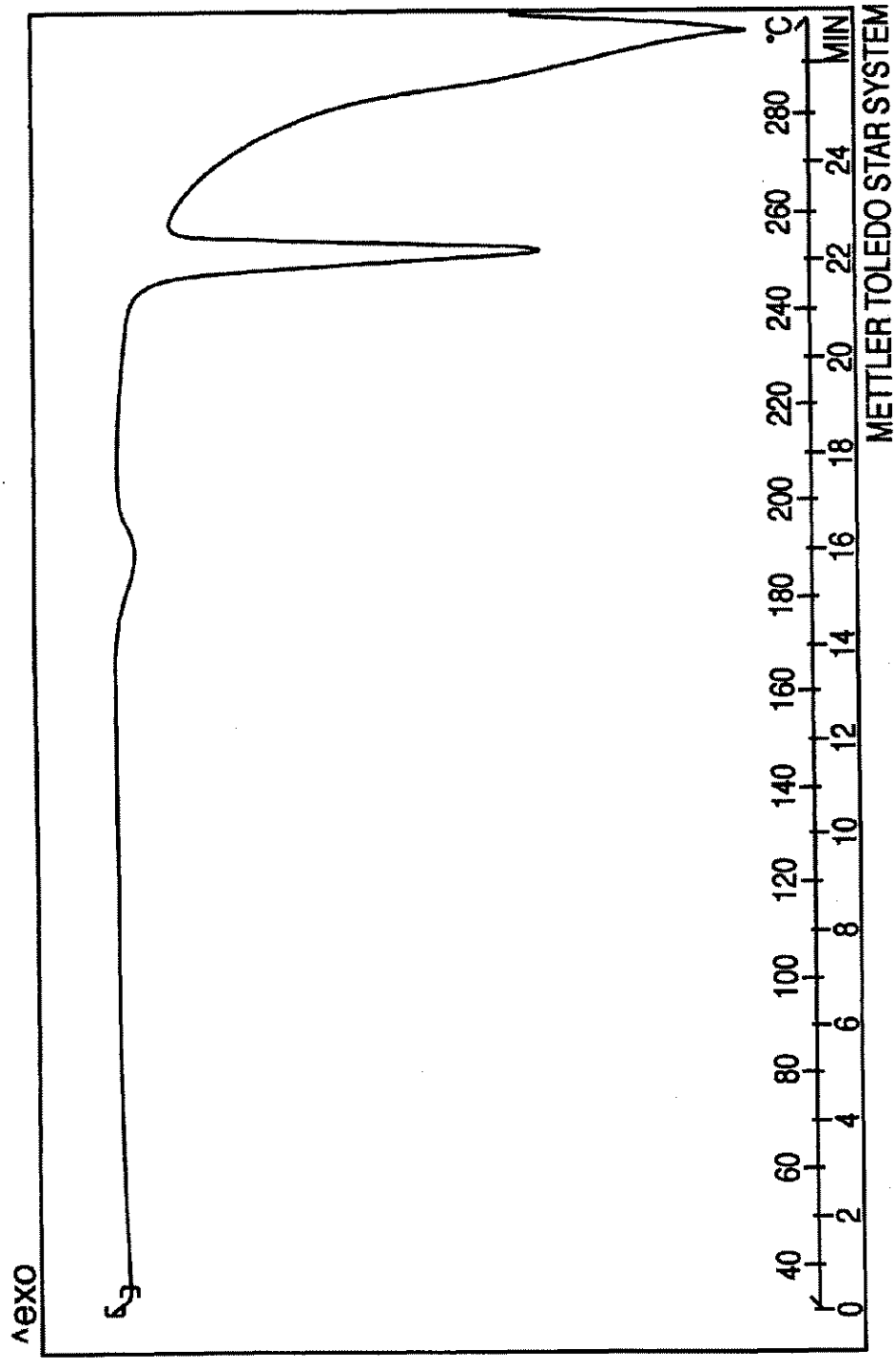

Stability: Interval 2W Temp 25C RH -
Scanning Speed (0/min): 2
Paper Speed (cm/min): 2
Method: XRD-2 Ed: 001
Range: (Counts/Sec.): 103
T.C. (Sec.): 2
X-RAY POWDER DIFFRACTOGRAM OF SERTRALINE HCL NOVEL FORM X FOR PATENT

FIG. 14



FTIR SPECTRUM OF SERTRALINE HCL FORM X FOR PATENT

FIG. 15



DSC OF FORM X

FIG. 16

SERTRALINE HYDROCHLORIDE POLYMORPHS

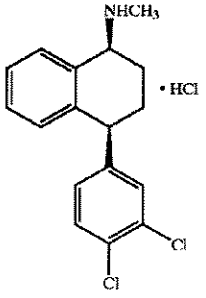
This application is a provisional of No. 60/110,113 filed Nov. 27, 1998 and a provisional of No. 60/125,172 filed Mar. 19, 1999 and a provisional of No. 60/133,117 filed May 7, 1999 and a provisional of No. 60/147,888 filed Aug. 9, 1999.

FIELD OF THE INVENTION

The present invention relates to novel crystalline forms of sertraline hydrochloride, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenaminehydrochloride, denominated Forms VI through X, an amorphous form and novel, reproducible methods for preparing them and for preparing previously reported polymorphs II, III and V.

BACKGROUND OF THE INVENTION

Sertraline hydrochloride, (1S-cis)4-(3,4 dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride, having the formula



is approved, under the trademark Zoloft®, by the U.S. Food and Drug Administration, for the treatment of depression, obsessive-compulsive disorder and panic disorder.

U.S. Pat. No. 4,536,518 describes a synthesis of sertraline hydrochloride. U.S. Pat. No. 5,248,699 describes five crystalline forms of sertraline hydrochloride, designated Form I, Form II, Form III, Form IV and Form V.

U.S. Pat. No. 4,536,518 ("the '518 patent") describes the preparation of sertraline hydrochloride with a melting point of 243–245° C. by treating an ethyl acetate/ether solution of the free base with gaseous hydrogen chloride. The solid state properties of the sertraline hydrochloride so produced are not otherwise disclosed.

According to U.S. Pat. No. 5,248,699 ("the '699 patent"), the sertraline hydrochloride produced by the method of the '518 patent has a crystalline form denominated "Form II". The '699 patent discloses four other polymorphs I, III, IV, and V, and characterizes them by single crystal x-ray analysis, powder x-ray diffraction, infra-red spectroscopy, and differential scanning calorimetry. The '699 patent reports that Form II is produced by rapid crystallization of sertraline hydrochloride from an organic solvent, including isopropyl alcohol, hexane, generally describes methods for making sertraline hydrochloride Forms I–V. According to this patent, the preferential formation of Forms I, II or IV in an acidic solution consisting of isopropyl alcohol, hexane, and acetone, methyl isobutyl ketone, glacial acetic acid, or preferably, ethyl acetate depends on the rapidity of crystallization. Form I is described as being made by crystallizing sertraline hydrochloride in an acidic solution using an

organic solvent such as those listed above. The crystallization of Form I is carried out at a temperature from about 20° C. to about the solvent reflux temperature, preferably from about 40° to 60° C. The only method described in this patent for making Forms II and IV is by the rapid crystallization of sertraline hydrochloride from an organic solvent such as those listed above. Slow crystallization or granulation of sertraline hydrochloride will produce Form I. Form III is described as being formed by heating Forms I, II or IV to temperatures above about 180° C. Granulating either of Forms II, III or IV in isopropyl alcohol, ethyl acetate, hexane or any of the solvents listed above at a temperature from about 40° to 60° C. causes conversion to Form I. The only method described in this patent for making Form V is by sublimation of sertraline hydrochloride Form I at reduced pressure and at a temperature from about 180–190° C. onto a condenser. However, in our hands attempts to repeat this procedure to obtain Form V have been unsuccessful.

SUMMARY OF THE INVENTION

It has now been discovered that sertraline hydrochloride Form V can be formed by crystallization from various solvents rather than by sublimation. The existence of new crystal forms of sertraline hydrochloride, denominated Forms VI, VII, VIII, IX and X, and an amorphous of sertraline hydrochloride have been discovered. Form VI is a useful intermediate in the formation of previously reported sertraline hydrochloride Forms I, II and V.

The present invention also relates to sertraline hydrochloride ethanolate and processes for making sertraline hydrochloride ethanolate.

The present invention also relates to sertraline hydrochloride methanolate and processes for making sertraline hydrochloride methanolate.

The present invention also relates to sertraline hydrochloride solvate and processes for making sertraline hydrochloride solvate.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form V.

FIG. **2** is a characteristic x-ray powder diffraction spectrum of amorphous sertraline hydrochloride Form V.

FIG. **3** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form V.

FIG. **4** is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form V.

FIG. **5** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form VI.

FIG. **6** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form VII.

FIG. **7** is a characteristic x-ray powder diffraction spectrum of settraline hydrochloride Form VIII.

FIG. **8** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form IX.

FIG. **9** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form VIII.

FIG. **10** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form IX.

FIG. **11** is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form VIII.

FIG. **12** is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form IX.

FIG. **13** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form VI.

FIG. 14 is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form X

FIG. 15 is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form X.

FIG. 16 is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form X.

DETAILED DESCRIPTION OF THE INVENTION

Form V

The present invention provides new processes for making sertraline hydrochloride Form V from sertraline hydrochloride, sertraline base or amorphous sertraline hydrochloride. The methods provided in the present invention are more commercially practicable than the sublimation-condensation method of U.S. Pat. No. 5,248,699, which we have not been able to reproduce. It has also surprisingly been found that, by the present method, Form V is formed even at different crystallization rates.

Where the present invention provides methods for the conversion of sertraline hydrochloride to sertraline hydrochloride Form V, sertraline hydrochloride is combined with a solvent selected from the group consisting of methanol, ethanol, 1-methoxy-2-propanol and a mixture of isopropyl alcohol and water. If a mixture of isopropyl alcohol and water is used, it is preferably an about 6:1 mixture. Preferably the solvent is methanol or ethanol, and most preferably the solvent is ethanol. Sertraline hydrochloride Form V is isolated by allowing the solution to cool. One preferred method is to rapidly cool the solvent to 5° C. Another preferred method comprises seeding the solution with sertraline hydrochloride Form V crystals, followed by slow cooling to room temperature, followed by filtration and drying. Sertraline hydrochloride Form V can also be prepared by recrystallizing sertraline hydrochloride Form VI (described below) from water.

The present invention also provides methods for the conversion of sertraline hydrochloride Form I or II to sertraline hydrochloride Form V wherein the solvate sertraline hydrochloride Form VI is an intermediate. In this embodiment of the present invention, sertraline hydrochloride Form I and Form II is dissolved in either methanol or ethanol thereby forming sertraline hydrochloride Form VI. Where ethanol is the solvent, the sertraline hydrochloride Form VI is the ethanolate solvate. Where methanol is the solvent, the sertraline hydrochloride Form VI is the methanolate solvate. This intermediate sertraline hydrochloride Form VI is then dried, with or without a separate isolation step, to remove all solvent and sertraline hydrochloride Form V is isolated.

The present invention also provides methods for the conversion of sertraline hydrochloride Form II to sertraline hydrochloride Form V wherein the sertraline hydrochloride Form VIII is an intermediate. In this embodiment of the present invention, sertraline hydrochloride Form II is dissolved in water thereby forming sertraline hydrochloride Form VIII. This intermediate sertraline hydrochloride Form VIII is then dried, with or without a separate isolation step, to remove all solvent and sertraline hydrochloride Form V is isolated.

The present invention also provides methods for the conversion of sertraline base to i sertraline hydrochloride Form V, wherein sertraline base is added to at least one solvent, and hydrogen chloride gas is bubbled through the solution. Preferred solvents include methanol, ethanol, water, or mixtures of ethanol, methanol, isopropyl alcohol, hexane, ethyl acetate with each other or with water.

Alternatively, an appropriate amount of hydrogen chloride gas dissolved in methanol, ethanol, water, hexane, isopropyl alcohol, ethyl acetate, or a mixture thereof is combined with the sertraline base solution. Sertraline hydrochloride Form V is isolated by allowing precipitation to occur from about 0° to about 60° C. followed by filtration and drying. Preferably the solvent is hexane, isopropyl alcohol or a mixture thereof. In another method, sertraline base is added to a solvent and the resulting solution is added to a hydrochloric acid solution of pH 0–4; preferably the pH of the solution is about 1.

Alternatively, sertraline base is added to a solvent selected from the group consisting of methanol, ethanol, water, hexane, isopropyl alcohol, and ethyl acetate or a mixture thereof. The solution is heated and concentrated hydrochloric acid is added. Water may also be added. Sertraline hydrochloride Form V is isolated by allowing the mixture to cool to room temperature and remain at room temperature overnight, followed by filtration and drying.

Alternatively, sertraline base may be combined with a solvent selected from the group consisting of ethanol, ethanol and water, ethyl acetate, and a mixture of ethyl acetate and water. The solution is heated to about 50–60° C. and water is added. The solvent is partially removed by distillation. Sertraline hydrochloride Form V is isolated by allowing the solution to cool to room temperature, followed by filtration and drying at the precipitate.

Alternatively, sertraline base may be combined with a solvent selected from the group consisting of methanol, ethanol and a mixture thereof. A saturated solution of hydrogen chloride gas in isopropyl alcohol is added to induce formation of sertraline hydrochloride Form V. Sertraline hydrochloride Form V is isolated by allowing the solution to stand at room temperature overnight, followed by filtration and drying of the precipitate.

Sertraline base for use in the processes of the present invention may be produced by dissolving sertraline mandelate in ethyl acetate followed by neutralization of the sertraline mandelate with aqueous sodium hydroxide. The organic phase is separated from the aqueous phase and dried using magnesium sulfate. The solvent is removed under reduced pressure to produce sertraline base as an oil. Methods for making sertraline base are set forth in U.S. Pat. Nos. 4,536,518 and 5,248,699.

Where the present invention provides methods for the conversion of amorphous sertraline hydrochloride to sertraline hydrochloride Form V, amorphous sertraline hydrochloride is kept in a closed container, such as a bag, and warmed to about 40° C. to about 80° C. or is stored at room temperature for a period between a few hours and several days depending on the temperature.

The sertraline hydrochloride Form V that results from practicing the invention as exemplified herein can be characterized by its powder X-ray diffraction pattern. FIG. 1 is a representative pattern of sertraline hydrochloride Form V. The principal peaks observed are at about 5.20°±0.2, 10.40°±0.2, 11.0°±0.2, 14.30°±0.2, 16.50°±0.2, 17.30°±0.2, 18.40°±0.2, 19.7°±0.2, 20.9°±0.2, 22.0°±0.2, 23.2°±0.2, 23.6°±0.2, 25.5°±0.2, 26.0°±0.2, and 29.1°±0.2 degrees 2 theta.

Three experiments were performed in order to repeat the procedure described in U.S. Pat. No. 5,248,699 for preparing Form V by sublimation. Two experiments were performed by sublimating a sample of Form I under 30 mm Hg vacuum and temperature between 170–190° C. A third experiment was performed by sublimating a sample of Form I under high vacuum (0.1 mm Hg) and temperature between 180–195° C.

The three samples of sertraline hydrochloride prepared by sublimation were analyzed by powder x-ray diffraction. In all cases, the typical broad featureless pattern without sharp peaks typical of amorphous materials was obtained. FIG. 2 is one such pattern.

In conclusion, sertraline hydrochloride could not be obtained by following the procedure set forth in U.S. Pat. No. 5,248,699 for preparing Form V by sublimation of Form I.

The IR spectrum of sertraline hydrochloride Form V produced by the present process is characterized by the following bands: 773 cm^{-1}, 822 cm^{-1}, cm^{-1}, 1012 cm^{-1}, 1032 cm^{-1}, 1054 cm^{-1}, 1133 cm^{-1}, 1328 cm^{-1}, 1562 cm^{-1}, and 1590 cm^{-1}, as shown in FIG. 4.

The sertraline hydrochloride Form V of the present process is further characterized by the DSC thermogram data, for example, as disclosed in FIG. 3. The DSC thermogram is characterized by a small endotherm (~3 Joule per gram) at about 210° C., believed to be a solid-solid transformation (based upon observation under a hot stage microscope) to Form III and a melting peak. Form III at 251° C.

Form VI

Sertraline hydrochloride Form VI is a solvated crystal form of sertraline hydrochloride. In the present invention, sertraline hydrochloride Form VI may be an ethanolate, wherein ethanol is incorporated into the crystal structure of Form VI. Alternatively, sertraline hydrochloride Form VI may be a methanolate, wherein methanol is incorporated into the crystal structure of sertraline hydrochloride Form VI. All sertraline hydrochloride Form VI solvates have identical powder x-ray diffraction patterns. Therefore, when referring to sertraline hydrochloride Form VI all sertraline hydrochloride Form VI solvates such as, sertraline hydrochloride Form VI ethanolate and sertraline hydrochloride Form VI methanolate, are necessarily included.

To form the novel crystalline form sertraline hydrochloride Form VI, sertraline base is added to absolute ethanol or methanol. Hydrogen chloride gas is then bubbled through the solution. Sertraline hydrochloride Form VI is isolated by allowing precipitation to occur, followed by filtration. The DSC thermogram of Form VI crystallized from ethanol displays a desolvation peak at 95° C. (see FIG. 13) and loses 11.2% weight (by TGA); Form VI crystallized from methanol loses 8.3% weight (by TGA) upon desolvation; Form VI crystallized from ethanol is an ethanolate, and more specifically is a monoethanolate. Form VI crystallized from methanol is a methanolate, and more specifically is a monomethanolate.

The present invention also provides new processes for making sertraline hydrochloride ethanolate Form VI by reslurry of Forms I, II and V. In the conversion of sertraline hydrochloride Form I, II, V to sertraline hydrochloride ethanolate Form VI, sertraline hydrochloride Form I, II or V is dissolved or suspended in ethanol or in methanol and stirred for about 18–36 hours, 24 hours is preferred. Sertraline hydrochloride ethanolate Form VI is isolated by filtration.

The sertraline hydrochloride Form VI so isolated exhibits the powder x-ray diffraction pattern of FIG. 5, comprising peaks at 7.30±0.2, 12.1°±0.2, 12.7°±0.2, 14.0°±0.2, 15.60°±0.2, 17.60°±0.2, 20.1°±0.2, 20.60°±0.2, 21.90°±0.2, 22.70°±0.2, 23.0°±0.2, 23.8°±0.2, 24.3°±0.2, 25.4°±0.2, and 26.3°±0.2 degrees two-theta. Sertraline hydrochloride Form VI so obtained is a solvate. Drying of the precipitated sertraline hydrochloride Form VI at 50–60° C. overnight yields sertraline hydrochloride Form V.

Form VI

It has also been discovered that a new crystalline form of sertraline hydrochloride Form VII, may be obtained by suspending Form V in water, and filtrating the suspension after one day without further drying.

In another embodiment of the invention, sertraline hydrochloride Form VII is made from sertraline hydrochloride Form VI. Sertraline hydrochloride Form VI is dispersed in water and the mixture is heated to facilitate the dissolution of sertraline hydrochloride Form VI. The solution may be heated to about 30° C. to 90° C., preferably to about 80° C. The pH is then lowered, preferably to about pH 1 and the mixture is allowed to cool to room temperature and stirred until the reaction is complete. Preferably the reaction is stirred for two hours at room temperature. Sertraline hydrochloride Form VII is isolated by filtration and washing with water.

As shown in FIG. 6, sertraline hydrochloride Form VII is characterized by two unique strong x-ray powder diffraction peaks at 4.0°±0.2, and 20.0 degrees two-theta and medium intensity peaks at 8.0°±0.2, 11.6°±0.2, 12.0°±0.2, 13.8°±0.2, 16.5°±0.2, 22.8°±0.2, 24.1°±0.2, 25.0°±0.2, 26.6°±0.2, 30.70°±0.2, 34.7°±0.2 2 two-theta. The TGA curve shows a loss on drying of about 45%.

Forms VIII and IX

Additional new crystalline forms of sertraline hydrochloride, Forms VIII and IX, have also been discovered. Sertraline hydrochloride hydrate Form VIII may be produced by suspending sertraline base in water followed by acidification and filtration. Form IX is obtained by drying of Form VIII. Preferably the sertraline base is suspended in water, heated to approximately 80° C., adding hydrochloric acid to reduce the pH to about 1, and cooling the resulting solution to room temperature.

The present invention also provides new processes for making sertraline hydrochloride Form VIII from sertraline hydrochloride ethanolate Form VI. In one embodiment of the present invention, a slurry of sertraline hydrochloride ethanolate Form VI in water is stirred, preferably for about one hour. The slurry is then filtered and washed with water and sertraline hydrochloride hydrate Form VIII is isolated.

The present invention also provides processes of making sertraline hydrochloride form VIII from sertraline hydrochloride Form II. In the conversion of sertraline hydrochloride Form II to sertraline hydrochloride Form VIII, sertraline hydrochloride Form II is suspended in water and stirred, preferably stirred overnight and sertraline hydrochloride hydrated Form VIII is isolated by filtration.

Sertraline hydrochloride Form VIII is characterized by x-ray powder diffraction peaks at 4.7°±0.2, 11.8°±0.2, 16.3°±0.2, 17.8°±0.2, 19.6°±0.2, 23.2°±0.2, 24.2°±0.2, 25.1°±0.2, and 26.0°±0.2 two-theta, as described in FIG. 7.

The DSC thermogram for Form VIII is characterized by a strong endotherm below 100° C., small endothermic and exothermic events at about 220° C. and a melting peak at 247° C. as described in FIG. 9.

The TGA curve shows a loss on drying step of about 20% below 100° C.

The IR spectrum of Form VIII is characterized by the following bands: 740 cm^{-1}, 779 cm^{-1}, 822 cm, 887 cm^{-1}, 915 cm^{-1} , 1031 cm^{-1}, 1053 cm^{-1}, 1110 cm^{-1}, 1134 cm^{-1}, 1153 cm^{-1}, 1217 cm^{-1}, 1307 cm^{-1}, and 1377 cm^{-1}, as described in FIG. 11.

Sertraline hydrochloride Form IX is characterized by x-ray powder diffraction peaks at 5.1°±0.2, 14.2°±0.2, 15.8°±0.2, 16.8°±0.2, 19.2°±0.2, 19.7°±0.2, 22.4°±0.2, 23.2°±0.2, 25.3°±0.2 and 26.1°±0.2 two-theta, as described in FIG. 8.

The IR spectrum of Form IX is characterized by the following bands: 701 cm^{-1}, 715 cm^{-1}, 741 cm^{-1}, 758 cm^{-1}, 780 cm^{-1}, 816 cm^{-1}, 823 cm^{-1}, 1030 cm, 1053 cm^{-1}, 1078 cm^{-1}, 1110 cm^{-1}, 1204 cm^{-1}, 1217 cm^{-1}, 1307 cm^{-1}, and 1350 cm^{-1}, as described in FIG. **12**.

Form X

It has further been discovered that another crystalline form of sertraline hydrochloride, denominated Form X, may be obtained by suspending sertraline hydrochloride in benzyl alcohol heating to facilitate dissolution. The precipitate is then filtered, washed with benzyl alcohol and dried, to yield sertraline hydrochloride Form X.

The Form X produced in this manner is characterized by a powder x-ray diffraction pattern having its principal peaks at 15.0°±0.2, 16.0°±0.2, 16.5°±0.2, 17.0°±0.2, 18.1°±0.2, 21.0°±0.2, 22.4°±0.2, 24.9°±0.2, 25.4°±0.2, 26.2°±0.2, 27.1°±0.2, 28.4°±0.2, and 29.0°±0.2 degrees two-theta as described in FIG. **14**.

The IR spectrum of Form X is characterized by the following bands: 742 cm^{-1}, 776 cm^{-1}, 806 cm^{-1}, 824 cm^{-1}, 1002 cm^{-1}, 1017 cm^{-1}, 1028 cm^{-1}, 1060 cm , 1079 cm^{-1}, 1135 cm^{-1}, 1218 cm^{-1}, 1314 cm^{-1}, 1336 cm^{-1}, and 1560 cm^{-1} as described in FIG. **15**.

The DSC of Form X shows a small endotherm at about 190° C. followed by a melting endotherm at about 250° C., (see FIG. **16**).

Form II

The present invention provides new processes for making sertraline hydrochloride Form II from sertraline hydrochloride Form VI by reslurry or granulation in organic solvents at temperatures between 25–80° C., followed by drying. The methods provided in the present invention have advantages over the rapid recrystallization method of U.S. Pat. No. 5,248,699. The method of the present invention does not require complete dissolution of sertraline hydrochloride, controlling the rate of heating or cooling of a sertraline solution, or controlling the rate of crystallization. The present method utilizes less solvent than the method of the '699 patent, since the sertraline hydrochloride starting material need not be completely dissolved.

In the conversion of sertraline hydrochloride Form VI to sertraline hydrochloride Form II, sertraline hydrochloride Form VI is combined with an aprotic organic solvent. Suitable solvents include acetone, t-butyl-methyl ether (MTBE), ethyl acetate and cyclohexane. One preferred method is to heat sertraline hydrochloride Form VI and solvent, preferably MTBE, to reflux for one hour. The slurry is cooled to room temperature and sertraline hydrochloride Form II is isolated by filtration. Another preferred method of making sertraline hydrochloride Form II comprises stirring sertraline hydrochloride Form VI and suitable solvent, preferably acetone, at room temperature for 2 hours, followed by filtration. About 1 to about 10 volumes of solvent are preferred, based on the weight of the sertraline hydrochloride starting material. See Examples 9 (3 volumes of solvent) and 10 (5 volumes of solvent) below. However, smaller amounts of solvent will also effect the transformation, albeit in some instances more slowly. The reaction is carried out for a time sufficient to convert the Form VI to Form II. We have not observed any further conversion of Form II upon treatment under these conditions for times longer than the minimum time necessary to effect the transformation.

The present invention also provides new processes for making sertraline hydrochloride Form II from sertraline hydrochloride Form V by granulation. In the conversion of sertraline hydrochloride Form V to sertraline hydrochloride Form II, sertraline hydrochloride Form V is combined with ethanol. The sertraline hydrochloride Form V ethanol mixture is stirred for at least a few hours to several days, preferably about two days to induce the formation of sertraline hydrochloride Form II.

Sertraline hydrochloride Form II may also be made by recrystallization of sertraline hydrochloride from suitable solvents such as dimethyl formamide or cyclohexanol. Sertraline hydrochloride is dissolved by warming in the solvent followed by cooling the solution at room temperature. Sertraline Form II is isolated by filtration.

The present invention also provides a new process for making sertraline hydrochloride Form II form sertraline base. Sertraline base is dissolved in a suitable such as acetone and the pH of the solution is lower by the addition of a hydrogen chloride solution, such as isopropyl alcohol and hydrogen chloride. The hydrogen chloride solution is added to induce the formation of sertraline hydrochloride Form II. Upon cooling of the mixture, for example to room temperature, sertraline hydrochloride Form II is isolated by filtration.

An experiment was performed in order to repeat the procedure described in U.S. Pat. No. 4,536,518 for preparing Form II. Sertraline base was dissolved in ethyl acetate, ether was added and the solution was acidified with hydrogen chloride gas. The material obtained after filtration and air drying was sertraline hydrochloride amorphous, not Form II as was expected.

The present invention also provides new processes for making a mixture of sertraline hydrochloride Form II and sertraline hydrochloride Form V. In this embodiment of the present invention, sertraline hydrochloride Form VI is heated to induce the transformation of sertraline hydrochloride Form VI to a mixture of both sertraline hydrochloride Form II and sertraline hydrochloride Form V. In this embodiment of the present invention, the heating of sertraline hydrochloride Form VI may be done under reduced pressure or atmospheric pressure.

Form III

The present invention provides new processes for making sertraline hydrochloride Form III from sertraline hydrochloride From V. In the conversion of sertraline hydrochloride Form V to sertraline hydrochloride Form III, Form V is heated to a temperature between about 150° to about 180° C. for about 24 hours to induce the formation of sertraline hydrochloride Form III. The reaction may be stirred. The method of the present invention has the advantage of using no solvent.

The methods of the present invention also provides new processes for making sertraline hydrochloride Form III from sertraline hydrochloride ethanolate Form VI by heating sertraline hydrochloride Form VI at about 150° to about 180° C. for about 24 hours. The dried material is sertraline hydrochloride Form III.

Amorphous Sertraline Hydrochloride

The present invention provides new processes for making amorphous sertraline hydrochloride from sertraline hydrochloride by sublimation or by precipitating, from a nonpolar solvent such as toluene, ether and t-butyl-methyl ether sertraline base.

In an embodiment of the present invention, amorphous sertraline is made by dissolving hydrochloride Form V in water and drying the solution by the spray dryer technique. Amorphous sertraline hydrochloride may also be made by sublimation of sertraline hydrochloride.

The amorphous sertraline hydrochloride produced by methods of the present invention is characterized by a

powder x-ray diffraction pattern having the typical broad featureless pattern without sharp peaks typical of amorphous materials. FIG. 2 is one such pattern.

Pharmaceutical Compositions Containing Sertraline Hydrochloride Polymorphs

In accordance with the present invention, these new crystalline forms of sertraline hydrochloride and known forms of sertraline hydrochloride prepared by the new methods disclosed herein may be prepared as pharmaceutical compositions that are particularly useful for the treatment of depression, obsessive-compulsive disorder and panic disorder. Such compositions comprise one of the new crystalline forms of sertraline hydrochloride with pharmaceutically acceptable carriers and/or excipients known to one of skill in the art.

For example, these compositions may be prepared as medicaments to be administered orally, parenterally, rectally, transdermally, bucally, or nasally. Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or gelatin capsules, sub-lingual tablets, syrups and suspensions. Suitable forms of parenteral administration include an aqueous or non-aqueous solution or emulsion, while for rectal administration suitable forms for administration include suppositories with hydrophilic or hydrophobic vehicle. For topical administration the invention provides suitable transdermal delivery systems known in the art, and for nasal delivery there are provided suitable aerosol delivery systems known in the art.

Experimental

The powder X-ray diffraction patterns were obtained by methods known in the art using a Philips X-ray powder diffractometer, Goniometer model 1050/70 at a scanning speed of 2° per minute, with a Cu radiation of λ=1.5418 Å.

The differential scanning calorimeter thermograms were obtained by methods known in the art using a DSC Mettler 821 Star°. The weight of the samples was less than 5 mg. The temperature range of scans was 30° C.–300° C. at a rate of 10° C./min. Samples were purged with nitrogen gas at a flow rate of 40 mL/min. Standard 40 μl aluminum crucibles were used having lids with three small holes.

The infrared spectra were obtained by methods known in the art using a Perkin Elmer FT-IR Paragon 1000 spectrometer. Samples were analyzed in Nujol mulls. Spectra were obtained at 4 cm^{-1} resolution and 16 scans each.

EXAMPLES

The present invention will now be further explained in the following examples. However, the present invention should not be construed as limited thereby. One of ordinary skill in the art will understand how to vary the exemplified preparations to obtain the desired results.

Example 1

Preparation of Sertraline Base

Sertraline mandelate (5 g) was stirred at room temperature with 50 mL ethyl acetate. Aqueous sodium hydroxide was added dropwise until the sertraline mandelate was completely neutralized. The phases were separated and the organic phase was dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure resulting sertraline base as an oil (3.2 g).

Example 2

Preparation of Sertraline Hydrochloride Form VI and Form V

Sertraline base (25 g) was dissolved in methanol (125 mL) at room temperature. The solution was acidified with hydrogen chloride until pH 1.5 was reached. (Precipitation occurred during acidification.) The temperature rose to approximately 40° C. The slurry was allowed to cool to room temperature and stirred for about 2 hours. The solid was separated by filtration to give sertraline hydrochloride methanolate—Form VI. Drying the product overnight gave sertraline hydrochloride Form V.

Example 3

Preparation of Sertraline Hydrochloride Form VI and Form V

Sertraline base (3.2 g) was dissolved in absolute ethanol (32 mL) at room temperature and then hydrogen chloride gas was bubbled in until pH 0.5 was reached. The temperature rose to 40° C. The slurry was allowed to cool to room temperature and stirred for about 16 hours. The solid was separated by filtration, and washed with ethanol (3×2 mL). FIG. 5 sets forth the X-ray diffraction pattern of the product (sertraline hydrochloride Form VI) so obtained. Drying overnight at 50–60° C. of that product yields 2.95 g (82%) of sertraline hydrochloride Form V.

Example 4

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was dissolved in absolute ethanol (15 mL) at room temperature. A saturated solution of hydrogen chloride in isopropyl alcohol was added dropwise to reach a pH of 1.3. The resulting slurry was stirred at room temperature overnight. The solid was separated by filtration and dried overnight at 50–60° C. yielding 2.75 g (81.8%) sertraline hydrochloride Form V.

Example 5

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was dissolved in absolute ethanol (15.5 mL) at room temperature and then the solution was cooled to approximately 0° C. Hydrogen chloride gas was bubbled until pH 0.5 was reached. The temperature rose to approximately 7° C. Precipitation occurred and the slurry was stirred at about 10° C. for 2 hours. The solid was isolated by filtration, washed with ethanol and dried at approximately 50° C. The dried material (2.87 g, yield 82.7%) was sertraline hydrochloride Form V.

Example 6

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was stirred with 35 mL water. The slurry was heated at ~70° C. and, while maintaining this temperature, concentrated hydrochloric acid was added until pH 1 was reached. During acidification, almost complete dissolution was observed followed by precipitation. The mixture was cooled to room temperature and stirred for 2 hours. The solid was isolated by filtration, washed with water and dried overnight at 50–60° C., yielding 3.23 g (96%) sertraline hydrochloride Form V.

Example 7

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was dissolved in 10 mL absolute ethanol at 40° C. The solution was heated to 50°–60° C. and

concentrated hydrochloric acid 32% (1.2 mL) was added until pH 1.3 was reached. Water (12 mL) was added. The resulting clear solution was concentrated to half its volume and was allowed to cool naturally to room temperature. The solid was isolated by filtration, washed with water and dried overnight at 50–60° C., yielding 3.18 g (94.65%) sertraline hydrochloride Form V.

Example 8

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3.7 g) was dissolved in 18.5 mL absolute ethanol and the solution was heated to 60° C. Hydrogen chloride gas was bubbled through the ethanol solution until pH ~0.5 was reached. The mixture was cooled to room temperature and the stirring was continued for 2 hours. The solid obtained after filtration, washing with ethanol and drying at 50° C. was sertraline hydrochloride Form V (3.16 g, yield 76%).

Example 9

Preparation of Sertraline Hydrochloride Form V

Sertraline free base was dissolved in ethanol absolute and the solution was acidified with hydrogen chloride gas to about pH 3. Precipitation occurs and the slurry was stirred at room temperature for 2 hours. The resulting solid was filtered, washed with ethanol and dried to yield sertraline hydrochloride Form V.

Example 10

Preparation of Sertraline Hydrochloride Form V

Sertraline free base (13.3 g) was dissolved in absolute ethanol (60 mL) and was added dropwise over one hour to ethanol (20 mL) containing hydrogen chloride gas (17.5 g) at 35° C. After 2 hours, the solid was filtrated, washed with ethanol and dried at about 80° C. to yield sertraline hydrochloride Form V(12.9 gr., yield 87%).

Example 11

Preparation of Sertraline Hydrochloride Form V

Anhydrous sertraline hydrochloride (2 g) was stirred with 14 mL absolute ethanol and heated to reflux to obtain a clear solution. The solution was seeded with sertraline hydrochloride Form V and cooled naturally to room temperature. Massive precipitation was observed at about 50° C. The slurry was stirred at room temperature during 2 hours. The solid was filtered, washed with ethanol (3 mL) and dried overnight at 50–60° C. yielding 1.71 g (85.5%) of sertraline hydrochloride Form V.

Example 12

Preparation of Sertraline Hydrochloride Form V

Sertraline hydrochloride ethanolate (Form VI) (40 g) in 400 mL water was heated to 80° C. and complete dissolution was obtained The pH was adjusted to approximately one with hydrochloric acid and the solution was naturally cooled to room temperature and stirred for 2 hours. The solid was filtered and dried at 50° C. for approximately 16 hours, yielding sertraline hydrochloride Form V.

Example 13

Preparation of Sertraline Hydrochloride Form V

Sertraline hydrochloride ethanolate (Form VI) (2 g) was mechanically stirred with ethanol (0. 5 mL) at room temperature for 40 hours. The resulting solid was sertraline hydrochloride Form V.

Table I sets forth a summary of additional experiments conducted generally following procedures described above.

TABLE 1

PREPARATION OF SERTRALINE HCL-FORM V

Exp't	Method of Crystallization	XRD	Yield (%)
	SERTRALINE BASE AS STARTING MATERIAL		
A	Methanol/HCl gas	V	78.7
B	Methanol/HCl gas	V	69
C	Methanol/HCl aqueous	V	87.8
D	Ethanol/HCl gas	V	80.9
E	Water/HCl aqueous	V	96
F	Hexane/Isopropyl alcohol/HCl gas	V	89.9
G	Methanol/HCl aqueous/water	V	89
H	Isopropyl alcohol/HCl aqueous/water	V	78
I	Ethanol/HCl aqueous/evaporation of ethanol	V	96.1
J	Ethyl acetate/HCl aqueous/water/evaporation of ethyl acetate	V	96.1
K	Ethanol/isopropyl alcohol/HCl gas	V	81.8
L	Methanol/isopropyl alcohol/HCl gas	V	82.4
	SERTRALINE HCl AS STARTING MATERIAL		
M	Methanol (Form I and amorphous)	V	60
N	Ethanol (Form V)	V	85.5
O	Isopropyl alcohol/water (Form V)	V	28

PXRD=powder x-ray diffraction.

Example 14

Preparation of Sertraline Hydrochloride Form VII

1.003 g Sertraline hydrochloride Form V was stirred for 24 hours at room temperature in 20 mL water (HPLC grade). At the end of the stirring the mixture looked like a jelly suspension. The suspension was filtrated and the compound obtained was kept at cold conditions (4° C.) until analyzed by x-ray diffraction.

Example 15

Preparation of Sertraline Hydrochloride Form VII from Sertraline Hydrochloride Form VI

A solution of sertraline hydrochloride ethanolate (Form VI) (40 g) in water (400 mL) was heated at 80° C. and complete dissolution of sertraline hydrochloride ethanolate (Form VI) was obtained. The pH was adjusted to about 1 and the solution was allowed to cool to room temperature and then stirred for 2 additional hours. The solid was isolated by filtration and washed with water to yield sertraline hydrochloride Form VII.

Example 16

Preparation of Sertraline Hydrochloride Forms VIII and IX

Sertraline base (2.7 g) was suspended in 27 mL of water. This mixture was heated to 80° C. and treated with hydrochloric acid until about pH 1 was reached. A clear solution was obtained which on cooling gave a precipitate. After 2 hours stirring at room temperature the solid was isolated by filtration. This solid was characterized by powder x-ray diffraction (see FIG. 7). Drying for 24 hours at ~50° C. yielded 2.32 g (76.8%) of sertraline hydrochloride Form IX, characterized by powder x-ray diffraction, infra-red absorption, differential scanning calorimetry, and thermal gravimetric analysis as set forth above and depicted in FIGS. **8**, **10**, and **12**.

Example 17

Preparation of Sertraline Hydrochloride Form VIII

Sertraline hydrochloride ethanolate (Form VI) (40 g) was stirred with water (80 ml.) for 1 hour at room temperature. The slurry was filtrated and washed with water to yield sertraline hydrochloride hydrate—Form VIII.

Example 18

Preparation of Sertraline Hydrochloride Form VIII from Sertraline Hydrochloride Form II

Sertraline hydrochloride Form II (0.4 g) and water (8 mL) were stirred at room temperature over night. The solid was filtrated to yield sertraline hydrochloride hydrate Form VIII.

Example 19

Preparation of Sertraline Hydrochloride Form II From Form VI

A slurry of sertraline hydrochloride Form VI (50 g) and t-butyl-methyl-ether (150 ml) were heated to reflux and the reflux was continued for 1 hour. The slurry was then allowed to cool to room temperature and filtered. The solid was washed with t-butyl-methyl-ether (50 ml) and dried in a reactor under vacuum of 30 mm Hg with stirring. The dried solid so obtained is sertraline hydrochloride Form II (38.26 g: yield 86.7%).

Example 20

Preparation of Sertraline Hydrochloride Form II from Form VI

Sertraline hydrochloride Form VI (25 g) was stirred with acetone (250 ml) at room temperature for 2 hours. The solid material was filtered and washed twice with acetone (25 ml). The wet solid was dried in a vacuum agitated drier to afford sertraline hydrochloride Form II (20.09 g: yield 98.6%).

Example 21

Preparation of Polymorph II by Granulation of V

Sertraline hydrochloride Form V (2 g) and absolute ethanol (0.5 mL) were stirred in rotavapor at room temperature for 2 days. At the end of two days, the material contained sertraline hydrochloride Form II.

Example 22

Preparation of Polymorph II by Drying of the Sertraline Hydrochloride Form VI

Sertraline hydrochloride ethanolate-Form VI was dried at 105° C. under vacuum (<10 mm Hg) over 24 hours. The resulting dried material was Sertraline hydrochloride Form II mixed with sertraline hydrochloride Form V.

Example 23

Preparation of Sertraline Hydrochloride Form II

Sertraline base (3 g) was dissolved in acetone (10 mL). Isopropanol containing hydrogen chloride (20 mL) was added to the solution until the pH is ~2. The stirring was continued over night at room temperature. The resulting solid was filtrated, washed with acetone and dried to yield sertraline hydrochloride Form II (2.61 gr., yield 77.6%).

Example 24

Preparation of Sertraline Hydrochloride Form II

Sertraline hydrochloride Form V (10 gr.) was suspended in dimethylformamide (DMF) (30 mL). The heating was started and at about 70° C. a clear solution is obtained. The solution was cooled to room temperature and the solid was filtered. After drying at 80° C. for 24 hrs. Sertraline hydrochloride Form II was obtained (6.6 gr.,yield 66%).

Example 25

Preparation of Sertraline Hydrochloride Form X

In a 0.1 liter three-necked bottom round flask equipped with a mechanical stirrer, a condenser and a thermometer, 30 mL benzyl alcohol is added to 10 g sertraline hydrochloride. The suspension is heated to 100° C. when a clear solution is obtained. The solution is cooled 2 hours to 25° C. and the precipitate is filtered and washed with benzyl alcohol. After drying under vacuum at 80° C. for 24 hours, 6.2 g of sertraline hydrochloride polymorph X is obtained (yield 62%). The sertraline hydrochloride Form X was characterized by powder x-ray diffraction and infrared absorption analysis as set forth above and in FIG. **14** and FIG. **15**.

Example 26

Preparation of Sertraline Hydrochloride Ethanolate Form VI by Reslurry of Form I

Sertraline hydrochloride Form I (1 g) and absolute ethanol (20 mL) were stirred at room temperature for 24 hours. Filtration of the mixture yielded sertraline hydrochloride ethanolate-Form VI.

Example 27

Preparation of Sertraline Hydrochloride Ethanolate Form VI-by Reslurry of Form II

Sertraline hydrochloride Form II (1 g) and absolute ethanol (20 mL) were stirred at room temperature for 24 hours. Filtration of the mixture yielded sertraline hydrochloride ethanolate Form VI.

Example 28

Preparation of Sertraline Hydrochloride Ethanolate-Form VI-by Reslurry of Form V

Sertraline hydrochloride Form V (1 gr.) and ethanol absolute (20 mL.) were stirred at room temperature for 24 hrs. Filtration of the mixture yielded sertraline hydrochloride ethanolate Form VI.

Example 29

Preparation of Amorphous Sertraline Hydrochloride

Sertraline free base (10 g) was dissolved in ethyl acetate (690 mL). At room temperature, ether (690 mL) was added to the sertraline ethyl acetate solution and the solution was acidified with HCl gas to about pH 0.5. The resulting gelatinous suspension was stirred at room temperature over night. Filtration and air drying of the suspension yielded amorphous sertraline hydrochloride (9.39 gr., yield 83.8%).

Example 30

Preparation of Sertraline Hydrochloride Form III from Form V

Sertraline hydrochloride Form V was heated at 150° C. in a reactor under mechanical stirring for 24 hrs. The resulting material obtained was sertraline hydrochloride Form III.

Example 31

Preparation of Sertraline Hydrochloride from III from Form VI

Sertraline hydrochloride form VI was heated to 180° C. for 24 hours. The dried material is Sertraline hydrochloride Form III.

Example 32

Preparation of Sertraline Hydrochloride Form III from Form V

Sertraline hydrochloride Form V was heated at a temperature ≦180° C. for 24 hours. The resulting material was Sertraline hydrochloride Form III.

Example 33

Preparation of Amorphous Sertraline Hydrochloride

Sertraline hydrochloride Form V (10 g) was dissolved in water (2 L) and this solution was dried by the spray dryer technique. The material obtained in this way is Sertraline hydrochloride amorphous.

Example 34

Preparation of Amorphous Sertraline Hydrochloride by Sublimation

Sertraline hydrochloride Form I was sublimated at 190–200° C., at a vacuum of 30–0.1 mm Hg, using a laboratory—type sublimator. The resulting material was amorphous sertraline hydrochloride.

A similar procedure starting from Form V also gave amorphous sertraline hydrochloride.

Example 35

Preparation of Sertraline Hydrochloride Form V from Amorphous Sertraline

Sertraline hydrochloride amorphous was heated to 80° C. for 24 hours. The resulting product was sertraline hydrochloride Form V.

Example 36

Preparation of Sertraline Hydrochloride Amorphous by Precipitation from Toluene

Sertraline base (5.8 gr.) was dissolved in toluene (200 mL). HCl gas was bubbled (about pH 1.5) through the solution. A gel is formed. Filtration and drying at 50° C. for 16 hours gives amorphous sertraline hydrochloride (6.61 gr.).

It should be understood that some modification, alteration and substitution is anticipated and expected from those skilled in the art without departing from the teachings of the invention. Accordingly, it is appropriate that the following claims be construed broadly and in a manner consistent with the scope and spirit of the invention.

What is claimed is:

1. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) dissolving sertraline hydrochloride in a suitable solvent;

(b) removing the solvent; and

(c) drying to form sertraline hydrochloride Form V.

2. The process of claim 1, wherein the solvent is selected from the group consisting of methanol, ethanol, water, 1-methoxy-2-propanol, and, isopropyl alcohol and mixtures thereof.

3. The process of claim 2 wherein the solvent is methanol.

4. The process of claim 2 wherein the solvent is ethanol.

5. The process of claim 2 wherein the solvent is a mixture of isopropyl alcohol and water.

6. The process of claim 1, further comprising the steps of seeding the solution with sertraline hydrochloride Form V.

7. The process of claim 1 wherein the sertraline hydrochloride of step (a) is sertraline hydrochloride Form I.

8. The process of claim 1 wherein the sertraline hydrochloride of step (a) is sertraline hydrochloride Form VI.

9. The process of claim 1 wherein the sertraline hydrochloride of step (a) is sertraline hydrochloride Form VII.

10. The process of claim 1 wherein the sertraline hydrochloride of step (a) is sertraline hydrochloride Form VIII.

11. The process of claim 1 wherein the sertraline hydrochloride of step (a) is sertraline hydrochloride Form IX.

12. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) dissolving or suspending sertraline base in a solvent,

(b) adding hydrogen chloride or hydrochloric acid to reduce the pH of the solution or suspension; and

(c) isolating sertraline hydrochloride Form V.

13. The process of claim 12 wherein the pH of the solution or suspension of sertraline base and hydrogen chloride or hydrochloric acid in a solvent is about 0 to about 4.

14. The process of claim 12 wherein the solvent is selected from the group consisting of methanol, ethanol, water, ethyl acetate, isopropyl alcohol, hexane, and toluene, and mixtures thereof.

15. The process of claim 14 wherein the solvent is methanol.

16. The process of claim 14 wherein the solvent is ethanol.

17. The process of claim 14 wherein the solvent is water.

18. The process of claim 14 wherein the solvent is a mixture of hexane and isopropyl alcohol.

19. The process of claim 14 wherein the solvent is a mixture of isopropyl alcohol and water.

20. The process of claim 14 wherein the solvent is a mixture of ethanol and water.

21. The process of claim 14 wherein the solvent is a mixture of ethyl acetate and water.

22. The process of claim 14 wherein the solvent is a mixture of ethanol and isopropyl alcohol.

23. The process of claim 14 wherein the solvent is a mixture of methanol and isopropyl alcohol.

24. A process for making sertraline hydrochloride Form V comprising the step of drying sertraline hydrochloride ethanolate Form VI.

25. A process for making sertraline hydrochloride Form V comprising the step of drying sertraline hydrochloride Form VII.

26. A process for making sertraline hydrochloride Form V comprising the step of drying sertraline hydrochloride hydrate Form VIII.

27. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) suspending or dissolving sertraline hydrochloride in a solvent selected form the group consisting of ethanol, methanol and water and mixtures thereof; and

(b) isolating sertraline hydrochloride Form V.

28. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) dissolving sertraline hydrochloride Form VI in water;

(b) adding a sufficient amount of hydrochloric acid or hydrogen chloride to facilitate precipitation of sertraline hydrochloride Form V;

(c) removing the water; and

(d) isolating sertraline hydrochloride Form V.

29. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) heating amorphous sertraline hydrochloride for a time sufficient to effect the transformation to sertraline hydrochloride Form V; and

(b) isolating sertraline hydrochloride Form V.

30. The process of claim 29 wherein amorphous sertraline hydrochloride is heated to a temperature up to about 80° C.

31. Sertraline hydrochloride Form VI.

32. Sertraline hydrochloride Form VI ethanolate.

33. Sertraline hydrochloride Form VI methanolate.

34. Sertraline hydrochloride Form VI, which is characterized by an x-ray powder diffraction pattern comprising peaks at about 7.3°±0.2, 12.1°±0.2, 12.7°±0.2, 22.0°±0.2, 22.9°±0.2, 23.2°±0.2, 24.0°±0.2, and 24.5°±0.2 degrees two-theta.

35. A pharmaceutical composition comprising a therapeutically effective amount of sertraline hydrochloride Form VI and a pharmaceutically acceptable carrier.

36. A process for making sertraline hydrochloride Form VI comprising the steps of:

(a) dissolving sertraline base in a solvent;

(b) adding hydrogen chloride gas to the solution; and

(c) isolating sertraline hydrochloride Form VI without further drying.

37. The process of claim 36 wherein the isolation step comprises precipitation of sertraline hydrochloride Form VI followed by filtration.

38. The process of claim 36 wherein the solvent is ethanol or methanol.

39. The product of the process of claim 36.

40. A process for making sertraline hydrochloride Form VI comprising the steps of:

(a) dissolving or suspending sertraline hydrochloride in ethanol or methanol;

(b) stirring for a time sufficient to induce the transformation of sertraline hydrochloride to sertraline hydrochloride Form VI; and

(c) isolating sertraline hydrochloride Form VI.

41. The process of claim 40 wherein the sertraline hydrochloride of step (a) is Form I.

42. The process of claim 40 wherein the sertraline hydrochloride of step (a) is Form II.

43. The process of claim 40 wherein the sertraline hydrochloride of step (a) is Form V.

44. Sertraline hydrochloride Form VII.

45. A pharmaceutical composition comprising a therapeutically effective amount of sertraline hydrochloride Form VII, and a pharmaceutically acceptable carrier.

46. A process for making sertraline hydrochloride Form VII comprising the steps of:

(a) suspending sertraline hydrochloride Form V in water; and

(b) filtering the suspension without drying.

47. The product of the process of claim 40.

48. A process for making sertraline hydrochloride Form VII comprising the steps of:

(a) dissolving sertraline hydrochloride ethanolate Form VI in water such that the sertraline hydrochloride Form VI is converted to sertraline hydrochloride Form VII;

(b) filtering the sertraline hydrochloride Form VII; and

(c) washing the filtered sertraline hydrochloride Form VII with water.

49. A process for making sertraline hydrochloride Form VII comprising the steps of:

(a) dissolving sertraline hydrochloride ethanolate Form VI in water;

(b) heating the solution to facilitate dissolution of sertraline hydrochloride Form VI; and

(c) isolating sertraline hydrochloride Form VII without drying.

50. The process of claim 49 comprising the additional step of lowering the pH to facilitate precipitation of sertraline hydrochloride Form V.

51. Sertraline hydrochloride Form VII, which is characterized by an x-ray powder diffraction pattern comprising the peaks at about 4.0°±0.2, 8.0°±0.2, 11.6°±0.2, 12.0°±0.2, 13.8°±0.2, 16.5°±0.2, 20.0°±0.2, 22.8°±0.2, 24.1°±0.2, 25.0°±0.2, 26.62°±0.2, 30.7°±0.2, 34.7°±0.2 2 two-theta.

52. Sertraline hydrochloride hydrate Form VIII.

53. Sertraline hydrochloride Form VIII, which is characterized by an x-ray powder diffraction pattern comprising peaks at about 4.7°±0.2, 16.3°±0.2, 17.8°±0.2, 19.6°±0.2, 23.2°±0.2, 24.2°±0.2, 25.1°±0.2, and 26.0°±0.2 two-theta.

54. A pharmaceutical composition comprising a therapeutically effective amount of sertraline hydrochloride Form VIII, and a pharmaceutically acceptable carrier.

55. A process for making sertraline hydrochloride Form VIII comprising the steps of:

(a) suspending sertraline base in water;

(b) adding hydrochloric acid; and

(c) filtrating the precipitate so obtained without further drying.

56. The product of the process of claim 55.

57. A process for making sertraline hydrochloride Form VII comprising the steps of:

(a) suspending or dissolving sertraline hydrochloride ethanolate Form VI in water; and

(b) isolating sertraline hydrochloride Form VIII.

58. A process for making sertraline hydrochloride Form VIII comprising the steps of:

(a) suspending or dissolving sertraline hydrochloride Form II in water; and

(b) isolating sertraline hydrochloride Form VIII.

59. Sertraline hydrochloride Form IX.

60. Sertraline hydrochloride Form IX, which is characterized by an x-ray powder diffraction pattern comprising peaks at about 5.1°±0.2, 14.2°±0.2, 15.8°±0.2, 16.8°±0.2, 19.2°±0.2, 19.7°±0.2, 22.4°±0.2, 23.2°±0.2, 25.3°±0.2 and 26.1°±0.2 two-theta.

61. A pharmaceutical composition comprising a therapeutically effective amount of sertraline hydrochloride Form IX, and a pharmaceutically acceptable carrier.

62. A process for making sertraline hydrochloride Form IX comprising the steps of:

(a) suspending sertraline base in water;

(b) adding hydrochloric acid such that a precipitate is formed;

(c) filtrating the precipitate; and

(d) drying the precipitate.

63. The product of the process of claim 62.

64. A process for making sertraline hydrochloride Form IX comprising the step of drying sertraline hydrochloride Form VIII and isolating sertraline hydrochloride Form IX.

65. A process for making sertraline hydrochloride Form X comprising the steps of:

(a) suspending sertraline hydrochloride in benzyl alcohol;

(b) heating the suspension to facilitate dissolution;

(c) cooling the solution such that a precipitate is formed;

(d) heating the solution to about 80° C.; and

(e) isolating sertraline hydrochloride Form X.

66. The process of claim 65 wherein the sertraline hydrochloride Form X is isolated by filtration and washing with benzyl alcohol and heating.

67. The product of the process of claim 65.

68. Sertraline hydrochloride Form X.

69. Sertraline hydrochloride Form X which is characterized by an x-ray powder diffraction pattern comprising peaks at about 15.0°±0.2, 16.0°±0.2, 16.5°±0.2, 17.0°±0.2, 18.1°±0.2, 21.0°±0.2, 22.4°±0.2, 24.9°±0.2, 25.4°±0.2, 26.2°±0.2, 27.1°±0.2, 28.4°±0.2, and 29.0°±0.2 degrees two-theta.

70. A pharmaceutical composition comprising a therapeutically effective amount of sertraline hydrochloride Form X, and a pharmaceutically acceptable carrier.

71. A process for making Form II comprising the steps of:

(a) heating sertraline hydrochloride Form V for a time sufficient to induce the transformation of sertraline hydrochloride Form V to sertraline hydrochloride Form III; and

(b) isolating sertraline hydrochloride Form III.

72. The process of claim 71 wherein sertraline hydrochloride Form V is heated to about 150° C. to about 180° C.

73. A process for making sertraline hydrochloride Form III comprising the steps of:

(a) heating sertraline hydrochloride Form VI for a time sufficient to induce the transformation of sertraline hydrochloride Form VI to sertraline hydrochloride Form III; and

(b) isolating sertraline hydrochloride Form III.

74. The process of claim 73 wherein sertraline hydrochloride is heated to about 180° C.

75. A process for making amorphous sertraline hydrochloride comprising the steps of:

(a) suspending or dissolving sertraline base in a non-polar organic solvent;

(b) adding gaseous hydrochloric acid; and

(c) and isolating amorphous sertraline hydrochloride.

76. The process of claim 75 wherein the solvent is selected from the group consisting of ether, toluene and t-butyl-methyl ether.

77. A process for making amorphous sertraline hydrochloride comprising the steps of:

(a) spray drying of sertraline hydrochloride; and

(b) isolating amorphous sertraline hydrochloride.

78. Amorphous sertraline hydrochloride, which is characterized by the x-ray diffraction pattern substantially as depicted in FIG. 2.

79. Sertraline hydrochloride ethanolate.

80. Sertraline hydrochloride methanolate.

81. A method for the treatment of depression, comprising the step of administering to a human subject in need of such treatment the pharmaceutical composition of claim 35.

82. A method for the treatment of depression, comprising the step of administering to a human subject in need of such treatment the pharmaceutical composition of claim 45.

83. A method for the treatment of depression, comprising the step of administering to a human subject in need of such treatment the pharmaceutical composition of claim 54.

84. A method for the treatment of depression, comprising the step of administering to a human subject in need of such treatment the pharmaceutical composition of claim 61.

85. A method for the treatment of depression, comprising the step of administering to a human subject in need of such treatment the pharmaceutical composition of claim 70.

86. A process for preparing amorphous sertraline hydrochloride comprising sublimating sertraline hydrochloride to obtain a sublimate, and recovering the sublimate as amorphous sertraline hydrochloride.

87. The process of claim 86, wherein the sertraline hydrochloride sublimated is Form I or V.

88. A process for preparing amorphous sertraline hydrochloride comprising spray drying an aqueous solution of sertraline hydrochloride.

89. The process of claim 88, wherein the sertraline hydrochloride that is spray dried is Form V.

* * * * *

EXHIBIT C

US006495721B1

(12) **United States Patent**
Schwartz et al.

(10) **Patent No.: US 6,495,721 B1**
(45) **Date of Patent: Dec. 17, 2002**

(54) **SERTRALINE HYDROCHLORIDE FORM II AND METHODS FOR THE PREPARATION THEREOF**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/575,634**

(22) Filed: **May 22, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/448,985, filed on Nov. 24, 1999.
(60) Provisional application No. 60/182,159, filed on Feb. 14, 2000, and provisional application No. 60/147,888, filed on Aug. 9, 1999.

(51) **Int. Cl.**[7] **C07C 211/42**
(52) **U.S. Cl.** **564/308**
(58) **Field of Search** 564/308

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Primary Examiner—Samuel Barts
(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon

(57) **ABSTRACT**

The present invention is directed to Form II of sertraline hydrochloride and novel methods for its preparation. According to the present invention, sertraline hydrochloride Form II may be produced directly form sertraline base or sertraline mandelate. It may also be produced from sertraline hydrochloride solvate and hydrate forms, and crystallized from new solvent systems. Pharmaceutical compositions containing sertraline hydrochloride Form II and methods of treatment using such pharmaceutical compositions are also disclosed.

22 Claims, 3 Drawing Sheets

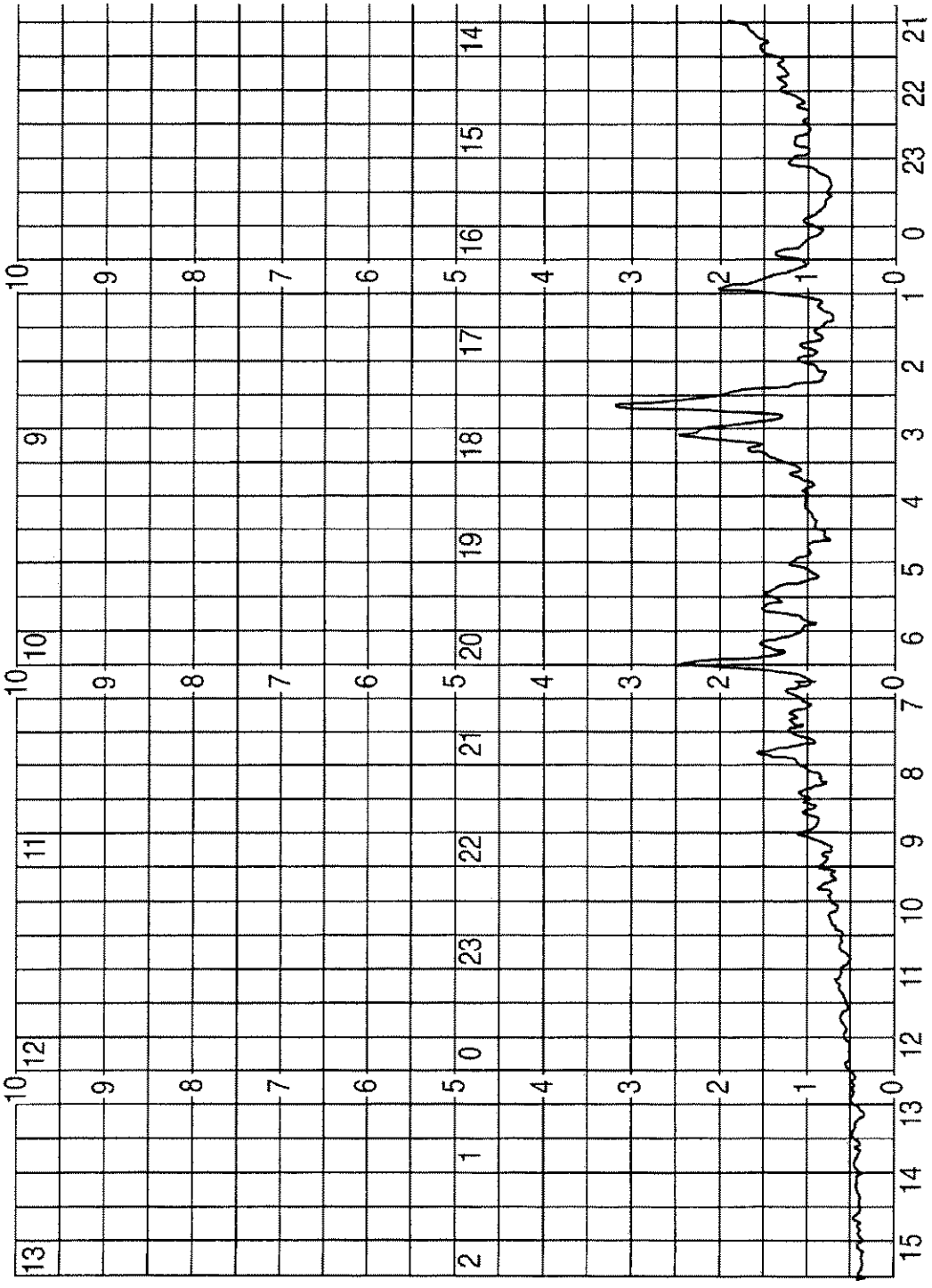


FIG. 1

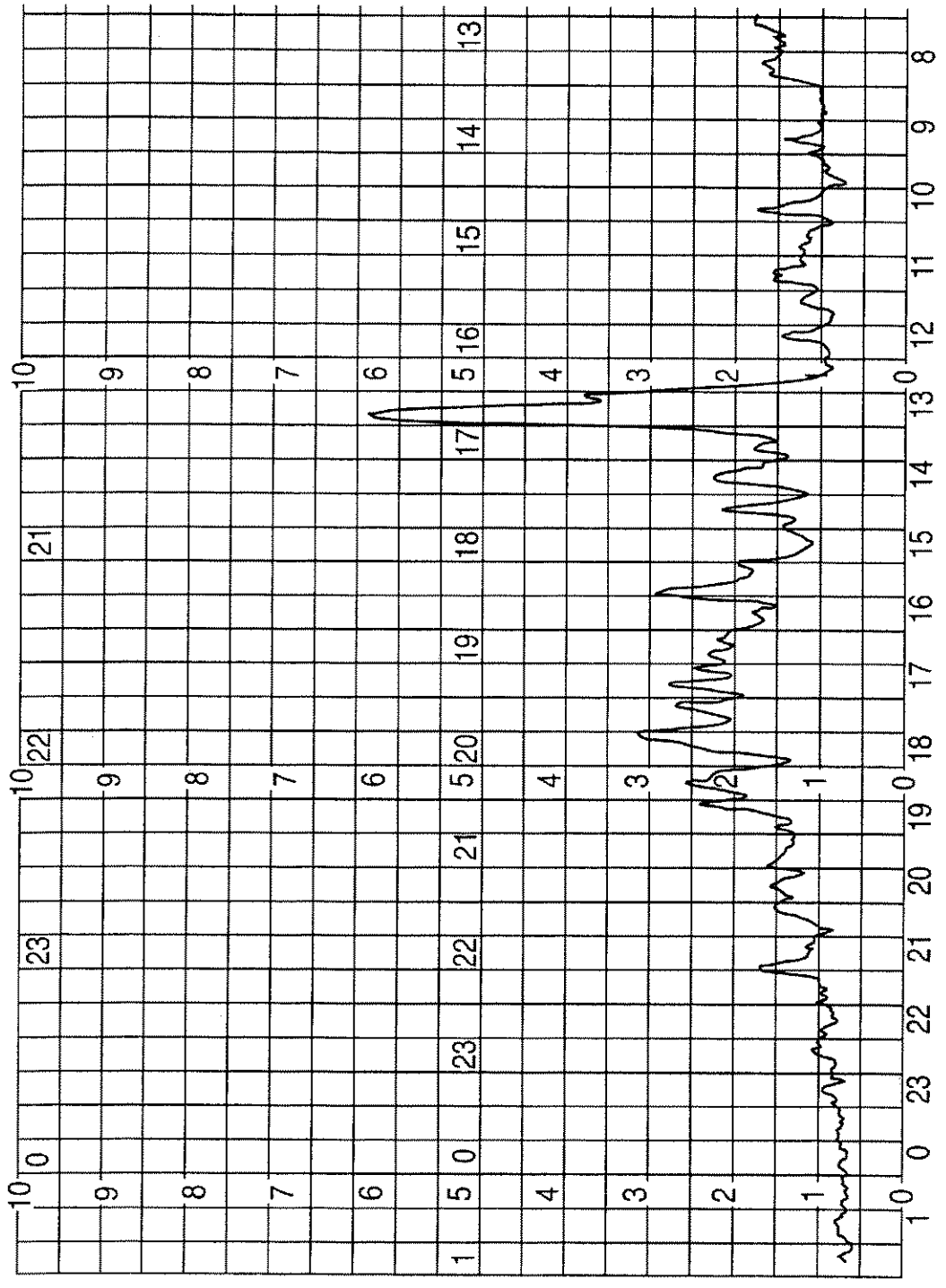


FIG. 2

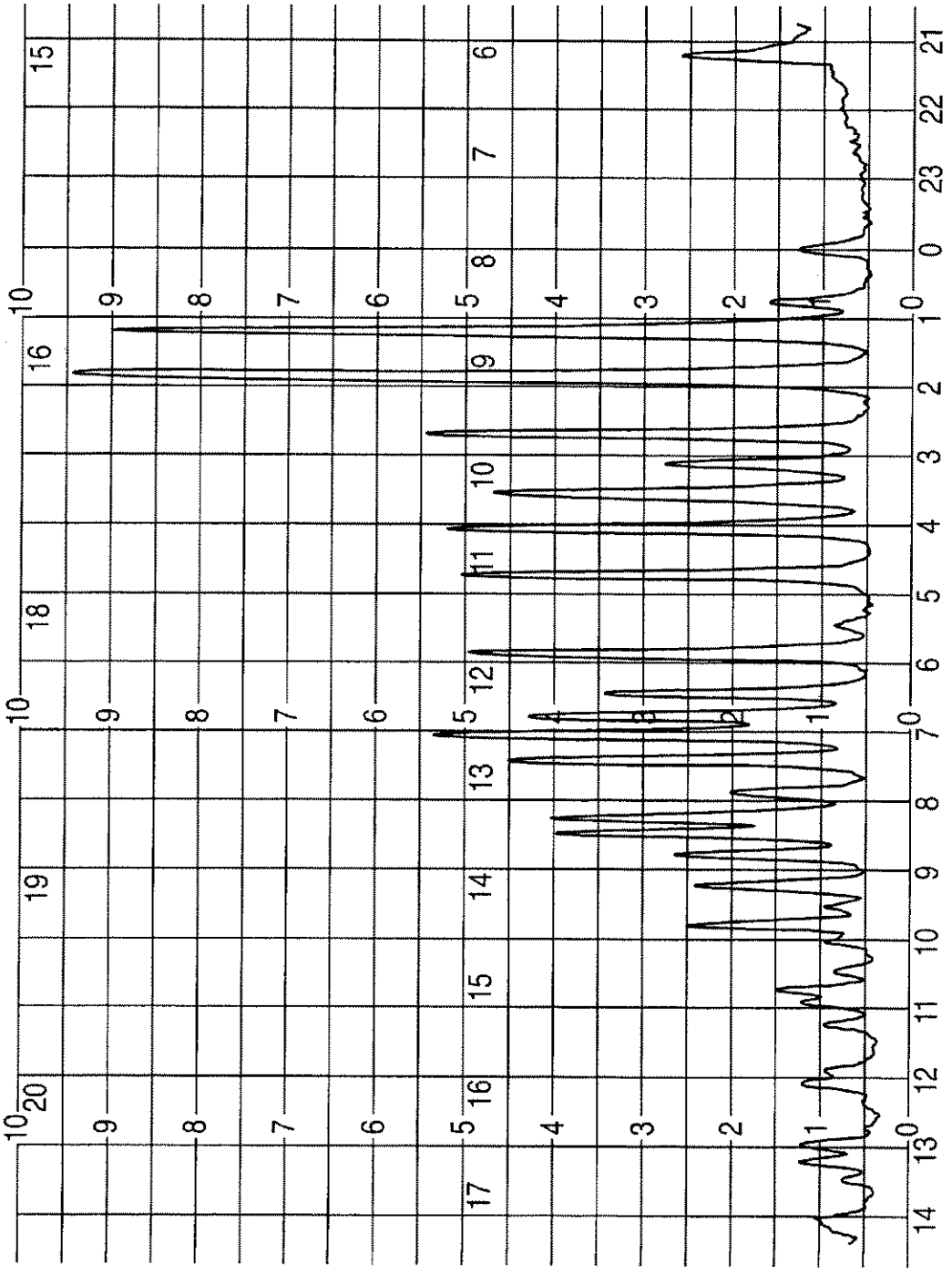


FIG. 3

SERTRALINE HYDROCHLORIDE FORM II AND METHODS FOR THE PREPARATION THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

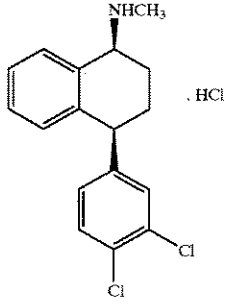
This application claims the benefit of provisional application Serial No. 60/182,159, filed Feb. 14, 2000, and is a continuation-in-part of application Ser. No. 09/448,985, filed Nov. 24, 1999, which claims the benefit of provisional application No. 60/147,888, filed Aug. 9, 1999. The contents of each of these applications are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to a novel crystalline form of sertraline hydrochloride, and reproducible methods for its preparation.

BACKGROUND OF THE INVENTION

Sertraline hydrochloride, (1S-cis)-4-(3,4dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride, having the formula



is approved, under the trademark Zoloft®, by the U.S. Food and Drug Administration, for the treatment of depression, obsessive-compulsive disorder and panic disorder.

U.S. Pat. No. 4,536,518 ("the '518 patent") describes the preparation of sertraline hydrochloride with a melting point of 243–245° C. by treating an ethyl acetate/ether solution of the free base with gaseous hydrogen chloride. The solid state properties of the sertraline hydrochloride so produced are not otherwise disclosed.

U.S. Pat. No. 5,734,083 describes the preparation of a form of sertraline hydrochloride denominated polymorph "T1."

According to U.S. Pat. No. 5,248,699 ("the '699 patent"), the sertraline hydrochloride produced by the method of the '518 patent has a crystalline form denominated "Form II." The '699 patent discloses four other polymorphs of sertraline hydrochloride designated Forms I, III, IV, and V, and characterizes them by single crystal x-ray analysis, powder x-ray diffraction, infra-red spectroscopy, and differential scanning calorimetry. The '699 patent reports that Form II is produced by rapid crystallization of sertraline hydrochloride from an organic solvent, including isopropyl alcohol, ethyl acetate or hexane, and generally describes methods for making sertraline hydrochloride Forms I–V. According to this patent, the preferential formation of Forms I, II or IV in an acidic solution consisting of isopropyl alcohol, hexane, acetone, methyl isobutyl ketone, glacial acetic acid or, preferably, ethyl acetate, depends on the rapidity of crystallization. The only method described in this patent for making Forms II and IV is by the rapid crystallization of sertraline hydrochloride from an organic solvent such as those listed above.

The experimental procedure for the preparation of sertraline hydrochloride described in the '518 patent, was repeated in the laboratory. According to the '699 patent, the '518 procedure produces sertraline hydrochloride Form II. Four experiments were performed according to the description in the '518 patent. By following the procedures described in the '699 patent for preparation of sertraline hydrochloride Form II, we were unable to obtain sertraline hydrochloride Form II. Thus there remains a need for reproducible methods for the preparation of sertraline hydrochloride Form II.

SUMMARY OF THE INVENTION

The present invention relates to a process for making sertraline hydrochloride Form II comprising the steps of dissolving sertraline base or sertraline mandelate in an organic solvent to form a solution; adding hydrogen chloride to the solution; heating the solution to a temperature between about room temperature and about reflux for a time sufficient to induce the formation of sertraline hydrochloride Form II; and isolating sertraline hydrochloride Form II.

The present invention also relates to a process for making sertraline hydrochloride Form II comprising the steps of dissolving sertraline hydrochloride in dimethylformamide, cyclohexanol, acetone or a mixture thereof; heating the solution for a time sufficient to effect transformation to sertraline hydrochloride Form II; and isolating sertraline hydrochloride Form II.

The present invention further relates to a process for making sertraline hydrochloride Form II comprising the steps of granulating sertraline hydrochloride Form V in ethanol or methanol; and stirring the mixture of sertraline hydrochloride Form V and ethanol or methanol for a time sufficient to induce transformation to sertraline hydrochloride Form II.

The present invention still further relates to a process for making a mixture of sertraline hydrochloride Form II and Form V comprising the steps of heating sertraline hydrochloride ethanolate Form VI at up to 1 atmosphere pressure; and isolating a mixture of sertraline hydrochloride Form II and Form V.

The present invention still further relates to a process for making sertraline hydrochloride Form II comprising the steps of suspending a water or solvent adduct of sertraline hydrochloride in a solvent selected from the group consisting of acetone, t-butyl-methyl ether, cyclohexane, n-butanol, and ethyl acetate such that a slurry is formed, for a time sufficient to effect transformation to sertraline hydrochloride Form II; and filtering the slurry to isolate sertraline hydrochloride Form II.

The present invention still further relates to sertraline hydrochloride Form II, characterized by an x-ray powder diffraction pattern comprising peaks at about 5.5, 11.0, 12.5, 13.2, 14.7, 16.4, 17.3, 18.1, 19.1, 20.5, 21.9, 22.8, 23.8, 24.5, 25.9, 27.5, and 28.0 degrees two theta; pharmaceutical compositions for the treatment of depression comprising sertraline hydrochloride Form II together with a pharmaceutically acceptable carrier, and a method for treating depression comprising the step of administering to a subject in need of such treatment a therapeutically effective amount of the such a pharmaceutical composition.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride prepared by the methods of U.S. Pat. No. 4,536,518.

FIG. **2** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride prepared by the methods of U.S. Pat. No. 5,248,699.

FIG. **3** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form II prepared by the methods of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Form II from Sertraline Base or Sertraline Mandelate

The present invention provides new processes for making sertraline hydrochloride Form II from sertraline base or sertraline mandelate. Sertraline base may be made by methods known in the art, including the methods of the '518 patent. Sertraline base is dissolved in a suitable solvent. Suitable solvents include ethyl acetate, acetone, t-methylbutyl ether, isopropyl alcohol, n-butanol, t-butanol, isobutanol, hexane, and cyclohexane, and mixtures thereof The pH of the sertraline base solution is lowered by the addition of hydrogen chloride, which may result in a temperature increase. As used herein, "hydrogen chloride" includes both gaseous hydrogen chloride and aqueous hydrogen chloride (i.e. hydrochloric acid). Hydrogen chloride also may be added as a solution with an organic solvent, such as a solution of isopropyl alcohol and hydrogen chloride, n-butanol and hydrogen chloride, acetone and hydrogen chloride, or the like. The solution of sertraline base or sertraline mandelate in the solvent is heated to a temperature between about room temperature and the reflux temperature of the solvent and maintained at that temperature for a period of time sufficient to effect the transformation to sertraline hydrochloride Form II. Preferably the solution is heated to a temperature between about 45° C. and the reflux temperature of the solvent. Most preferably the solution is heated to at or about the reflux temperature of the solvent. Upon cooling of the mixture, for example to room temperature, sertraline hydrochloride Form II is isolated by filtration.

In a preferred variation of this method, the solution of sertraline base or sertraline mandelate in a solvent is heated to the reflux temperature of the solvent. The mixture is refluxed for a time sufficient to effect the transformation to sertraline hydrochloride Form II. Preferably the mixture is refluxed for about 1 to 4 hours.

Numerous experiments were performed in an attempt to repeat the procedure described in U.S. Pat. No. 4,536,518 for preparing Form II wherein sertraline base was dissolved in ethyl acetate, ether was added and the solution was acidified with gaseous hydrogen chloride. The material obtained after filtration and air drying was sertraline hydrochloride amorphous, not Form II as was expected. These experiments are set forth in Examples 13–16 below.

The x-ray powder diffraction graphs for the products of each of these experiments are equivalent, containing peaks at 11.0, 12.0, 15.4, 16.2, 22.4, 22.9 degree two-theta (See FIG. **1** for a representative example). FIG. **1** does not contain the typical peaks of sertraline hydrochloride Form II, indicating an absence of sertraline hydrochloride Form II in those samples. Thus, none of these experiments, which follow the procedure described in the '518 patent for preparation of sertraline hydrochloride Form II, leads to sertraline hydrochloride Form II.

The '699 patent provides experimental procedures for preparation of sertraline hydrochloride. The '699 patent does not provide experimental procedure for preparation of sertraline hydrochloride Form II, but it is mentioned that sertraline hydrochloride Form II may be prepared by "rapid crystallization" from the same solvents.

The procedure of the '699 patent was repeated in an attempt to prepare sertraline hydrochloride form 11 from ethyl acetate. In a trial of the methods according to the '699 patent: An aqueous solution of sodium hydroxide, 10%, was added to a slurry of sertraline mandelate crystals (44.6 g) in ethyl acetate (290 mL), until complete dissolution. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (280 mL) and combined with the organic phase. The resulting organic solution was washed with water (5×100 mL) then with brine (100 mL) and concentrated on a rotavapor to a volume of 356 mL. The concentrated solution was cooled to 58° C. and seeded with sertraline hydrochloride Form II. Concentrated hydrochloric acid (32%, 8.1 mL) was added to this solution. The solution was then rapidly cooled to 30° C. over 5 minutes. A heavy gel was obtained and the stirring was continued overnight. The solid was filtrated, washed with ethyl acetate and dried at 50° C. The dried solid, sertraline hydrochloride, was not sertraline hydrochloride Form II, as shown by the x-ray diffraction pattern of FIG. **2**.

By following the procedures described in the '699 patent for preparation of sertraline hydrochloride Form II, we did not obtain sertraline hydrochloride Form II. It is thus apparent that neither the '699 patent nor the '518 patent disclose a useful method for the preparation of sertraline hydrochloride Form II.

Form II from Sertraline Hydrochloride

The present invention also provides new processes for making sertraline hydrochloride Form II from sertraline hydrochloride Form V by granulation. In the conversion of sertraline hydrochloride Form V to sertraline hydrochloride Form II, sertraline hydrochloride Form V is combined with a small amount of ethanol or methanol. The mixture of sertraline hydrochloride Form V and ethanol or methanol is stirred for at least a period of at least a few hours, up to several days, preferably about two days, to induce the transformation of Form V to Form II. Sertraline hydrochloride Form II is then isolated by filtration.

The present invention also provides new processes for making sertraline hydrochloride Form II by recrystallization of sertraline hydrochloride under heating conditions. In the conversion of sertraline hydrochloride to sertraline hydrochloride Form II, sertraline hydrochloride is dissolved in a suitable organic solvent. The solution is then heated for a time sufficient to effect transformation to sertraline hydrochloride Form II. Suitable solvents include dimethylformamide, cyclohexanol and acetone. Dimethylformamide is preferred. The suspension may be heated to a temperature between about 70° C. and 120° C. Sertraline hydrochloride Form II is then isolated by filtration.

The present invention provides new processes for making sertraline hydrochloride Form II from sertraline hydrochloride Form VI, Form VII or Form VIII by reslurry in organic solvents at temperatures between 25–80° C., followed by drying. Sertraline hydrochloride Form VI may be made following the methods of Examples 2 and 3. Sertraline hydrochloride Form VII is a water adduct and may be made by the methods of Examples 19 and 20. Sertraline hydrochloride Form VIII may be made by the methods of Examples 17 and 18. The methods provided in the present invention have advantages over the rapid recrystallization method of U.S. Pat. No. 5,248,699. The method of the present invention does not require complete dissolution of sertraline hydrochloride, controlling the rate of heating or cooling of a sertraline solution, or controlling the rate of crystallization. The present method utilizes less solvent than the method of the '699 patent, since the sertraline hydrochloride starting material need not be completely dissolved.

In the conversion of sertraline hydrochloride Form VI, Form VII or Form VIII to sertraline hydrochloride Form II, according to the present invention, sertraline hydrochloride Form VI, Form VII water adduct, or Form VIII is combined with an aprotic organic solvent to form a slurry. Suitable solvents include n-butanol, acetone, t-butyl-methyl ether (MTBE), ethyl acetate and cyclohexane. The conversion may take place at room temperature, but preferably the sertraline hydrochloride Form VI, Form VII water adduct, or VIII and solvent are heated to temperatures between 25° C. and 80° C. About 1 to about 10 volumes of solvent are preferred, based on the weight of the sertraline hydrochloride starting material. See Examples 8 (3 volumes of solvent) and 9 (5 volumes of solvent) below. Smaller amounts of solvent will also effect the transformation, albeit in some instances more slowly. The reaction is carried out for a time sufficient to convert the Form VI, Form VII or Form VIII to Form VI. We have not observed any further conversion of Form II upon treatment under these conditions for times longer than the minimum time necessary to effect the transformation.

The present invention also provides new processes for making a mixture of sertraline hydrochloride Form II and sertraline hydrochloride Form V. In this embodiment of the present invention, sertraline hydrochloride Form VI is heated to induce the transformation of sertraline hydrochloride Form VI to a mixture of both sertraline hydrochloride Form II and sertraline hydrochloride Form V. In this embodiment of the present invention, the heating of sertraline hydrochloride Form VI may be done under reduced pressure or atmospheric pressure.

Pharmaceutical Compositions Containing Sertraline Hydrochloride Polymorphs

In accordance with the present invention, sertraline hydrochloride Form II as prepared by the new methods disclosed herein may be used in pharmaceutical compositions that are particularly useful for the treatment of depression, obesity, chemical dependencies or addictions, premature ejaculation, obsessive-compulsive disorder and panic disorder. Such compositions comprise at least one of the new crystalline forms of sertraline hydrochloride with pharmaceutically acceptable carriers and/or excipients known to one of skill in the art.

For example, these compositions may be prepared as medicaments to be administered orally, parenterally, rectally, transdermally, bucally, or nasally. Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or gelatin capsules, sub-lingual tablets, syrups and suspensions. Suitable forms of parenteral administration include an aqueous or non-aqueous solution or emulsion, while for rectal administration suitable forms for administration include suppositories with hydrophilic or hydrophobic vehicle. For topical administration the invention provides suitable transdermal delivery systems known in the art, and for nasal delivery there are provided suitable aerosol delivery systems known in the art.

Suitable non-toxic pharmaceutically acceptable carriers and/or excipients will be apparent to those skilled in the art of pharmaceutical formulation, and are discussed in detail in the tet entitled *Remington's Pharmaceutical Science*, 17th edition (1985), the contents of which are incorporated herein by reference. Obviously, the choice of suitable carriers will depend on the exact nature of the particular dosage form, e.g. for a liquid dosage form, whether the composition is to be formulated into a solution, suspension, gel, etc, or for a solid dosage form, whether the composition is to be formulated into a tablet, capsule, caplet or other solid form, and whether the dosage form is to be an immediate- or controlled-release product.

Experimental Details

The powder X-ray diffraction patterns were obtained by methods known in the art using a Philips X-ray powder diffractometer, Goniometer model 1050/70 at a scanning speed of 2° per minute, with a Cu radiation of λ=1.5418 Å

EXAMPLES

The present invention will now be further explained in the following examples. However, the present invention should not be construed as limited thereby. One of ordinary skill in the art will understand how to vary the exemplified preparations to obtain the desired results.

Example 1

Preparation of Sertraline Base

Sertraline mandelate was prepared according to procedures in U.S. Pat. No. 5,248,699. Sertraline mandelate (5 g) was stirred at room temperature with 50 mL ethyl acetate. Aqueous sodium hydroxide was added dropwise until the sertraline mandelate was completely neutralized. The phases were separated and the organic phase was dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure resulting sertraline base as an oil (3.2 g).

Example 2

Preparation of Sertraline Hydrochloride Ethanolate Form VI by Reslurry of Form I

Sertraline hydrochloride Form I (1 g) and absolute ethanol (20 mL) were stirred at room temperature for 24 hours. Filtration of the mixture yielded sertraline hydrochloride ethanolate Form VI.

Example 3

Preparation of Sertraline Hydrochloride Ethanolate Form VI by Reslurry of Form V

Sertraline hydrochloride Form V (1 g) and ethanol absolute (20 mL) were stirred at room temperature for 24 hrs. Filtration of the mixture yielded sertraline hydrochloride ethanolate Form VI.

Example 4

Preparation of Sertraline Hydrochloride Form II

Sertraline base (3 g) was dissolved in acetone (10 mL). Isopropanol containing hydrogen chloride (20 mL) was added to the solution until the pH is ~2. The stirring was continued overnight at room temperature. The resulting solid was filtered, washed with acetone and dried to yield sertraline hydrochloride Form II (2.61 g, yield 77.6%).

Example 5

Preparation of Sertraline Hydrochloride Form II in n-Butanol

HCl (g) was bubbled through a solution of sertraline base (33 g) in n-butanol (264 mL). The temperature rose to about 45° C. A gel-like solid was formed. The addition of HCl (g) was continued until pH 0.5 was reached. Then the stirring was continued at room temperature for 2.5 h. During the stirring the solid became a fine crystalline solid. The solid

was filtered, washed with n-butanol (2×10 mL) and dried at 80° C. for 24 h. The product is sertraline hydrochloride Form II. The x-ray powder diffraction spectrum obtained is FIG. 3.

Example 6

Preparation of Sertraline Hydrochloride Form II

Sertraline hydrochloride Form V (10 g) was suspended in dimethylformamide (DMF) (30 mL). Heating was started and at about 70° C. a clear solution is obtained. The solution was cooled to room temperature and the solid was filtered. After drying at 80° C. for 24 hrs., sertraline hydrochloride Form II was obtained (6.6 g, yield 66%).

Example 7

Preparation of Sertraline Hydrochloride Form II by Granulation of Form V

Sertraline hydrochloride Form V (2 g) and absolute ethanol (0.5 mL) were stirred in a rotavapor at room temperature for 2 days. At the end of two days, the material contained sertraline hydrochloride Form II.

Example 8

Preparation of Sertraline Hydrochloride Form II from Form VI

A slurry of sertraline hydrochloride Form VI (50 g) and t-butyl-methyl ether (150 mL) were heated to reflux and the reflux was continued for 1 hour. The slurry was then allowed to cool to room temperature and filtered. The solid was washed with t-butyl-methyl ether (50 mL) and dried in a reactor under vacuum of 30 mm Hg with stirring. The dried solid so obtained is sertraline hydrochloride Form II (38.26 g: yield 86.7%).

Example 9

Preparation of Sertraline Hydrochloride Form II from Form VI

Sertraline hydrochloride Form VI (25 g) was stirred with acetone (250 mL) at room temperature for 2 hours. The solid material was filtered and washed twice with acetone (25 mL). The wet solid was dried in a vacuum agitated drier to afford sertraline hydrochloride Form II (20.09 g: yield 98.6%).

Example 10

Preparation of Sertraline Hydrochloride Form II and Sertraline Hydrochloride Form V by Drying Form VI

Sertraline hydrochloride ethanolate Form VI was dried at 105° C. under vacuum (<10 mm Hg) over 24 hours. The resulting dried material was sertraline hydrochloride Form II mixed with sertraline hydrochloride Form V.

Example 11

Preparation of Sertraline Hydrochloride Form II from Sertraline Mandelate in n-Butanol

Sertraline mandelate (20 g) and n-butanol were stirred at room temperature. The mixture was acidified with hydrogen chloride until pH 0 was reached. During the acidification the temperature of the reaction mixture rose to ~50° C. After the natural cooling to room temperature, the mixture was stirred at room temperature for two hours. The solid was filtrated, washed with n-butanol and dried at 80° C. to afford sertraline hydrochloride Form II (9.02 g).

Example 12

Preparation of Sertraline Hydrochloride Form I from Sertraline Hydrochloride Form VIII

Sertraline hydrochloride Form VIII (13 g) was heated in acetone (130 mL) at reflux for 1 hour. The slurry was than cooled to room temperature and the solid was filtrated and washed with acetone (2×10 mL). After drying sertraline hydrochloride Form II was obtained (7.9 g).

Example 13

An aqueous sodium hydroxide solution, 10%, was added drop-wise to a slurry of sertraline mandelate crystals (10 g) in ethyl acetate (650 mL), until complete dissolution was obtained (25 mL). After separation of the phases, the organic phase was washed with water (300 mL) and then dried with $MgSO_4$. The organic solution was diluted with ether (690 mL) and gaseous hydrochloric acid was bubbled through the solution until pH 1.3 was reached. The addition of hydrogen chloride resulted in a temperature increase to about 30° C. The resulting slurry of sertraline was stirred at room temperature overnight. The solid was then isolated by filtration, washed twice with ether (2×20 mL) and air dried. The dried solid, sertraline hydrochloride, was not sertraline hydrochloride Form II, as shown in FIG. 1.

Example 14

An aqueous sodium hydroxide solution, 10%, was added drop-wise to a slurry of sertraline mandelate crystals (15 g) in ethyl acetate (810 mL), until complete dissolution was obtained (35 mL). The organic and aqueous phases were separated and, the organic phase was dried over $MgSO_4$ The organic solution was then diluted with ether (820 mL) and gaseous hydrogen chloride (2.36 g, 2 eq.) was bubbled through the solution until pH 1.5 was reached. The temperature was about 25° C. The slurry was stirred at room temperature overnight. The solid was filtrated, washed with ether (2×15 mL) and air-dried. The dried solid, sertraline hydrochloride, was not sertraline hydrochloride Form II.

Example 15

An aqueous sodium hydroxide solution, 10%, was added drop-wise to a slurry of sertraline mandelate crystals (15 g) in ethyl acetate (810 mL), until complete dissolution was obtained. The organic and aqueous phases were separated and the organic phase was dried over $MgSO_4$ and diluted with an equal volume of ether (820 mL). Gaseous hydrochloric acid (4.82 g) was bubbled through the solution until pH 1 was reached. The slurry was stirred at room temperature overnight. The solid was filtrated, washed with ether (2×15 mL) and air-dried. The dried solid, sertraline hydrochloride, was not sertraline hydrochloride Form II.

Example 16

An aqueous sodium hydroxide solution, 10%, was added drop-wise to a slurry of sertraline mandelate crystals (15 g) in ethyl acetate (810 mL), until complete dissolution is obtained. The phases were separated and the organic phase was dried over $MgSO_4$ and diluted with an equal volume of ether (820 mL). Gaseous hydrogen chloride was slowly bubbled through the solution (over about 3 hours) until pH 1.5 was reached. The slurry was stirred at room temperature over night. The dried solid, sertraline hydrochloride, was not sertraline hydrochloride Form II.

Example 17

Preparation of Sertraline Hydrochloride Form VIII

Sertraline base (2.7 g) was suspended in 27 mL of water. This mixture was heated to 80° C. and treated with hydro-

chloric acid until about pH 1 was reached. A clear solution was obtained which on cooling gave a precipitate. After 2 hours stirring at room temperature the solid was isolated by filtration. This solid was characterized by powder x-ray diffraction and found to be sertraline hydrochloride Form VIII.

Example 18

Preparation of Sertraline Hydrochloride Form VIII

Sertraline hydrochloride ethanolate (Form VI) (40 g) was stirred with water (80 mL) for 1 hour at room temperature. The slurry was filtrated and washed with water to yield sertraline hydrochloride hydrate Form VIII.

Example 19

Preparation of Sertraline Hydrochloride Form VII

Sertraline hydrochloride Form V (1.003 g) was stirred for 24 hours at room temperature in 20 mL water (HPLC grade). At the end of the stirring the mixture looked like a jelly suspension. The suspension was filtrated and the compound obtained was kept at cold conditions (4° C.) until analyzed by x-ray diffraction.

Example 20

Preparation of Sertraline Hydrochloride Form VII from Form VI

A solution of sertraline hydrochloride ethanolate (Form VI) (40 g) in water (400 mL) was heated at 80° C. and complete dissolution of sertraline hydrochloride ethanolate (Form VI) was obtained. The pH was adjusted to about 1 and the solution was allowed to cool to room temperature and then stirred for 2 additional hours. The solid was isolated by filtration and washed with water to yield sertraline hydrochloride Form VII.

Although certain presently preferred embodiments of the invention have been described herein, it will be apparent to those skilled in the art to which the invention pertains that variations and modifications of the described embodiments may be made without departing from the spirit and scope of the invention. Accordingly, it is intended that the invention be limited only to the extent required by the appended claims and the applicable rules of law.

What is claimed is:

1. A process for making sertraline hydrochloride Form II comprising the steps of:

(a) dissolving sertraline base or sertraline mandelate in an organic solvent to form a solution;

(b) adding hydrogen chloride to the solution;

(c) heating the solution to a temperature between about room temperature and about reflux for a time sufficient to induce the formation of sertraline hydrochloride Form II; and

(d) isolating sertraline hydrochloride Form II.

2. The process of claim **1** wherein the solvent is selected form the group consisting of ethyl acetate, acetone, hexane, t-butyl-methyl ether, isopropyl alcohol, n-butanol, t-butanol, iso-butanol, and cyclohexane, and mixtures thereof.

3. The process of claim **2** wherein the preferred solvent is t-butyl-methyl ether.

4. The process of claim **2** wherein the preferred solvent is n-butanol.

5. The process of claim **1** wherein the hydrogen chloride is added as gaseous hydrogen chloride.

6. The process of claim **1** wherein the hydrogen chloride is added as a solution of hydrogen chloride.

7. The process of claim **6** wherein the solution of hydrogen chloride is selected from the group consisting of isopropyl alcohol and hydrogen chloride, acetone and hydrogen chloride, and n-butanol and hydrogen chloride.

8. The process of claim **1** wherein the solution is heated to the reflux temperature of the solvent.

9. A process for making sertraline hydrochloride Form II comprising the steps of:

(a) dissolving sertraline hydrochloride in a solvent selected from the group consisting of dimethylformamide, cyclohexanol, acetone and mixtures thereof;

(b) heating the solution for a time sufficient to effect transformation to sertraline hydrochloride Form II; and

(c) isolating sertraline hydrochloride Form II.

10. A process for making sertraline hydrochloride Form II comprising the steps of:

(a) granulating sertraline hydrochloride Form V in ethanol or methanol; and

(b) stirring the mixture of sertraline hydrochloride Form V and ethanol or methanol for a time sufficient to induce transformation to sertraline hydrochloride Form II.

11. A process for making sertraline hydrochloride Form II comprising the steps of:

(a) suspending a water or solvent adduct of sertraline hydrochloride in a solvent selected from the group consisting of acetone, t-butyl-methyl ether, cyclohexane, n-butanol, and ethyl acetate, such that a slurry is formed, for a time sufficient to effect transformation to sertraline hydrochloride Form II; and

(b) filtering the slurry to isolate sertraline hydrochloride Form II.

12. The process of claim **11** wherein the process takes place at a temperature between about 25° C. and about 120° C.

13. The process of claim **11** wherein the process takes place under reflux conditions.

14. The process of claim **11** in which the sertraline hydrochloride is suspended in about 1 to about 10 volumes of organic solvent.

15. The process of claim **11** wherein the solvent is t-butyl-methyl-ether.

16. The process of claim **11** wherein the solvent is acetone.

17. The process of claim **11** wherein the solvent is ethyl acetate.

18. The process of claim **11** wherein the solvent is n-butanol.

19. The process of claim **11** wherein the sertraline hydrochloride water or solvate adduct is sertraline hydrochloride Form VI.

20. The process of claim **11** wherein the sertraline hydrochloride water or solvate adduct is sertraline hydrochloride Form VII.

21. The process of claim **11** wherein the sertraline hydrochloride water or solvate adduct is sertraline hydrochloride Form VIII.

22. A process for making a mixture of sertraline hydrochloride Form II and Form V comprising the steps of:

(a) heating sertraline hydrochloride ethanolate Form VI at up to 1 atmosphere pressure; and

(b) isolating a mixture of sertraline hydrochloride Form II and Form V.

* * * * *

EXHIBIT D

US006897340B2

(12) **United States Patent**
Borochovitch et al.

(10) **Patent No.: US 6,897,340 B2**
(45) **Date of Patent: May 24, 2005**

(54) **PROCESSES FOR PREPARATION OF POLYMORPHIC FORM II OF SERTRALINE HYDROCHLORIDE**

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(21) Appl. No.: **10/426,468**

(22) Filed: **Apr. 29, 2003**

(65) **Prior Publication Data**

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Related U.S. Application Data

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(51) **Int. Cl.**[7] **C07C 211/42**
(52) **U.S. Cl.** **564/428**; 564/424
(58) **Field of Search** 564/424, 428

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Primary Examiner—Brian Davis
(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon

(57) **ABSTRACT**

Provided are processes for preparation of crystalline sertraline hydrochloride Form II substantilly free of other polymorphic forms of sertraline hydrochloride, preferably on an industrial scale.

39 Claims, 3 Drawing Sheets

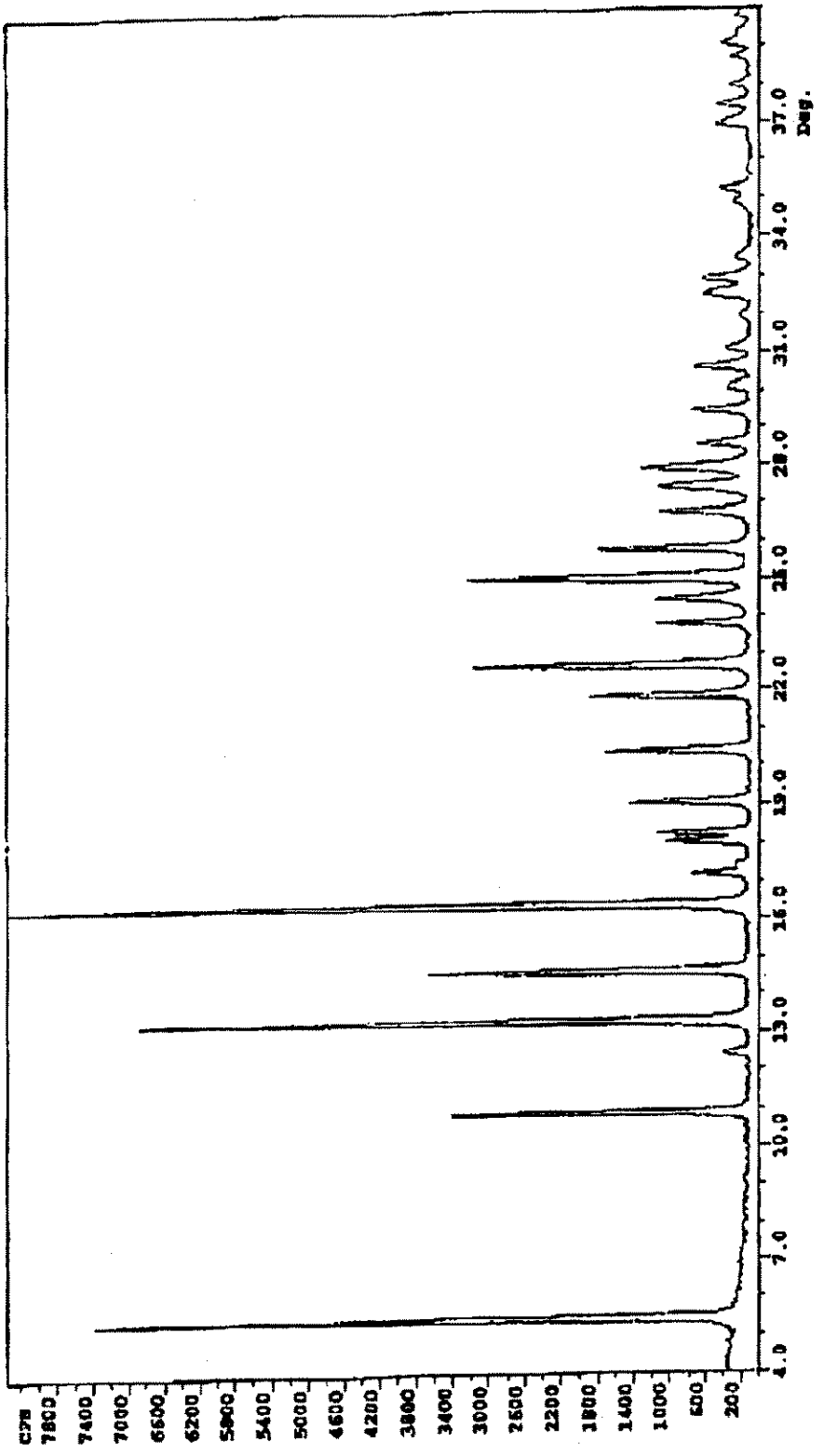


Figure 1
X-Ray powder diffraction pattern of pure Sertraline HCl form II

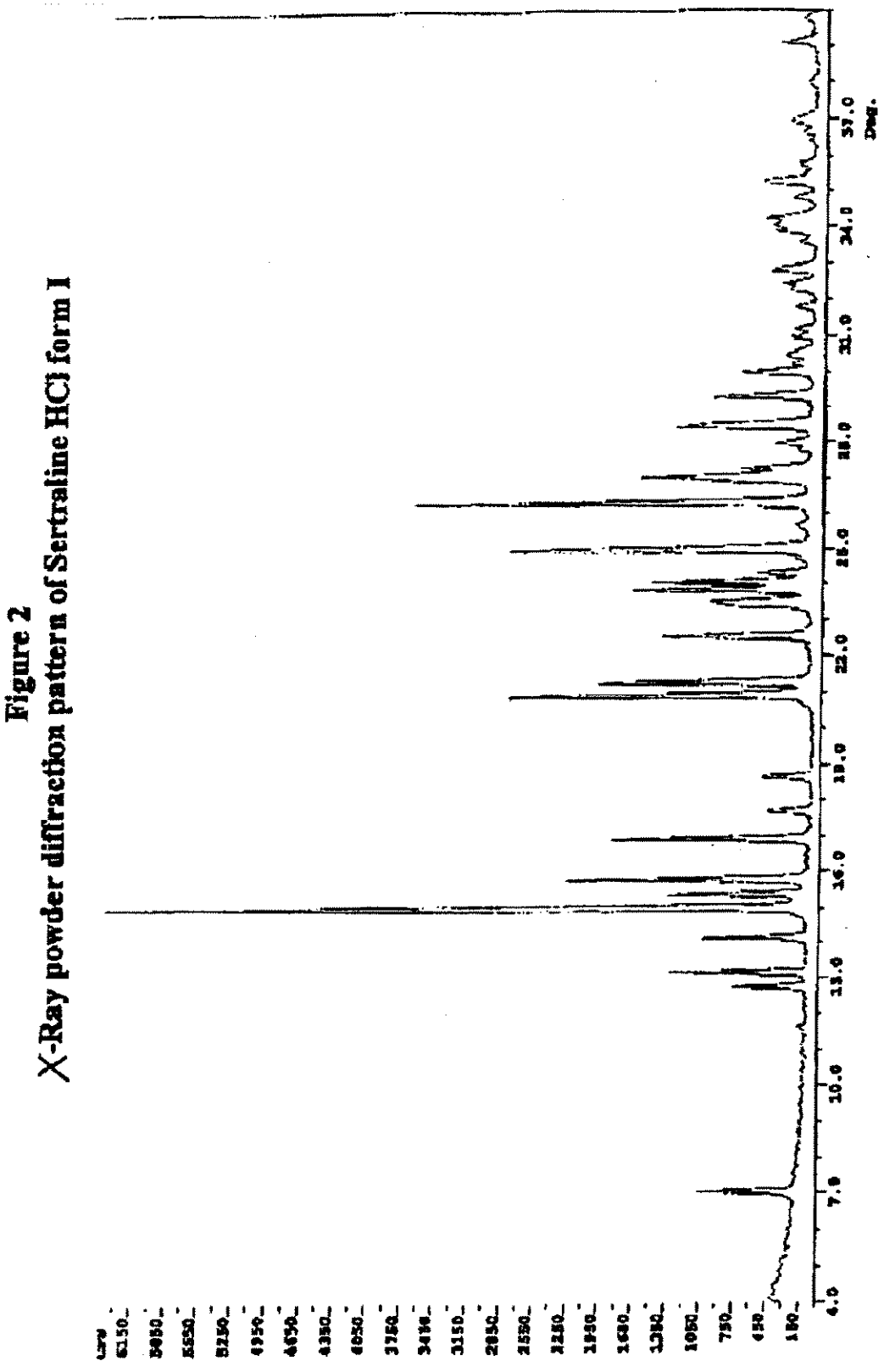


Figure 2
X-Ray powder diffraction pattern of Sertraline HCl form I

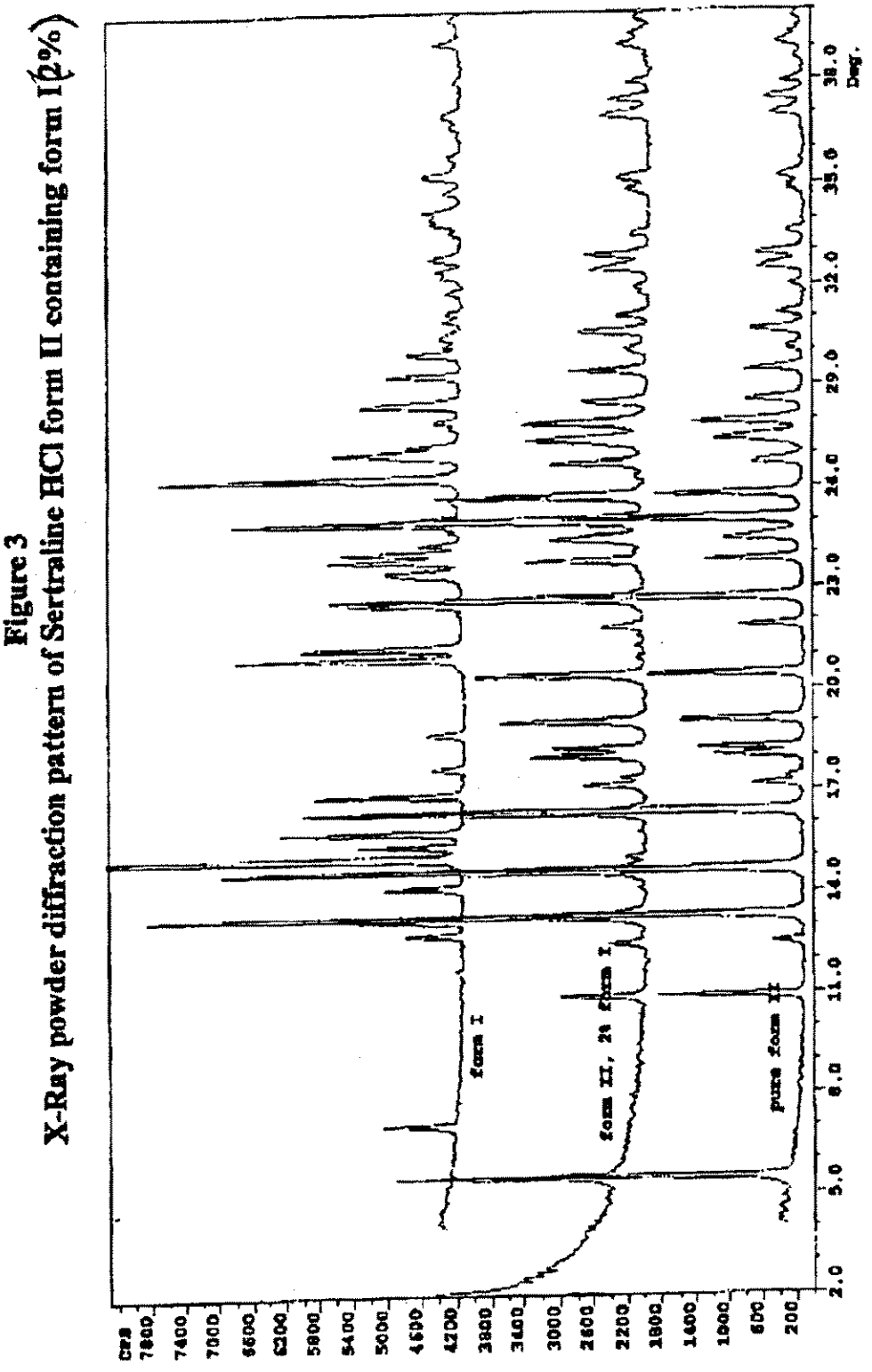


Figure 3

X-Ray powder diffraction pattern of Sertraline HCl form II containing form I(2%)

PROCESSES FOR PREPARATION OF POLYMORPHIC FORM II OF SERTRALINE HYDROCHLORIDE

CROSS REFERENCE TO RELATED APPLICATION

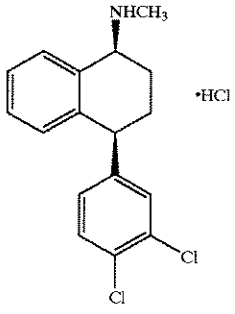
This application claims the benefit under 35 U.S.C. §119 (c) of provisional application Ser. No. 60/376,787, filed Apr. 29, 2002 which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to the solid state chemistry of sertraline hydrochloride.

BACKGROUND OF THE INVENTION

Sertraline hydrochloride, (1S-cis)-4-(3,4 dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride, having the formula:



is approved, under the trademark Zoloft®, by the U.S. Food and Drug Administration, as a serotonin re-uptake inhibitor for the treatment of depression, obsessive-compulsive disorder, panic disorder and post-traumatic disorder. In the solid state, sertraline hydrochloride exists in various crystalline forms having different physical properties.

The present invention relates to the solid state physical properties, i.e., polymorphism, of sertraline hydrochloride. These properties may be influenced by controlling the conditions under which sertraline hydrochloride is obtained in solid form. Solid state physical properties include, for example, the flowability of the milled solid. Flowability affects the ease with which the material is handled during processing into a pharmaceutical product. When particles of the powdered compound do not flow past each other easily, a formulation specialist must take that fact into account when developing a tablet or capsule formulation, which may necessitate the use of glidants such as colloidal silicon dioxide, talc, starch or tribasic calcium phosphate.

Another important solid state property of a pharmaceutical compound is its rate of dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's stomach fluid may have therapeutic consequences because it imposes an upper limit on the rate at which an orally-administered active ingredient may reach the bloodstream. The rate of dissolution is also a consideration in formulating syrups, elixirs and other liquid medicaments. The solid state form of a compound may also affect its behavior on compaction and its storage stability.

These practical physical characteristics are influenced by the conformation and orientation of molecules in the unit cell, which defines a particular polymorphic form of a substance. The polymorphic form may give rise to thermal

behavior different from that of the amorphous material or another polymorphic form. Thermal behavior is measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC), and may be used to distinguish some polymorphic forms from others. A particular polymorphic form may also give rise to distinct properties that may be detectable by powder X-ray diffraction, solid state ^{13}C NMR spectrometry and infrared spectrometry.

A solid form (polymorph) of sertraline hydrochloride is disclosed for example in WO 01/90049, which is directed to amorphous form of sertraline hydrochloride. The solid state chemistry of sertraline hydrochloride is also disclosed in JP 0026378 and JP 0026379. According to the English abstract of JP 0026379, "a sertraline free base is dissolved in a solvent (e.g. an ester-based organic solvent such as ethyl acetate, butyl acetate or the like or a ketone-based organic solvent such as acetone, methyl isobutyl ketone or the like) or a sertraline organic acid salt is suspended in a solvent, and hydrochloric acid or hydrogen chloride is introduced into the solution or suspension preferably at a room temperature or the reflux temperature of the solvent to give sertraline hydrochloride crystal of metastable form. The amount of the hydrochloric acid or hydrogen chloride used is preferably 1.0–5.0 mol based on 1.0 mol of the sertraline free base or the organic salt."

U.S. Pat. No. 4,536,518, incorporated herein by reference, describes a synthesis of sertraline hydrochloride. U.S. Pat. No. 5,248,699, incorporated herein by reference, describes five crystalline forms of sertraline hydrochloride, designated Form I, Form II, Form III, Form IV and Form V. These and additional forms of sertraline hydrochloride are also disclosed in U.S. Pat. Nos. 6,452,054, 6,495,721 and 6,500,987, incorporated herein by reference.

U.S. Pat. No. 4,536,518 ("the '518 patent") describes the preparation of sertraline hydrochloride with a melting point of 243–245° C. by treating an ethyl acetate/ether solution of the free base with gaseous hydrogen chloride. The solid state properties of the sertraline hydrochloride so produced are not otherwise disclosed.

According to U.S. Pat. No. 5,248,699 ("the '699 patent"), the sertraline hydrochloride produced by the method of the '518 patent has a crystalline form denominated "Form II". The method described in the '699 patent for making Forms II and IV is by the rapid crystallization of sertraline hydrochloride from an organic solvent. An actual example is not provided.

The '699 patent discloses that Forms II, III, IV and V are metastable, and that granulation of Forms II, III or IV in isopropyl alcohol, ethyl acetate, hexane at a temperature of 40° to 60° C. causes conversion to Form I.

The preparation of sertraline hydrochloride Form II is also disclosed in WO 01/32601. In Examples 9–12, sertraline hydrochloride Form II is prepared from a maximum of 50 grams of sertraline free base in solution. The specification further discloses regarding Form II: "Sertraline hydrochloride polymorphic form II may be formed from a solution of sertraline free amine with some seeding crystals of form II before the addition of a solution of hydrogen chloride; or from a stirred suspension of sertraline hydrochloride polymorphic form V with some seeding crystals of sertraline hydrochloride polymorphic form II; or by drying a sertraline hydrochloride alcohol solvate at temperatures from about 0 to 30° C. in high vacuum (<1 mbar); or from stirred suspensions of sertraline hydrochloride polymorphic form CSC1, CSC2 or T1 with some seeding crystals of sertraline hydrochloride polymorphic form II. Furthermore, Sertraline

hydrochloride polymorphic form II may be formed according to a process, wherein a solution of sertraline free amine is seeded with some crystals of polymorphic form II and a solution of hydrogen chloride is added."

WO 02/096859, also discloses processes for preparation of sertraline hydrochloride Form II. In the examples, sertraline hydrochloride is prepared from a maximum of 40 grams of sertraline mandelate salt; after obtaining a solution of the free base in isopropanol, hydrogen chloride in ethyl acetate is added at a controlled rate to obtain the hydrochloride salt.

There is a need in the art for preparation of sertraline hydrochloride Form II substantially free of other polymorphic forms of sertraline hydrochloride, particularly on an industrial scale.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a reproducible process for preparation of sertraline hydrochloride Form II substantially free of crystalline sertraline hydrochloride Form I comprising the steps of providing a solution of sertraline base, or a solution or slurry of sertraline mandelate, in an organic solvent, contacting the solution or the slurry with a flow of gaseous hydrogen chloride at a suitable rate at a temperature within the range of from about 30° C. to about 60° C., during which time sertraline hydrochloride Form II forms, wherein the temperature is kept substantially constant during the gas flow, and filtering the sertraline hydrochloride Form II at a temperature of from about 30° C. to about 60° C. to obtain sertraline hydrochloride Form II substantially free of sertraline hydrochloride Form I.

In another aspect, the present invention provides a reproducible process for preparation of sertraline hydrochloride Form II substantially free of sertraline hydrochloride Form I on an industrial scale comprising the steps of contacting a solution of sertraline base or a solution or slurry of sertraline mandelate in an organic solvent at a temperature within the range of about 30° C. to about 60° C. with a flow of gaseous hydrogen chloride to form sertraline hydrochloride Form II, and filtering the sertraline hydrochloride at a suitable temperature to obtain sertraline hydrochloride Form II containing less than about 1% sertraline hydrochloride Form I (wt/wt sertraline hydrochloride), wherein the temperature is kept substantially constant during the gas flow.

In another aspect, the present invention provides for a reproducible process for preparing sertraline hydrochloride Form II substantially free of sertraline hydrochloride Form I on an industrial scale comprising contacting a solution of sertraline base in a C_3 to a C_4 alcohol at a temperature within the range of from about 30° C. to about 60° C. with a flow of gaseous hydrogen chloride for about ½ hour to about 2 hours to obtain a slurry of sertraline hydrochloride, and filtering the slurry to obtain a sertraline hydrochloride Form II with less than about 1% sertraline hydrochloride Form I (wt/wt sertraline hydrochloride Form I/sertraline hydrochloride), wherein the temperature is kept substantially constant during the gas flow and the filtering steps.

In another aspect, the present invention provides for an industrial scale sized batch of crystalline sertraline hydrochloride Form II for preparation of a pharmaceutical oral dosage form of sertraline hydrochloride on an industrial scale, wherein the batch does not substantially convert to sertraline hydrochloride Form I when exposed to a temperature of about 40° C. and a relative humidity of about 75% for at least about 2 months. Preferably the conversion is less than about 1% weight of sertraline hydrochloride Form I to sertraline hydrochloride, more preferably the conversion is less than about 0.5% weight of sertraline hydrochloride Form I to sertraline hydrochloride, and most preferably the conversion is less than about 0.1% weight of sertraline hydrochloride Form I to sertraline hydrochloride. Preferably, the batch size is at least about 1 Kg, more preferably at least about 10 Kg. (measured after drying for a few hours at elevated temperature, such as that carried out in Example 5).

In another aspect, the present invention provides for an oral pharmaceutical dosage form prepared from an industrial scale sized batch of crystalline sertraline hydrochloride Form II, wherein the sertraline hydrochloride Form II in the oral pharmaceutical dosage form does not substantially convert over time to Form I when exposed to a temperature of about 40° C. and a relative humidity of about 75%. Preferably, the conversion is less than about 5% weight of sertraline hydrochloride Form I to sertraline hydrochloride after at least about 6 months of storage, more preferably the conversion is less than about 1% weight of sertraline hydrochloride Form I to sertraline hydrochloride after at least about 3 months of storage, and most preferably the conversion is less than about 1% weight of sertraline hydrochloride Form I to sertraline hydrochloride after at least about 1 month of storage.

In another aspect, the present invention provides for an industrial scale sized batch of crystalline sertraline hydrochloride Form II for preparation of a pharmaceutical oral dosage form of sertraline hydrochloride, wherein the batch is substantially free of sertraline hydrochloride Form I as an impurity. Preferably, the impurity is less than about 1% weight sertraline hydrochloride Form I as a wt/wt percentage to sertraline hydrochloride, more preferably the impurity is less than about 0.5%, and most preferably the impurity is less than about 0.1%.

In another aspect, the present invention provides for a tablet comprised of sertraline hydrochloride and the following excipients, in weight to weight percentages, wherein the tablet is prepared from an industrial sized batch of sertraline hydrochloride Form II substantially free of sertraline hydrochloride Form I: about 20% to about 35% sertraline hydrochloride Form II, about 25% to about 40% lactose monohydrate, about 5% to about 12% croscarmellose sodium NF, about 1% to about 3% povidone, about 20% to about 40% microcrystalline cellulose and about 0.5% to about 2.5% magnesium stearate; and methods of administration to inhibit serotonin re-uptake.

In another aspect, the present invention provides for an industrial scale sized batch of sertraline hydrochloride Form II prepared by a reproducible process on an industrial scale free of XRPD peaks at 14.1, 15.0, 15.3, 15.7, 21.2 and 26.3±0.2 degrees two theta.

In another aspect, the present invention provides an industrial sized batch of crystalline sertraline hydrochloride characterized by an X-ray powder diffraction **7232** pattern with peaks at 5.4, 10.8, 14.6, 16.3, 18.1, 19.0, 20.3, 21.8, 24.4 and 27.3±0.2 degrees two theta, with the said pattern being free of peaks between the region 15.0 to 16.0 degrees two theta, i.e., having substantially the 15.0 to 16.0 degrees two theta region depicted in FIG. **1**. Preferably, the pattern is free of peaks at 15.0, 15.3 and 15.7±0.2 degrees two theta, more preferably also free of peaks at 21.2 and 26.3±0.2 degrees two theta, and most preferably also free of a peak at 14.1±0.2 degrees two theta.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an x-ray powder diffraction pattern of sertraline hydrochloride Form II substantially free of sertraline hydrochloride Form I.

FIG. **2** is an x-ray powder diffraction pattern of sertraline hydrochloride Form I.

FIG. **3** is an x-ray powder diffraction pattern comparing the pattern of sertraline hydrochloride Form I, Form II and Form II containing about 2% Form I.

DETAILED DESCRIPTION OF THE INVENTION

Percentages of sertraline hydrochloride Form I and Form II are in respect to all forms of sertraline hydrochloride combined.

The present invention provides a pure and/or stable crystalline sertraline hydrochloride Form II in a batch and pharmaceutical formulations prepared from such batch, and reproducible processes for such batch, preferably on an industrial scale. The term "batch", which is used to refer to a pharmaceutical bulk preparation, preferably on an industrial scale, such as that illustrated in Example 5, means "A specific quantity of a drug of uniform specified quality produced according to a single manufacturing order during the same cycle of manufacture." (Ansel, H et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th Ed., Page 144). The term "pure" means sertraline hydrochloride Form II substantially free of sertraline hydrochloride Form I. The term "reproducible process" means a process that produces a product of a specified quality on a consistent basis.

The batch size for industrial scale is preferably at least about 0.5 Kg, more preferably at least about 1 Kg (10 liter batch volume), and most preferably at least about 10 Kg (100 liter batch volume). Example 5 illustrates such an industrial process, which prepares sertraline hydrochloride in a batch having about 20 Kg of sertraline hydrochloride.

The batch of crystalline sertraline hydrochloride Form II prepared is substantially free of other crystalline forms of sertraline hydrochloride, particularly crystalline Form I of sertraline hydrochloride. The batch of the pure sertraline hydrochloride Form II preferably has a level of Form I of less than about 1%, more preferrably less than about 0.5% and most preferrably less than about 0.1% w/w (% of sertraline hydrochloride Form I/sertraline hydrochloride). FIG. **1** is an X-Ray powder diffraction ("XRPD") pattern which substantially depicts such pure sample of sertraline hydrochloride Form II.

A suitable method for determining the presence of crystal Form I of sertraline hydrochloride in sertraline hydrochloride crystal Form II is analysis of an XRPD pattern. The XRPD pattern of sertraline hydrochloride From I (FIG. **2**) is characterized by peaks at 7.1, 12.7, 14.1, 15.0, 15.3, 15.7, 20.9, 21.2, 23.5 and 26.3±0.2 degrees two theta. The XRPD of pure sertraline hydrochloride Form II (FIG. **1**) is characterized by peaks at 5.4, 10.8, 14.6, 16.3, 18.1, 19.0, 20.3, 21.8, 24.4 and 27.3±0.2 degrees two theta.

Determination of presence of sertraline hydrochloride Form I in sertraline hydrochloride Form II may be made by analysis for the presence of various peaks associated with Form I, particularly at 14.1, 20.9, 21.2 and 26.3±0.2 degrees two theta and the region 15–16 degrees two theta. Preferred peaks for detection include 15.0, 15.3, 15.7, 21.2 and 26.3±0.2 degrees two theta. Under routine analytical conditions the level of detection of sertraline hydrochloride Form I in sertraline hydrochloride Form II is about 0.1% wt/wt.

The industrial sized batch of sertraline hydrochloride Form II of the present invention preferably does not substantially convert over time to Form I, preferably before formulation, upon storage at about 40° C. and about 75% relative humidity. The conversion does not occur for at least about 1–2 weeks, more preferably for at least about 1–2 months, and most preferably for at least about 3–4 months, into sertraline hydrochloride Form I. The conversion is preferably less than 1%, more preferrably less than about 0.5% and most preferrably less than about 0.1% w/w (% of sertraline hydrochloride Form I/sertraline hydrochloride).

The present invention also provides industrial scale processes (as well as on the lab scale) for crystallizing a highly pure and/or stable sertraline hydrochloride Form II. By controlling the process and engineering parameters, sertraline hydrochloride may be crystallized in pure Form II on a consistent basis, even on an industrial scale.

Sertraline hydrochloride Form II of the present invention is produced by contacting sertraline base in a suitable solvent with hydrogen chloride gas at a temperature range of about 30° C. to about 60° C., more preferably at a temperature of from about 30° C. to about 50° C., even more preferably of about 30° C. to about 45° C., and most preferably of about 40° C. to about 45° C. Salts, such as sertraline mandelate may also be used as a starting material. A solution or a slurry may be used with the process of the present invention, though the base is highly soluble in solvents such as n-butanol, making use of a solution preferable with the base.

Suitable solvents are those that allow for crystallization of sertraline hydrochloride Form II substantially free of sertraline hydrochloride Form I. Examples of such solvents for preparation of Form II are disclosed in U.S. Pat. Nos. 6,495,721 and 6,500,987, incorporated herein by reference. Examples of such solvents include cyclohexane, isopropanol, n-propanol, 2-butanol, t-butanol, i-butanol, n-butanol (also known as 1-butanol), ethyl acetate, acetone, hexane, t-butyl-methyl ether, DMF, and mixtures thereof, particularly mixtures of n-butanol and DMF. From the above C_3 to C_4 alcohols, a preferred alcohol is n-butanol.

A process criteria for crystallization of sertraline hydrochloride pure Form II is the stability of the temperature during crystal formation of pure Form II. Once a desired temperature is achieved, the temperature is substantially maintained, i.e. within about ±5° C. in the specified range (See e.g. Example 5). The ±5° C. allowance does not take the process out of the recited temperature range (See e.g. Example 5).

The process is carried out by adding hydrogen chloride gas to the solution. Preferably, the gas flow is relatively fast, but a gas flow that is too fast may cause operational problems. One problem is rapid precipitation, which may cause difficulty in stirring. Chemical purity or polymorphic purity may also be adversely affected by a very fast gas flow.

The optimal amount of gas flow is dependent on the scale of the process. Preferably, the gas flow is of about 4 to about 6 grams of gaseous hydrogen chloride per hour per about 25 grams of sertraline base. Based on this guidance, one of skill in the art would appreciate the proper amount of gas flow when sertraline mandelate or another salt is used as a starting material.

In a laboratory scale (about 1 liter reactor) or production (industrial) scale (about 100 to about 630 liter reactors (i.e. a batch volume in this size range is prepared; The batch volume for industrial scale may be smaller, for example at least about 5/10 liters, which would give product of about at least about 0.5/1 Kg respectively), the duration of the gas flow is preferably less than about 2 hours, more preferably about 1 hour. When the gas flow lasts for long durations,

traces of sertraline hydrochloride Form I inconsistently appear in small amounts (2–3% weight of sertraline hydrochloride Form I to sertraline hydrochloride). The gas flow is preferably for the duration of about ½ hour to about 2 hours, more preferably of about ¾ hour to about 1¼ hour, and most preferably for about 1 hour. One of skill in the art appreciates that the optimal duration of the gas flow and the flow rate are dependent on the specifics of a bubbling process, such as the size of the bubbles.

The pH of the resulting slurry may be used to monitor the gas flow. The gas flow is preferably stopped when reaching a pH of less than about 1.0, more preferably when reaching a pH of at least about 0.5.

The substantially pure Form II may the be recovered from the slurry by techniques well known in the art. In a particularly preferred embodiment, sertraline hydrochloride Form II is recovered by filtration. The temperature during filtration is preferably maintained from-about 30° C. to about 60° C., more preferably about 30° C. to about 50° C., even more preferably from about 30° C./35° C. to about 45° C. and most preferably at a temperature of from about 40° C. to about 45° C. (about the same range as the HC1 addition step). The temperature is preferably the same as that during the HC1 addition, and more preferably the temperature is kept substantially constant from the beginning of the HC1 addition to the end of the filtration step. (See e.g. Example 5)

Sertraline hydrochloride Form II is kinetically stable when crystallized as a highly pure sertraline hydrochloride Form II. The highly pure sertraline hydrochloride Form II is stable during storage under stress conditions for at least about 2 weeks, more preferably for at least about 1–2 months, even more preferably for at least about 3 months and most preferrably for at least about 6 months. In contrast, sertraline hydrochloride Form II that contains trace amounts of sertraline hydrochloride Form I (at least about 1% w/w of sertraline hydrochloride Form I/sertraline hydrochloride) is not stable during storage under such stress condition.

Without being bound by theory, it is believed that the level of purity presently achieved in the highly pure sertraline hydrochloride Form II imparts the polymorph with stability. It is believed that an unstable composition of sertraline hydrochloride Form II contains trace amounts of sertraline hydrochloride Form I, the presence of which facilitates the conversion of sertraline hydrochloride Form II to sertraline hydrochloride Form I, perhaps by providing a seed for crystallization.

The present invention also provides a pharmaceutical formulation, particularly oral dosage forms such as tablets containing fine crystals of highly pure sertraline hydrochloride Form II. The active ingredient of the formulation, sertraline hydrochloride Form II, does not substantially convert into sertraline hydrochloride Form I. Hence it is possible to formulate unit dosages such as tablets that are stable during storage.

Storage of a tablet containing highly pure sertraline hydrochloride Form II at about 40° C. and about 75% relative humidity, for at least about 1–2 weeks, more preferably from about 1–2 months and most preferably for at least about 3–4 months does not show any significant conversion to other polymorphic forms of sertraline hydrochloride, especially the stable Form I. Preferably, less than about 5%, more preferably, less than about 3% and most preferably, less than about 1% of the sertraline hydrochloride Form II in a tablet converts to polymorphic Form I of sertraline hydrochloride following storage of the tablet. The detection of sertraline hydrochloride Form I in a pharmaceutical formulation, to the extent of about 1% w/w (% of sertraline hydrochloride Form I/sertraline hydrochloride), may be accomplished by use of x-ray powder diffraction.

As in bulk sertraline hydrochloride Form II, the X-ray powder diffraction pattern of pure sertraline hydrochloride tablet does not show a substantial polymorphic change to Form I.

Pharmaceutical compositions of the present invention contain highly pure sertraline hydrochloride Form II. In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may contain one or more excipients. Excipients are added to the composition for a variety of purposes.

Diluents increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate and starch.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primellose®, colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) and starch.

Glidants may be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which may cause the product to have pitting and other surface irregularities. A lubricant may be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor

oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol and tartaric acid.

Solid and liquid compositions may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

In liquid pharmaceutical compositions of the present invention, sertraline hydrochloride and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

Liquid pharmaceutical compositions may contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar may be added to improve the taste.

Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid may be added at levels safe for ingestion to improve storage stability.

According to the present invention, a liquid composition may also contain a buffer such as guconic acid, lactic acid, citric acid or acetic acid, sodium guconate, sodium lactate, sodium citrate or sodium acetate.

Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches and losenges, as well as liquid syrups, suspensions and elixirs.

The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell may be made from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.

A composition for tableting or capsule filling may be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate may then be tableted, or other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

A tableting composition may be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tableting, however, they are not subjected to a final tableting step.

Preferably, the pharmaceutical formulations of the present invention are solid dosage forms in the form of a tablet for the oral administration of sertraline hydrochloride. The highly pure sertraline hydrochloride Form II used for preparing a tablet may be in the form of fine crystals. Preferably, the fine crystals have a particle size distribution such that 100% of the particles are below 200 microns, more preferably below 100 microns and most preferably below about 50 microns.

Methods known in the art, as described above, may be used to prepare tablets of sertraline hydrochloride Form II. Highly pure sertraline hydrochloride Form II tablets may be prepared for instance by mixing the active ingredient, sertraline hydrochloride pure Form II, with a combination of excipients including, lactose, povidone, microcrystalline cellulose and croscarmellose sodium. Purified water may be added to the powder mixture of sertraline modification II and excipients. The mixture may be then dried until only trace amounts of fluid remain in the granulate as residual moisture. Preferably, the mixture is dried to a loss on drying ("LOD") no more than ("NMT") about 0.5 to about 3%. The granulate may be then sieved, and magnesium stearate may be added to the milled granulate. The final blend of sertraline modification II, excipients and magnesium stearate is compressed into tablets and may be film coated, preferably with Opadry® (Colorcon, Westpoint Pa.). According to Colorcon, Opadry® is a one-step customized coating system

that combines polymer, plasticizer, and if desired, a pigment in dry concentrate. Table 1 shows suitable ranges of active ingredients and excipients (weight %) and the preferred amounts for the present pharmaceutical formulations.

TABLE 1

Material	Range of % composition (w/w)	Preferred % composition	Function
High purity sertraline modification II	20–35%	28.0	Active ingredient
Lactose Monohydrate	25–40	32.0	Filler
Croscarmellose Sodium NF	5–12	10.0	Disintegrant
Povidone USP (PVP K-30)	1–3	2.4	Binder
Microcrystalline Cellulose NF (Avicel PH 102)	20–40	26.6	Filler and disintegrant
Purified water USP	—	—	Granulation processing solvent
Magnesium Stearate NF	0.5–2.5	1.0	Lubricant

*Granulation processing solvent only (dried to achieve moisture content of LOD-NMT about 0.5–1.5%).

In accordance with the present invention, the pharmaceutical formulations of the present invention are useful for inhibiting the re-uptake of serotonin, thus resulting in an increased level of serotonin. An increased level of serotonin alleviates symptoms of psychiatric disorders such as depression. The oral pharmaceutical dosage forms of the present invention preferably contain of about 20 mg to about 100 mg of the base equivalent of sertraline hydrochloride, with about 25 mg, about 50 mg and about 100 mg tablets being preferred.

Instrumentation Used:

X-Ray powder diffraction data was obtained by using a SCINTAG powder X-Ray diffractometer model X'TRA equipped with a solid state detector. Copper radiation of 1.5418 Å was used. The diffractometer was equipped with a round aluminum sample holder with round zero background quartz plate having a cavity of 25(diameter)*0.5(depth) mm.

EXAMPLES

Example 1

Stability of bulk sertraline hydrochloride Form II and tablet

Polymorph Content of sertraline hydrochloride in tablet	Polymorph Content of bulk sertraline hydrochloride	Length of Storage
40° C., 75% RH Polymorphic Form detected (I or II)	40° C., 75% RH Polymorphic Form detected (I or II)	
II > I (<1%)	II > I (<1%)	t = 0
II > I (<3%)	II > I (<1%)	1 month
II > I (<3%)	II > I (2%)	2 months
II > I (3%)	II > I (2%)	3 months
—	II > I (4%)	4 months

Example 2

Stability of highly pure bulk sertraline hydrochloride Form II and tablet

Polymorph Content of sertraline hydrochloride in tablet	Polymorph Content of bulk sertraline hydrochloride	Length of Storage
40° C., 75% RH Polymorphic Form detected (I or II)	40° C., 75% RH Polymorphic Form detected (I or II)	
II*	II*	t = 0
II	II	1 month
II	II	2 months
—	—	3 months
—	II	6 months

*The presence of Form I was below the detection level in Examples 2–4. The detection level for the tablet was less than about 1% weight of sertraline hydrochloride Form I to the weight of sertraline hydrochloride, and in the bulk less than about 0.1%.

Example 3

Stability of highly pure bulk sertraline hydrochloride Form II and tablet

Polymorph Content of sertraline hydrochloride in tablet	Polymorph Content of bulk sertraline hydrochloride	Length of Storage
40° C., 75% RH Polymorphic Form detected (I or II)	40° C., 75% RH Polymorphic Form detected (I or II)	
II	II	t = 0
II	II	1 month
II	II	2 months
—	—	3 months
—	II	6 months

Example 4

Stability of highly pure bulk sertraline hydrochloride Form II and tablet

Polymorph Content of sertraline hydrochloride in tablet	Polymorph Content of bulk sertraline hydrochloride	Length of Storage
40° C., 75% RH Polymorphic Form detected (I or II)	40° C., 75% RH Polymorphic Form detected (I or II)	
II	II	t = 0
II	II	1 month
II	II	2 months
—	—	3 months
—	II	6 months

Example 5

Preparation of Pure Sertraline Hydrochloride Form II in Lot (Industrial) Scale

Sertraline base (27 kg) obtained directly from synthesis was dissolved in 105 kg of n-butanol. The solution was treated for 1 hour with 1 kg carbon at 40° C.–45° C., filtered and washed with 25 kg n-butanol. The solution was reheated to 40° C.–45° C. and the achieved temperature was kept constant during the gas flow and filtration. Hydrogen chloride gas was added at the rate of 4.5–5 kg/hr for the duration of 1 hour until pH 0.5 or less was reached. Immediately after, the slurry was filtered at 40° C.–45° C. The cake was washed with 25 kg of n-butanol, and dried for about 4 hours at 80° C. The yield was 70% (21.2 Kg).

Example 6

Preparation of Pure Sertraline Hydrochloride Form II in Lab Scale

Sertraline base (26 g) obtained directly from the synthesis was dissolved in n-butanol (6 volumes) (140 ml). The solution was treated for 1 hour with 1.1 g carbon at 40° C.–45° C., filtered and washed with 12 cc n-butanol. The solution was reheated to 40° C.–45° C. and the temperature achieved was kept constant during the gas flow and filtration. Hydrogen chloride gas was added at the rate of 4–6 g/hr for the duration of 1 hour until pH 0.5 or less was reached. Immediately after, the slurry was filtered at 40° C.–45° C. The cake was washed with 30 ml of n-butanol, and dried for about 4 hours at 80° C.

Example 7

Preparation of Sertraline Hydrochloride in n-BuOH at 70° C.

Sertraline base (30 g) in n-BuOH (240 ml) was heated to 50° C. HCl(g) was bubbled to the solution and the temperature rose to 70° C.; when the pH reached 1.5, precipitation was observed (the temperature was 68° C. More HCl was purged through the slurry (the temperature was 65° C.). After the pH reached 0.5, the mixture was cooled to room temperature and a solid was filtrered and washed with n-BuOH. After drying, a mixture of sertraline hydrochloride form II and form I was obtained (26.41 g).

Example 8

Preparation of Sertraline Hydrochloride in n-BuOH by Filtration at 10° C.

Sertraline base (30 g) was dissolved in n-BuOH(240 ml) and HCl (g) was bubbled through the solution. The temperature rose to 45° C. The reaction mixture turned to a gelly like mixture, which then became a slurry. The slurry was cooled to 10° C. and a solid was filtered, and washed with n-BuOH. After drying, a mixture of sertraline hydrochloride form II and I was obtained (25.9 g).

Example 9

Preparation of Sertraline Hydrochloride Form II in n-BuOH from Sertraline Mandelate

Sertraline mandelate (20 g) in n-BuOH (400 ml) was heated to 60° C. A slurry was obtained. HCl (g) was bubbled through the mixture and complete dissolution was observed. When the solution pH was ~0.5, the solution was cooled and seeded with sertraline hydrochloride Form II. The reaction mixture was srirred at room temperature over night and a solid was filtered and washed with n-BuOH. The solid was dried to afford sertraline hydrochloride Form II (7.21 g).

Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art may appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to, limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in numerous publications. Polymorphism in Pharmaceutical Solids, Drugs and the Pharmaceutical Sciences, Volume 95 may be used as a guidance. All references and priority documents mentioned herein are incorporated by reference in their entirety.

What is claimed is:

1. A reproducible process for preparation of sertraline hydrochloride Form II comprising the steps of:

a) providing a solution of sertraline base, or a solution or slurry of sertraline mandelate, in an organic solvent;

b) contacting the solution or the slurry with a flow of gaseous hydrogen chloride at a temperature within the range of from about 30° C. to about 60° C., during which time sertraline hydrochloride Form II forms, wherein the temperature is kept substantially constant during the gas flow; and

c) filtering the sertraline hydrochloride Form II at a temperature of from about 30° C. to about 60° C. to obtain sertraline hydrochloride Form II containing less than about 1% sertraline hydrochloride Form I as measured wt/wt sertraline hydrochloride Form I/sertraline hydrochloride.

2. The process of claim 1, wherein the solvent is an alcohol.

3. The process of claim 2, wherein the alcohol is a C_3 or a C_4 alcohol, or mixtures thereof.

4. The process of claim 3, wherein the alcohol is n-butanol.

5. The process of claim 1, wherein the solvent is selected from the group consisting of cyclohexane, ethyl acetate, acetone, hexane, t-butyl-methyl ether, DMF, and mixtures thereof.

6. The process of claim 1, wherein the solution of sertraline base is provided.

7. The process of claim 6, wherein the gas flows at a rate of about 4 to about 6 grams of gaseous hydrogen chloride per hour per about 25 grams of sertraline base.

8. The process of claim 1, wherein the temperature during the gas flow is about 30° C. to about 50° C.

9. The process of claim 8, wherein the temperature is about 35° C. to about 50° C.

10. The process of claim 9, wherein the temperature is about 40° C. to about 45° C.

11. The process of claim 1, wherein the gas flow is stopped when reaching a pH of less than about 1.

12. The process of claim 1, wherein the temperature is kept substantially constant during the gas flow and the filtering steps.

13. The process of claim 1, wherein the gas flow is stopped in less than about 2 hours.

14. The process of claim 1, wherein the amount of sertraline hydrochloride Form is less than about 0.5%.

15. The process of claim 14, wherein the amount of sertraline hydrochloride Form I is less than about 0.1%.

16. The process of claim 1, wherein the process results in at least about 0.5 kg of sertraline hydrochloride Form II after the filtering step.

17. The process of claim 16, wherein at least about 1 Kg of sertraline hydrochloride Form II is obtained after the filtering step.

18. The process of claim 17, wherein at least about 10 Kg of sertraline hydrochloride Form II is obtained after the filtering step.

19. The process of claim 16, wherein at least about a 100 liter solution is provided.

20. A reproducible process for preparation of sertraline hydrochloride Form II comprising the steps of contacting a solution of sertraline base, or a solution or slurry of sertraline mandelate in an organic solvent, at a temperature within the range of about 30° C. to about 60° C. with a flow of gaseous hydrogen chloride to form sertraline hydrochloride Form II, and filtering the sertraline hydrochloride to obtain sertraline hydrochloride Form II containing less than about 1% sertraline hydrochloride Form I (wt/wt sertraline hydrochloride), wherein the temperature is kept substantially constant during the gas flow.

21. The process of claim **20**, wherein the solution of sertraline base is used.

22. The process of claim **21**, wherein the gas flows at a rate of about 4 to about 6 grams of gaseous hydrogen chloride per hour per about 25 grams of sertraline base.

23. The process of claim **20**, wherein the solvent is an alcohol.

24. The process of claim **23**, wherein the alcohol is a C_3 or a C_4 alcohol, or mixtures thereof.

25. The process of claim **24**, wherein the alcohol is n-butanol.

26. The process of claim **20**, wherein the solvent is selected from the group consisting of cyclohexane, ethyl acetate, acetone, hexane, t-butyl-methyl ether, DMF, and mixtures thereof.

27. The process of claim **20**, wherein the temperature is about 30° C. to about 50° C. during the gas flow.

28. The process of claim **27**, wherein the temperature is about 30° C. to about 45° C.

29. The process of claim **28**, wherein the temperature is about 40° C. to about 45° C.

30. The process of claim **20**, wherein the filtering is carried out at a temperature of from about 30° C. to about 60° C.

31. The process of claim **20**, wherein the temperature is kept substantially constant during the gas flow and the filtering step.

32. The process of claim **20**, wherein at least about 1 Kg of sertraline hydrochloride Form II is obtained after the filtering step.

33. The process of claim **32**, wherein at least about 10 Kg of sertraline hydrochloride Form II is obtained after the filtering step.

34. The process of claim **20**, wherein at least about a 100 liter solution is prepared.

35. A reproducible process for preparing sertraline hydrochloride Form II comprising contacting a solution of sertraline base in a C_3 to a C_4 alcohol at a temperature within the range of from about 30° C. to about 60° C. with a flow of gaseous hydrogen chloride for about ½ hour to about 2 hours to obtain a slurry of sertraline hydrochloride, and filtering the slurry to obtain sertraline hydrochloride Form II with less than about 1% sertraline hydrochloride Form I (wt/wt sertraline hydrochloride Form I/sertraline hydrochloride), wherein the temperature is kept substantially constant during the gas flow and the filtering steps.

36. The process of claim **35**, wherein the temperature is from about 35° C. to about 50° C.

37. The process of claim **35**, wherein the alcohol is n-butanol.

38. The process of claim **35**, wherein at least about 1 Kg of sertraline hydrochloride Form II is obtained after the filtering step.

39. The process of claim **1**, **20** or **35**, wherein at temperature is about 30° C. to about 45° C.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,897,340 B2
DATED : May 24, 2005
INVENTOR(S) : Ronen Borochovitch et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [57], **ABSTRACT**,
Line 2, change "substantilly" to -- substantially --.

Column 4,
Line 55, remove "**7232**".

Column 5,
Lines 39 and 40, change "preferrably" to -- preferably --.

Column 6,
Lines 6 and 7, change "preferrably" to -- preferably --.

Column 7,
Line 35, change "preferrably" to -- preferably --.

Column 9,
Line 47, change "guconic" to -- gluconic --.
Line 48, change "goconate" to -- gluconate --.
Line 67, change "losenges" to -- lozenges --.

Column 13,
Line 25, change "filtrered" to -- filtered --.
Line 33, change "gelly" to -- jelly --.
Line 47, change "srirred" to -- stirred --.

Column 14,
Line 43, change "Form" to -- Form I --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

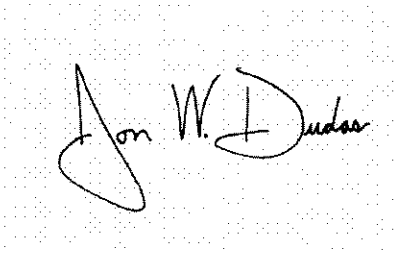
PATENT NO. : 6,897,340 B2
DATED : May 24, 2005
INVENTOR(S) : Ronen Borochovitch et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16,
Line 26, change "wherein at temperature" to -- wherein the temperature --.

Signed and Sealed this

Third Day of January, 2006



JON W. DUDAS
Director of the United States Patent and Trademark Office

AO 440 (Rev 1/90) Summons in a Civil Action

United States District Court

DISTRICT OF NEW JERSEY

SUMMONS IN A CIVIL ACTION

TEVA PHARMACEUTICAL INDUSTRIES LTD.
and TEVA PHARMACEUTICALS USA, INC., Civil Action No.:

Plaintiffs,

v.

CIPLA LTD., AND BYRON CHEMICAL CO., INC.,

Defendants.

TO: (Name Address of Defendant)

Byron Chemical Co.
40-11 23rd Street
Long Island City, NY 11101

YOU ARE HEREBY SUMMONED and required to file with the Clerk of this Court and serve upon

PLAINTIFF'S ATTORNEY (name and address)

Allyn Z. Lite, Esq.
Michael E. Patunas, Esq.
Lite DePalma Greenberg & Rivas, LLC
Two Gateway Center, 12th Floor
Newark, NJ 07102

an answer to the complaint which is herewith served upon you, within 20 days after service of this summons upon you, exclusive of the day of service. If you fail to do so, judgment by default will be taken against you for the relief demanded in the complaint.

CLERK DATE

BY DEPUTY CLERK

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TEVA PHARMACEUTICAL INDUSTRIES LTD. and TEVA PHARMACEUTICALS USA, INC.,	:	Civil Action No.
Plaintiffs,	:	
v.	:	
HETERO DRUGS LTD.,	:	
Defendants.	:	

COMPLAINT FOR DECLARATORY JUDGMENT

For their Complaint against Defendant Hetero Drugs Ltd. ("Hetero"), Plaintiffs Teva Pharmaceutical Industries Ltd. ("Teva Ltd.") and Teva Pharmaceuticals USA, Inc. ("Teva USA") allege as to their own acts, and on information and belief as to the acts of others, as follows:

THE PARTIES

1. Teva Ltd. is a corporation organized under the laws of Israel, and maintains its principal place of business at 5 Basel Street, Petah Tiqva 49131, Israel.

2. Teva USA is a Delaware corporation with its principal place of business located at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090. Teva USA is a wholly-owned subsidiary of Teva Ltd.

3. On information and belief, Hetero is an Indian corporation having a principal place of business at Hetero House, H. No. 8-3-166/7/1, Erragadda, Hyderabad-50018 AP India.

NATURE OF THE ACTION

4. This is an action for patent infringement arising under the Patent Laws of the United States, 35 U.S.C. § 1, et seq., and seeking damages and injunctive relief under 35 U.S.C. §§ 281-285.

JURISDICTION AND VENUE

5. This court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

6. This Court may declare the rights and other legal relations of the parties pursuant to 28 U.S.C. §§ 2201 and 2202 because this is a case of actual controversy within the Court's jurisdiction.

7. The Court has personal jurisdiction over Hetero because of its continuous and systematic contacts with the state of New Jersey.

8. Venue is proper in this judicial district based on 28 U.S.C. § 1400 (b) and/or 28 U.S.C. § 1391 (b), (c), and (d).

BACKGROUND

The Patents In Suit

9. Teva Ltd. is the owner of all right, title and interest in United States Patent Nos. 6,600,073 ("the '073 patent"), 6,500,987 ("the '987 patent"), 6,495,721 ("the '721 patent"), and 6,897,340 ("the '340 patent"; collectively, "the patents in suit") relating to, *inter alia*, methods for manufacturing certain crystalline forms of a chemical compound known as sertraline hydrochloride. Two of these crystalline forms of sertraline hydrochloride are known as "Form II" and "Form V."

10. The '073 patent was duly and legally issued by the United States Patent and Trademark Office ("PTO") on July 29, 2003 for an invention entitled "Methods for Preparation of Sertraline Hydrochloride Polymorphs." A copy of the '073 patent is attached as Exhibit A.

11. The '987 patent was duly and legally issued by the PTO on December 31, 2002 for an invention entitled "Sertraline Hydrochloride Polymorphs." A copy of the '987 patent is attached as Exhibit B.

12. Both the '073 patent and the '987 patent claim, *inter alia*, processes for preparation of sertraline hydrochloride Form V.

13. The '721 patent was duly and legally issued by the PTO on December 17, 2002 for an invention entitled "Sertraline Hydrochloride Form II and Methods For the Preparation Thereof." A copy of the '721 patent is attached as Exhibit C.

14. The '340 patent was duly and legally issued by the PTO on May 24, 2005 for an invention entitled "Processes for Preparation of Polymorphic Form II of Sertraline Hydrochloride." A copy of the '340 patent is attached as Exhibit D.

15. The '721 and '340 patents claim, *inter alia*, processes for the preparation of sertraline hydrochloride Form II.

Plaintiffs' Generic Exclusivity

16. Sertraline hydrochloride is a pharmaceutical compound useful in the treatment of depression. It is the active pharmaceutical ingredient ("API") in the product sold by Pfizer Inc. under the trade name ZOLOFT. Teva USA sells generic sertraline hydrochloride tablets in the United States that are manufactured by Teva Ltd.

17. Pursuant to the Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.* (1994) ("the Act"), Teva USA filed Abbreviated New Drug Application ("ANDA") No. 76-465 with the United States Food & Drug Administration ("FDA") for permission to market its generic sertraline hydrochloride tablets in the United States.

18. Ivax Pharmaceuticals, Inc. ("Ivax"), a separate wholly-owned subsidiary of Teva Ltd., filed ANDA No. 75-719 with the FDA, also seeking permission to market generic sertraline hydrochloride tablets in the United States.

19. Ivax's ANDA was approved on June 30, 2006. Under § 355(j) of the Act, Ivax obtained a limited period of exclusivity from the FDA for its generic sertraline products in the United States. Pursuant to this exclusivity, the FDA will not approve any other ANDA for generic sertraline hydrochloride tablets for a period of 180 days from the date Ivax first commercially marketed a product under its ANDA. This exclusivity period expires on February 6, 2007, *i.e.*, the FDA may grant final approval to other ANDA holders beginning on February 7, 2007.

20. Ivax has selectively waived its exclusivity period with respect to Teva USA's ANDA No. 76-465. Following this selective waiver, the FDA granted final approval to Teva's ANDA on August 11, 2006.

Defendant's Imminent Infringement of the Patents In Suit

21. Under the Act, ANDA holders must provide detailed information to the FDA about how the API to be used in their proposed generic products will be made. Suppliers of API typically are reluctant to disclose confidential information about their manufacturing processes to their customers. Such API suppliers typically submit this confidential information directly to the FDA in the form of a Drug Master File ("DMF"), which the FDA keeps on file. Customers of the API supplier who file ANDAs may then reference the DMF in their ANDAs. Upon receiving an ANDA referencing a DMF, the FDA will separately review the DMF as part of the ANDA approval process. Accordingly, the act of filing a DMF indicates the present intent of the filer is to supply API to at least one ANDA holder.

22. On information and belief, Defendant has filed DMF No. 15731 for sertraline hydrochloride API with the FDA.

23. On information and belief, Defendant plans and intends to supply sertraline hydrochloride API to one or more third party ANDA holders, with the knowledge and intent that the third party ANDA holder(s) will engage in the commercial importation, manufacture, use, sale and/or offer for sale of generic sertraline hydrochloride tablets in the United States. Plaintiffs have made a reasonable effort to determine the identity of third party ANDA holder(s) that Defendant intends to supply. Currently, Plaintiffs are unable to obtain from a public source any information regarding the entities that Defendant intends to supply.

24. On information and belief, Defendant plans and intends to supply the third party ANDA holder(s) with the knowledge and intent that the third party ANDA holder(s) will engage in the activities described in paragraph 23 immediately upon receiving final approval of the ANDA(s) by the FDA, and that said approval will occur shortly after Ivax's exclusivity period expires.

25. On information and belief, Defendant plans and intends to supply the third party ANDA holder(s) with the knowledge and intent that the third party ANDA holder(s) will engage in the activities described in paragraph 23 prior to the expiration of the patents in suit.

26. On information and belief, Defendant plans and intends to import sertraline hydrochloride into the United States for sale to third party ANDA holder(s).

27. On information and belief, Defendant's sertraline hydrochloride API is or will be made by a process that infringes one or more of the claims of the patents in suit. Accordingly, Defendant's plans and intentions to import and sell sertraline hydrochloride API in the United States constitute imminent, threatened acts of infringement under 35 U.S.C. § 271(g), which give rise to an actual controversy over which this Court may exercise jurisdiction.

28. On information and belief, Defendant's plans and intentions to supply sertraline hydrochloride API to third party ANDA holder(s) outside of the United States for incorporation into products that it knows will be imported and sold in the United States constitute imminent, threatened inducement of infringement under 35 U.S.C. §§ 271(b) and (g), which gives rise to an actual controversy over which this Court may exercise jurisdiction.

29. On information and belief, Defendant's sertraline hydrochloride API is Form II or Form V. On information and belief, sertraline hydrochloride Forms I, II and V are the only

crystalline forms that are most likely to be used in a pharmaceutical tablet. On information and belief, Form I is claimed by an unexpired United States patent assigned to Pfizer Inc., and thus it is unlikely that Defendant will attempt to market API containing that polymorph to customers intending to sell products in the United States.

30. On information and belief, Plaintiffs are not aware of any commercially viable process to manufacture Form V sertraline hydrochloride that is not covered by one or more claims of the '987 patent and/or the '073 patent. Thus, on information and belief, there is a substantial likelihood that Defendant's sertraline hydrochloride API, if Form V, is or will be made by a process that infringes one or more claims of the '987 patent and/or the '073 patent.

31. On information and belief, given the scope of Teva Ltd.'s patent rights to methods of making Form II, there is a substantial likelihood that Defendant's sertraline hydrochloride API, if Form II, is or will be made by a process that infringes one or more claims of the '721 patent and/or the '340 patent.

32. Plaintiffs have made a reasonable effort to determine the process by which Defendant's sertraline hydrochloride API is or will be made. Currently, Plaintiffs are unable to obtain from a public source any information regarding the method used to manufacture Defendant's API. On November 30, 2006, Teva Ltd. notified Defendant of the existence of the patents in suit and requested a description of the manufacturing process used by Defendant to make the API. In order to protect the confidentiality of Defendant's information, Teva Ltd. offered to enter into a confidentiality agreement.

33. Defendant has not responded to Teva Ltd.'s requests for information relating to its manufacturing process despite Teva Ltd.'s offer to review any material subject to a supplied

confidentiality agreement.

34. Further, Plaintiffs have been unable to obtain from a public source samples of the API Defendants are selling, or intend to sell, to the third party ANDA holder(s) they are supplying or will supply. However, on information and belief, even Plaintiffs had been able to obtain samples of Defendants' API from a public source, Plaintiffs are not aware of any analytical technique or combination of techniques that could be used to definitively establish that the API was made by one or more of the methods claimed in the patents in suit. For this reason, Plaintiffs cannot conclusively determine whether Defendant's API infringes the patents in suit unless and until Defendant discloses to Plaintiffs the method by which the API is made.

35. In the absence of a sufficient response from Defendant, Plaintiffs have no choice but to resort to judicial process and the aid of discovery to obtain, under appropriate judicial safeguards, the information required to confirm their beliefs as to infringement and to present to the Court evidence that Defendant will infringe the patents in suit.

36. On information and belief, Defendant's infringement will be willful and deliberate.

37. As a direct and proximate consequence of the planned and intended infringement by Defendant, Plaintiffs will be injured in their business and property rights unless the infringement is enjoined by the Court, and will suffer injury and damages for which they are entitled to relief.

COUNT I
DECLARATORY JUDGMENT OF PATENT INFRINGEMENT

38. The allegations of paragraphs 1 to 37 are incorporated by reference as if fully set forth herein.

39. The importation, sale and/or offer to sell by the Defendant of its sertraline hydrochloride API pursuant to DMF No. 15731 will infringe one or more claims of the '073, '987, '721 and/or '340 patents under 35 U.S.C. § 271.

COUNT II
DECLARATORY JUDGMENT OF INDUCEMENT OF PATENT INFRINGEMENT

40. The allegations of paragraphs 1 to 37 are incorporated by reference as if fully set forth herein.

41. The supply of sertraline hydrochloride API pursuant to DMF No. 15731 by the Defendant to companies who will engage in the importation, sale and/or offer to sell of products made with that API will induce the infringement of one or more claims of the '073, '987, '721 and/or '340 patents 35 U.S.C. § 271.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for the entry of a judgment from this Court:

a. Declaring that the '073, '987, '721 and '340 patents are valid and enforceable;

b. Declaring that Defendant will infringe one or more claims of the '073, '987, '721 and/or '340 patents;

c. Declaring that Defendant will induce infringement of one or more claims of the '073, '987, '721 and/or '340 patents;

d. Declaring that Defendant's infringement and inducement will be willful and that this is an exceptional case under 35 U.S.C. § 285;

e. Permanently enjoining Defendant, its respective officers, agents, servants and employees, and those persons in active concert or participation with any of them, from infringing or inducing the infringement of the '073, '987, '721 and '340 patents;

f. Awarding Plaintiffs damages in accord with 35 U.S.C. § 284;

g. Awarding Plaintiffs their attorneys fees, costs and expenses; and

h. Awarding Plaintiffs such other and further relief as this Court may deem to be just and proper.

LITE DEPALMA GREENBERG & RIVAS, LLC

Dated: January 12, 2007

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LOCAL CIVIL RULE 11.2 CERTIFICATION

Plaintiffs, by their attorneys, hereby certify that the matter in controversy is also the subject of the following action:

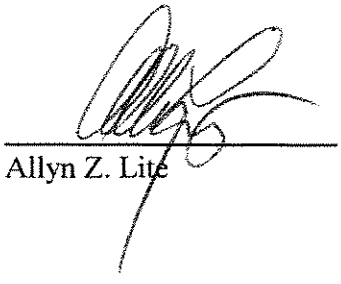
Teva Pharmaceutical Industries Ltd., et al. v. Pliva Inc., Filed on 1/12/07 D.N.J.

The following matters, of which this matter is one, are each being filed in the District of New Jersey on January 12, 2007. Each of the following matters is the subject of the same matter filed as *Teva Pharmaceutical Industries Ltd., et al. v. Pliva Inc.*, and is related to it.

Caption	Docket No.	Court
Teva Pharmaceutical Industries Ltd., et al. v. Sandoz Inc.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Apotex, Inc., et al.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Genpharm Inc.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Invagen Pharmaceuticals Inc.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Zydus-Cadila Healthcare, et al.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Lupin Limited, et al.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Cipla Ltd., et al.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Hetero Drugs Ltd.	Being filed on 1/12/07	D.N.J.
Teva Pharmaceutical Industries Ltd., et al. v. Andrx Corp.	Being filed on 1/12/07	D.N.J.

I hereby certify that the following statements made by me are true. I am aware that if any of the foregoing statements made by me are wilfully false, I am subject to punishment.

Dated: January 12, 2007



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Attorneys for Plaintiffs Teva Pharmaceutical Industries Ltd. and Teva Pharmaceuticals USA, Inc.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TEVA PHARMACEUTICAL INDUSTRIES LTD. and TEVA PHARMACEUTICALS USA, INC.,	:	Civil Action No.
Plaintiffs,	:	
v.	:	
HETERO DRUGS LTD.,	:	
Defendants.	:	

RULE 7.1 STATEMENT

Pursuant to Rule 7.1(a) of the Federal Rules of Civil Procedure, Plaintiff Teva Pharmaceuticals USA, Inc. hereby discloses that (1) the parent companies of Teva Pharmaceuticals USA, Inc. are: Orvet UK Ltd., Teva Pharmaceuticals Europe (Holland) and

Teva Pharmaceutical Industries Ltd. (Israel); and (2) Teva Pharmaceutical Industries Ltd. is the only publicly-traded company that owns – through the aforementioned chain – 10% or more of Teva Pharmaceuticals USA, Inc.

Plaintiff Teva Pharmaceutical Industries Ltd. hereby discloses that (1) it has no parent corporation; and (2) no publicly held corporation own 10% or more of its stock.

LITE DEPALMA GREENBERG & RIVAS, LLC

Dated: January 12, 2007

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Attorneys for Plaintiffs Teva Pharmaceutical Industries Ltd. and Teva Pharmaceuticals USA, Inc.

EXHIBIT A

US006600073B1

(12) **United States Patent**
Schwartz et al.

(10) **Patent No.: US 6,600,073 B1**
(45) **Date of Patent: Jul. 29, 2003**

(54) **METHODS FOR PREPARATION OF SERTRALINE HYDROCHLORIDE POLYMORPHS**

(75) Inventors: **Eduard Schwartz**, Rechovot; **Tamar Nidam**, Yehud; **Anita Liberman**, Tel-Aviv; **Marioara Mendelovici**, Rechovot; **Judith Aronhime**, Rehovot; **Claude Singer**, Kfar Saba; **Evgeni Valdman**, Petah Tikva, all of (IL)

(73) Assignee: **Teva Pharmaceutical Industries Ltd.**, Petah Tiqva (IL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/586,842**

(22) Filed: **Jun. 5, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/448,985, filed on Nov. 24, 1999.

(51) **Int. Cl.**[7] **C07C 211/00**
(52) **U.S. Cl.** **564/308**
(58) **Field of Search** 564/308

(56) **References Cited**

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Primary Examiner—Samuel Barts
(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon

(57) **ABSTRACT**

Novel methods for the preparation of sertraline hydrochloride Forms III, V, VI, VII, VII, IX and X are disclosed. According to the present invention, sertraline hydrochloride Form III may be produced by heating sertraline hydrochloride Forms V and VI. Sertraline hydrochloride Forms V and VI may be produced from either sertraline hydrochloride or sertraline base by crystallization. Sertraline hydrochloride Form VII may be produced by suspending sertraline chloride polymorph V in water, followed by filtration. Sertraline hydrochloride Forms VIII and IX may be produced by suspending sertraline base in water followed by acidification and filtration. Sertraline hydrochloride Form X may be produced by suspending sertraline hydrochloride in benzyl alcohol with heating, followed by filtration.

29 Claims, 16 Drawing Sheets

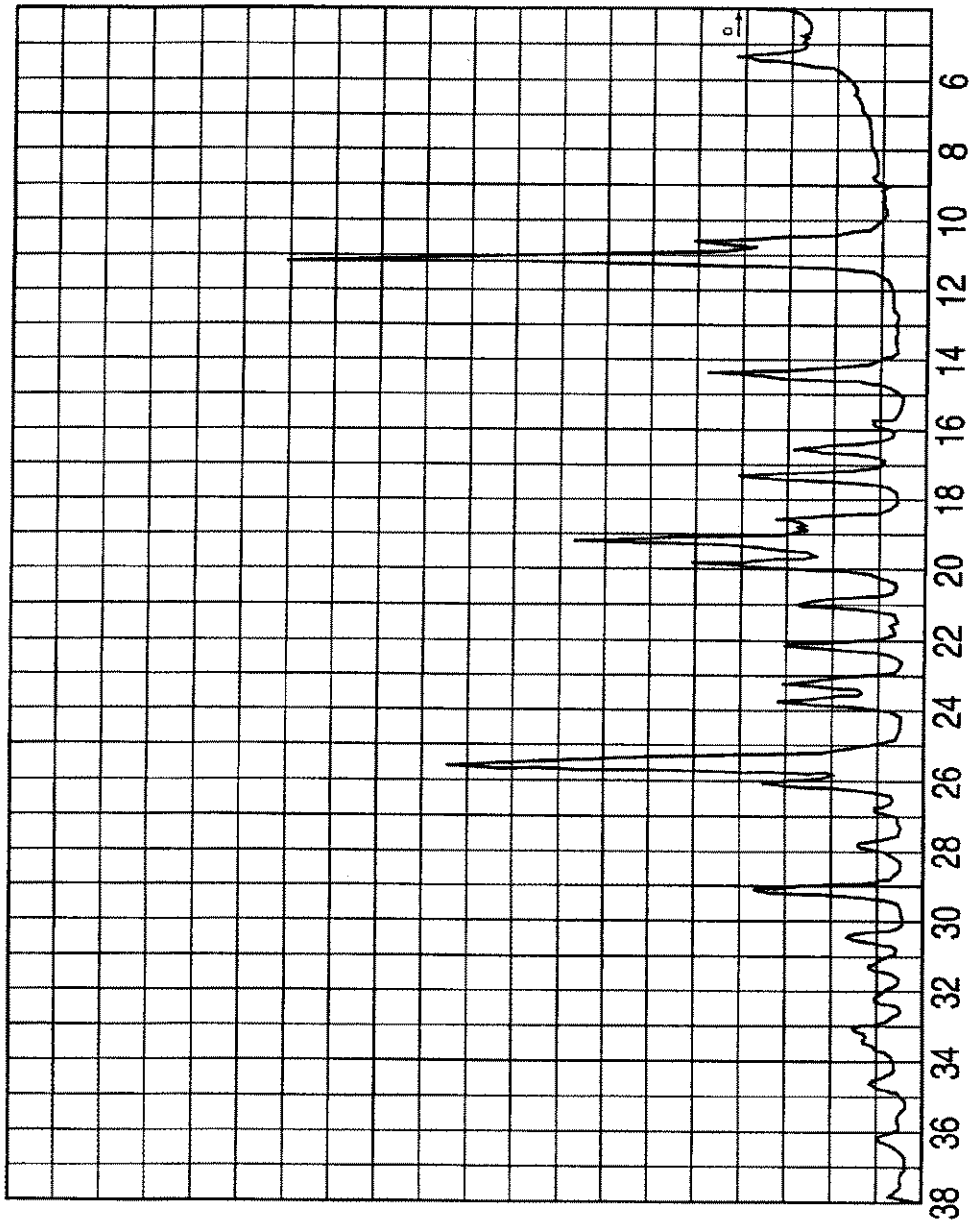

FIG. 1

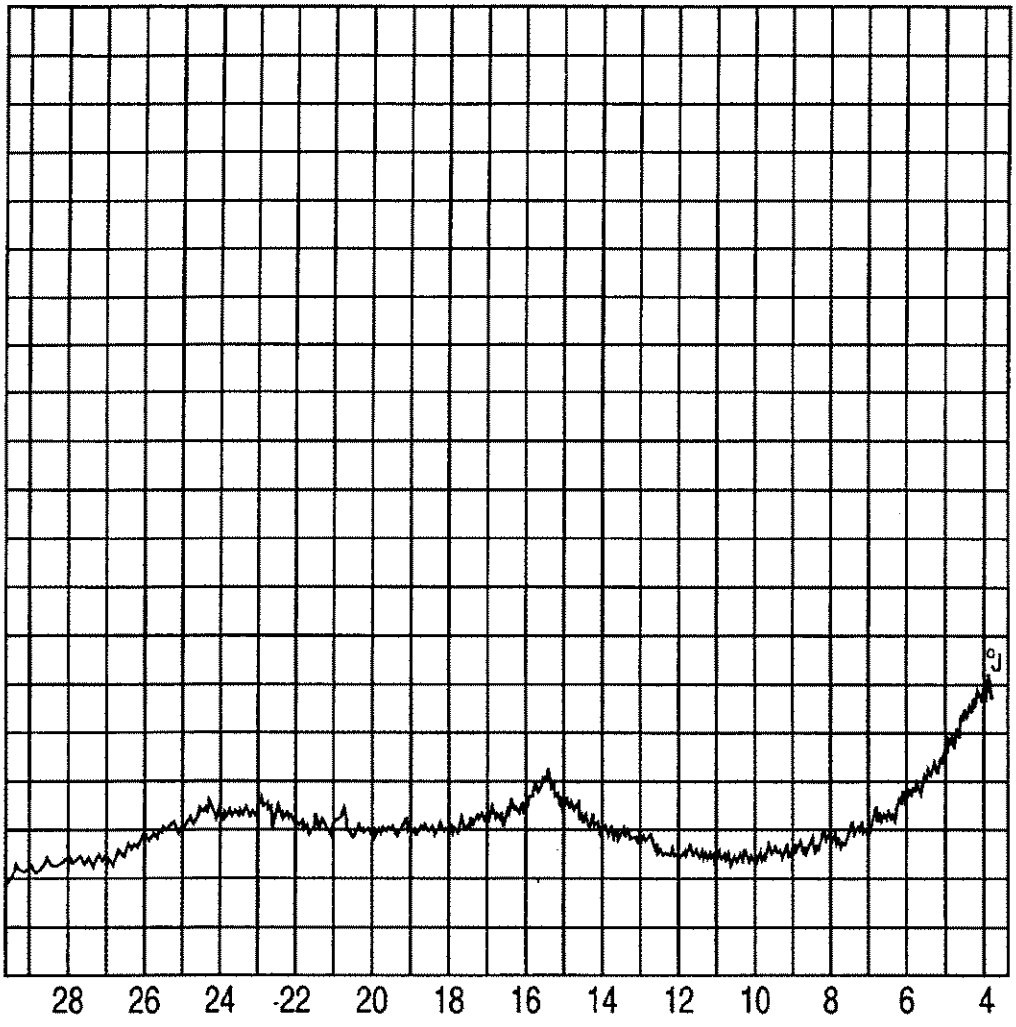

FIG. 2

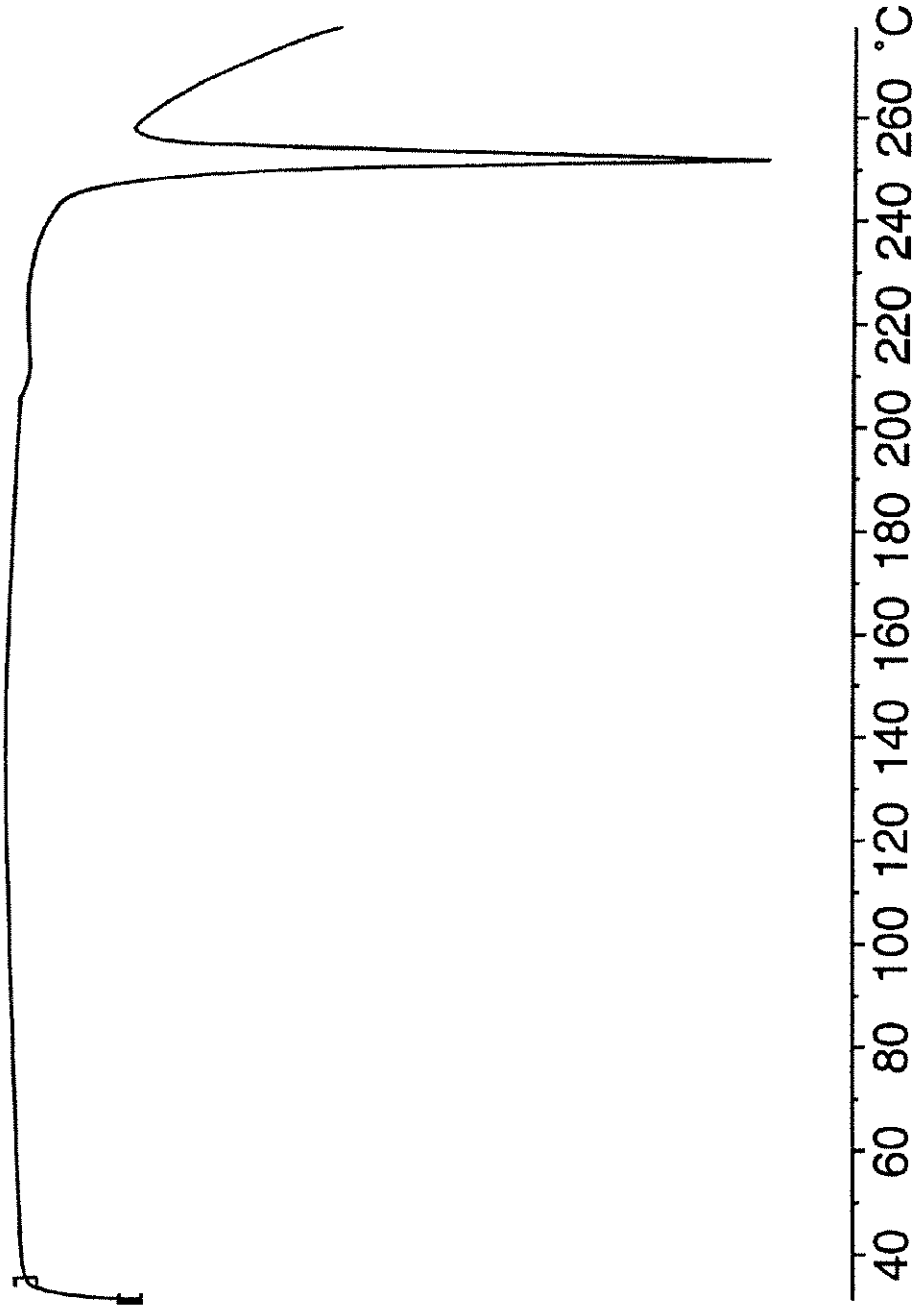

FIG. 3

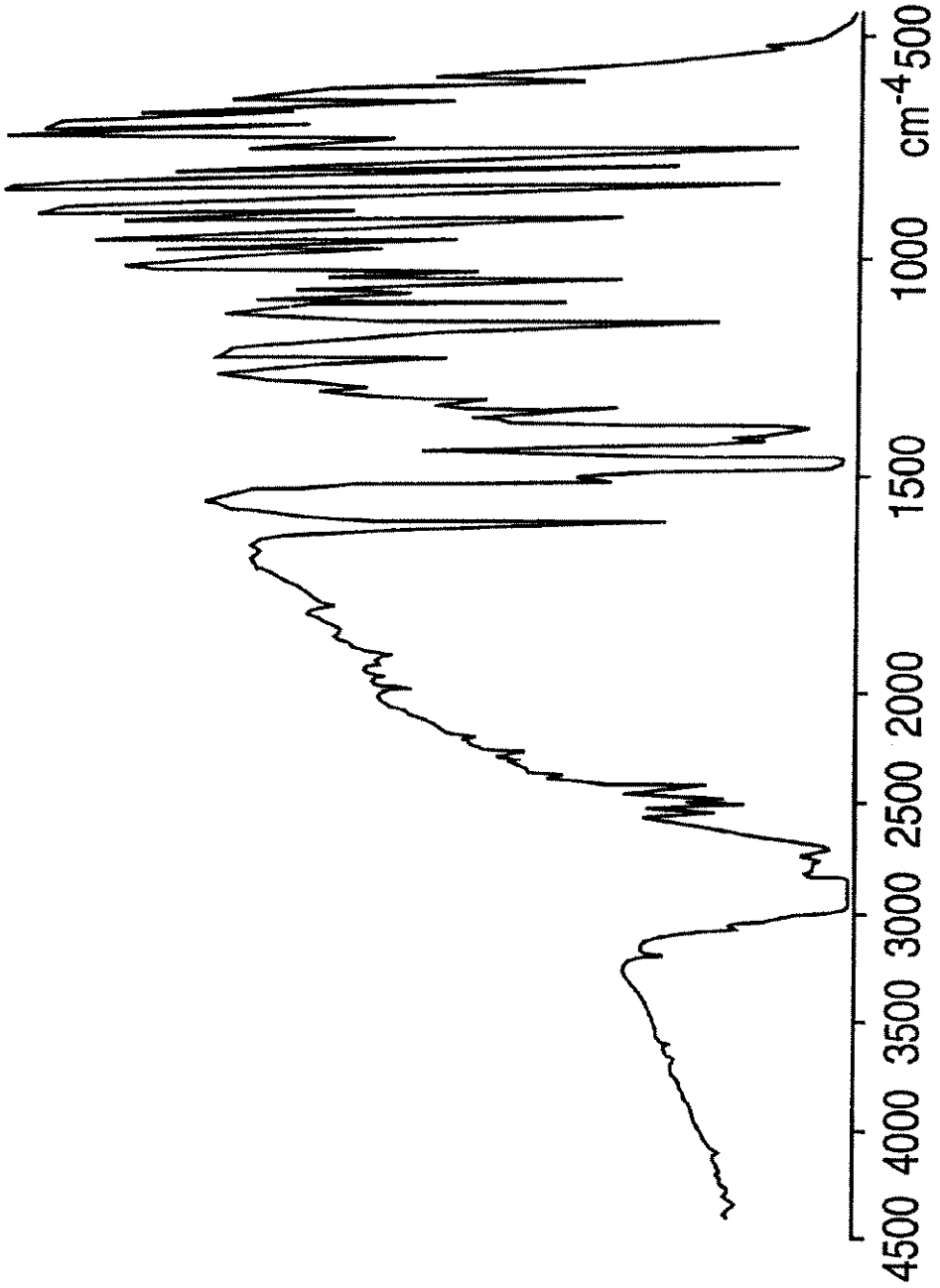

FIG. 4

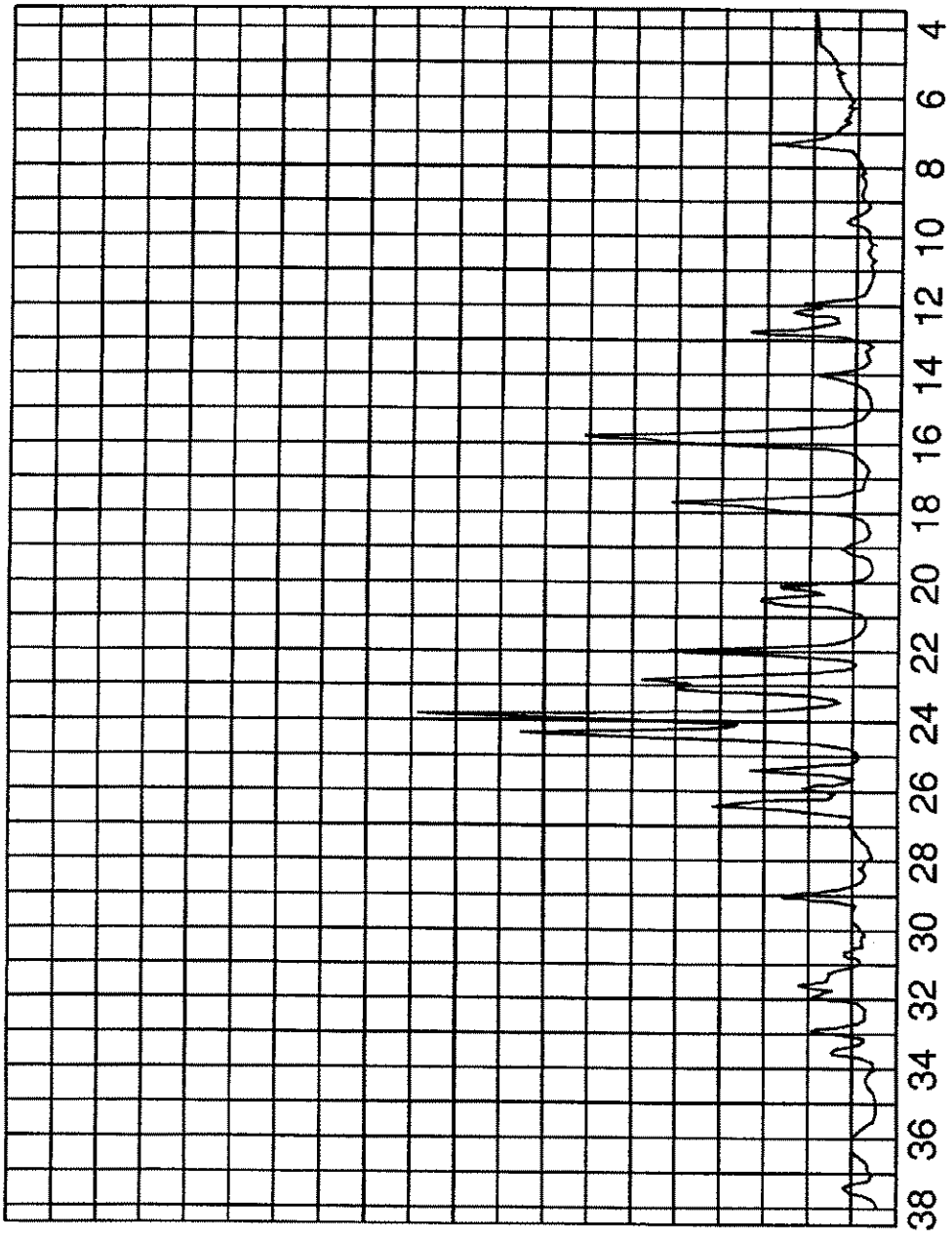

FIG. 5

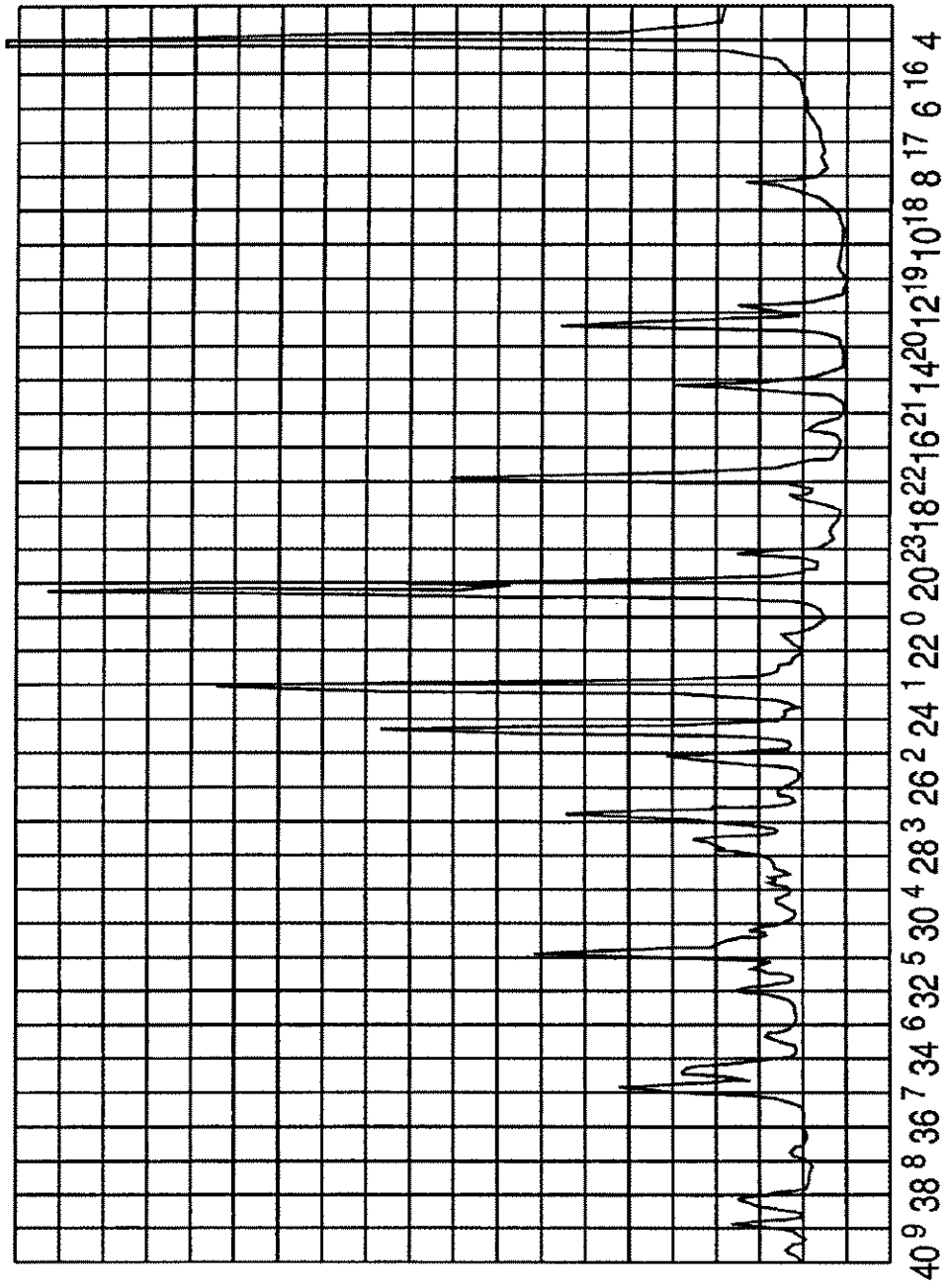
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FIG. 6

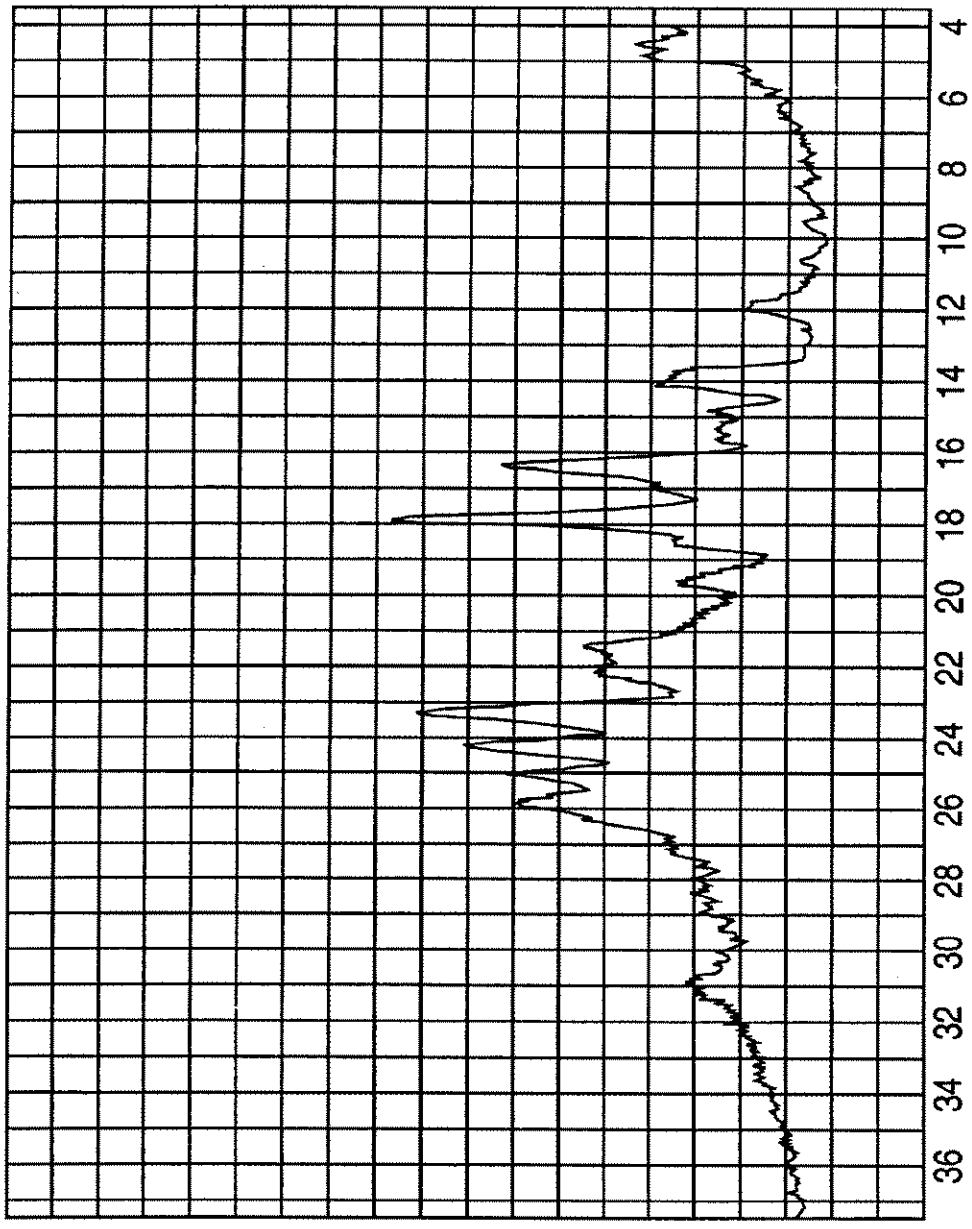

FIG. 7

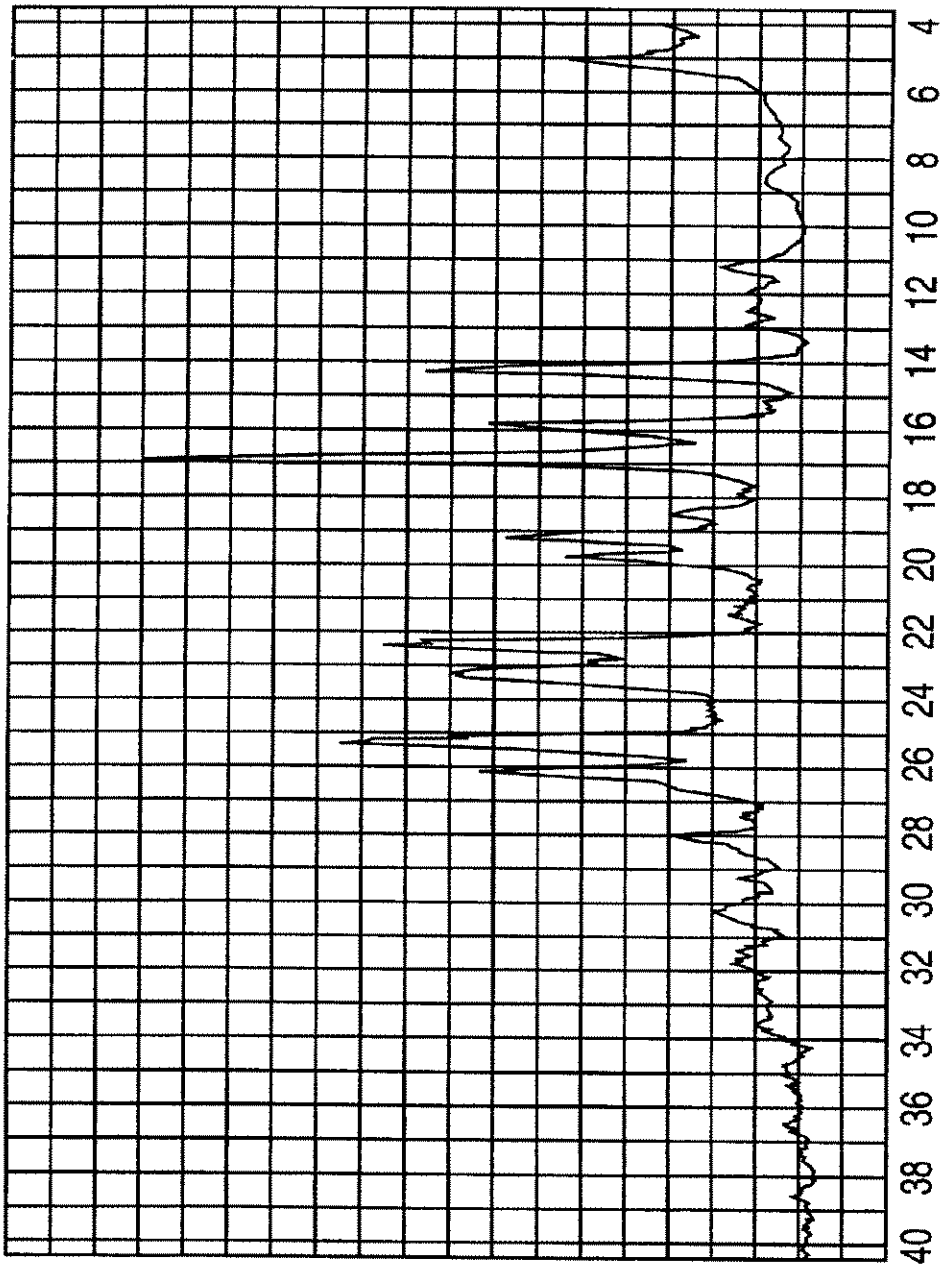

FIG. 8

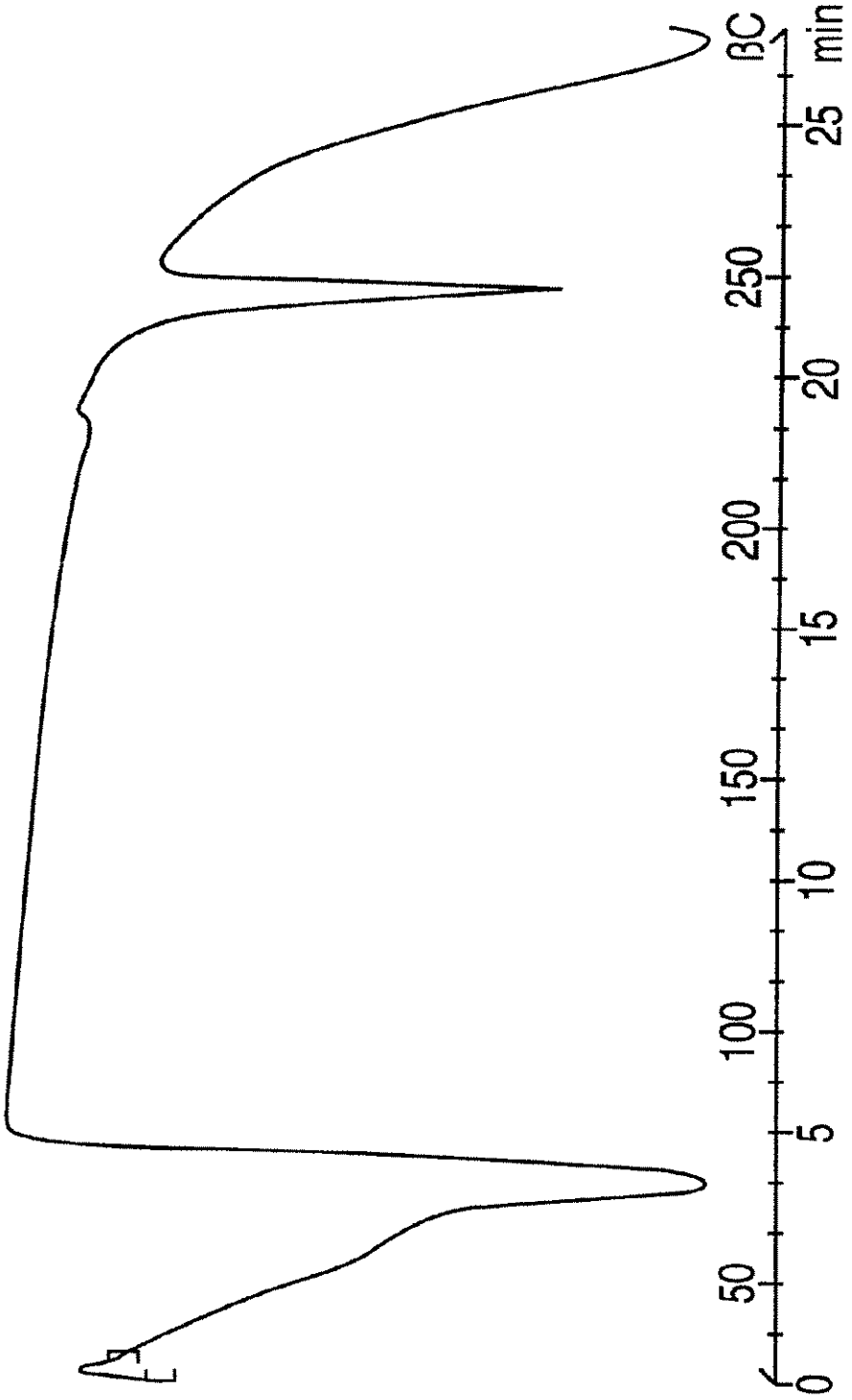

FIG. 9

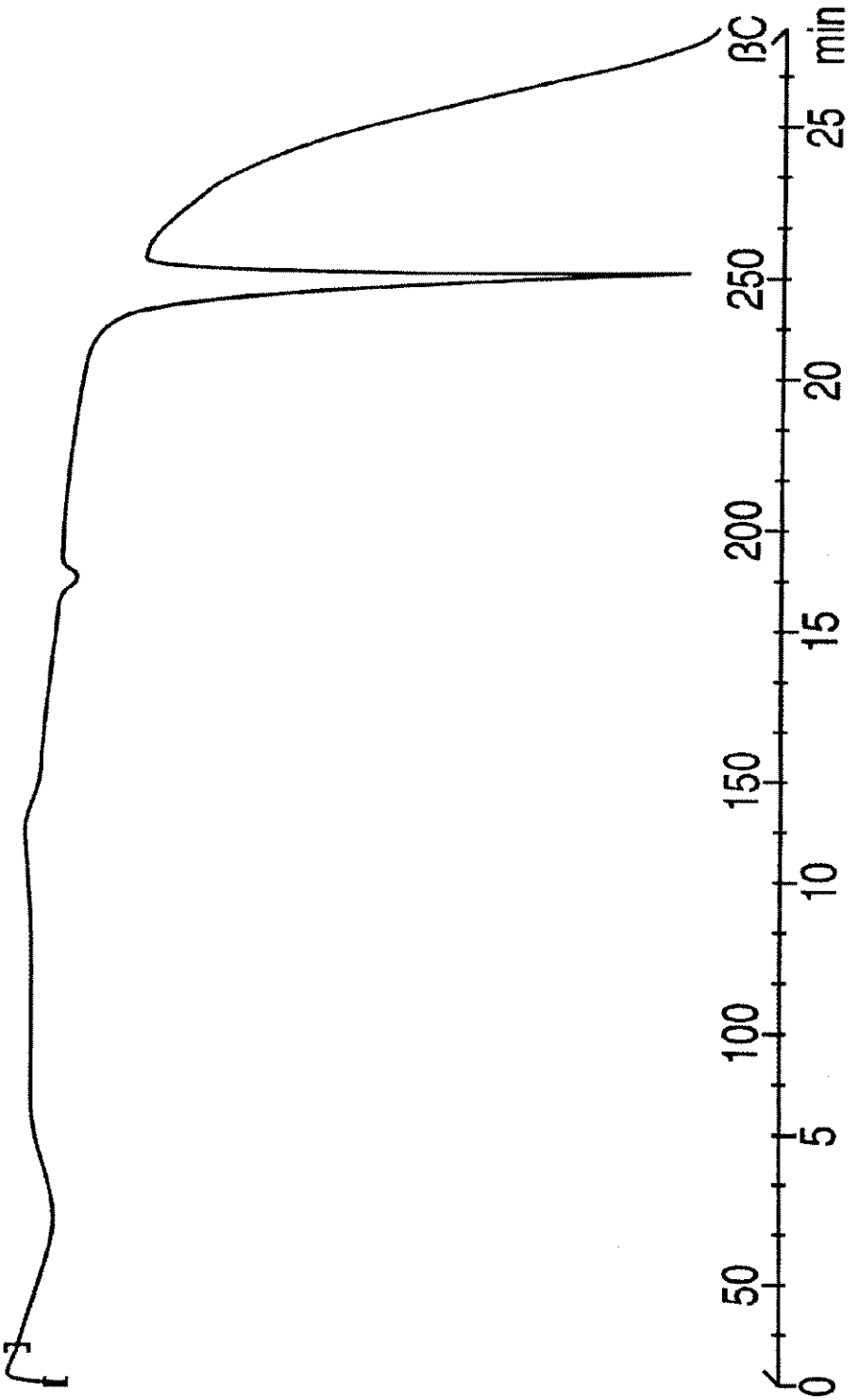

FIG. 10

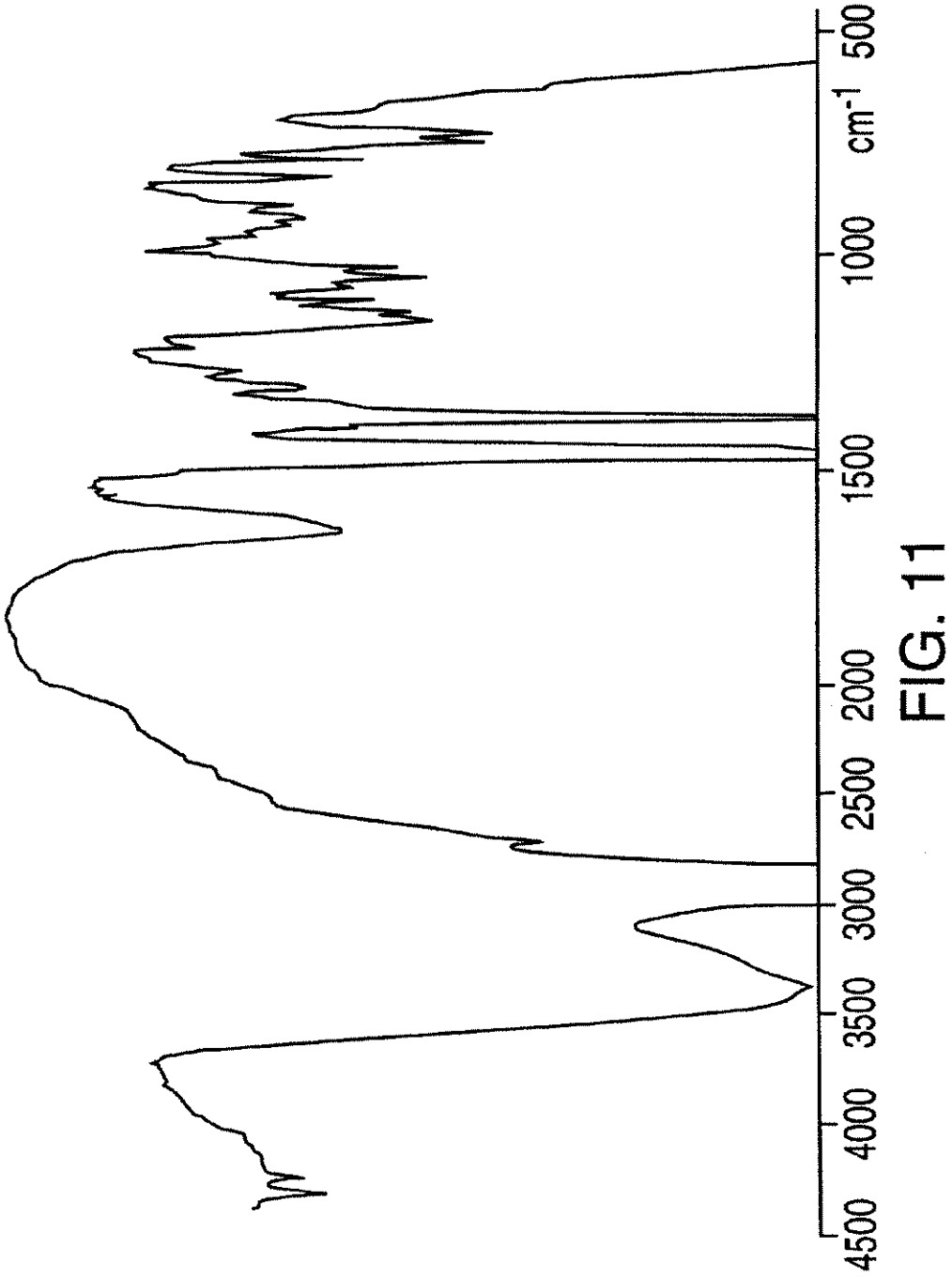

FIG. 11

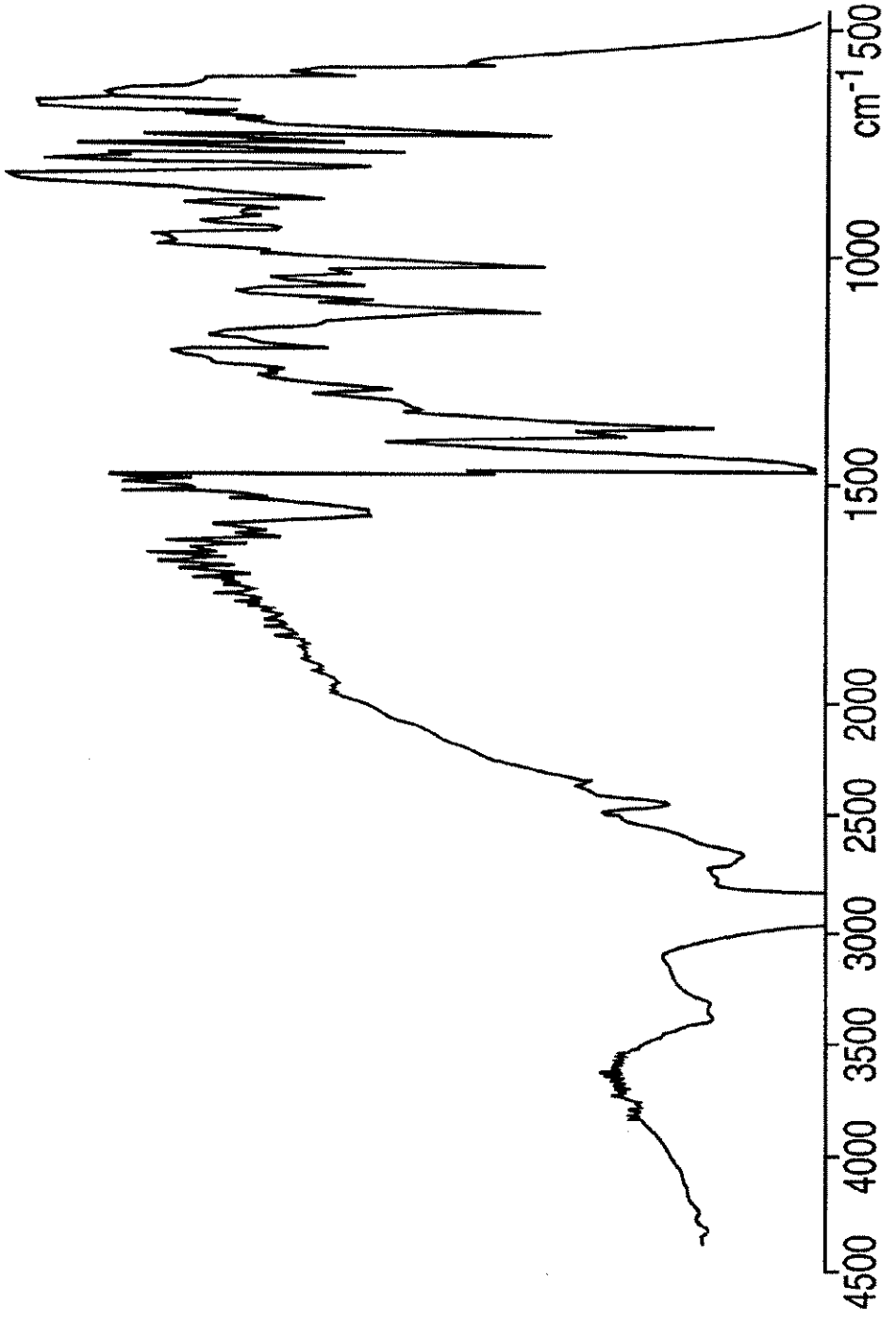

FIG. 12

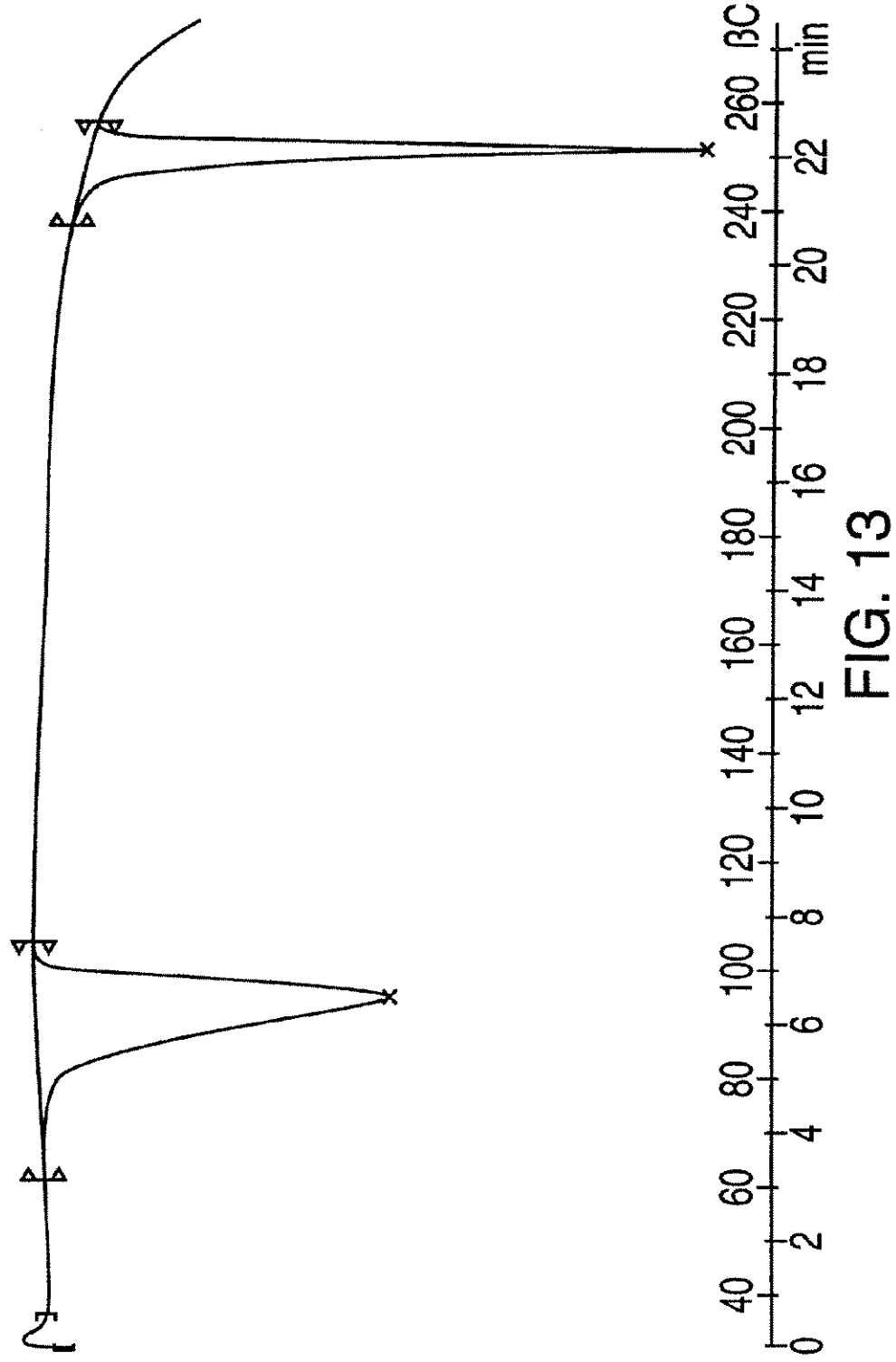
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FIG. 13

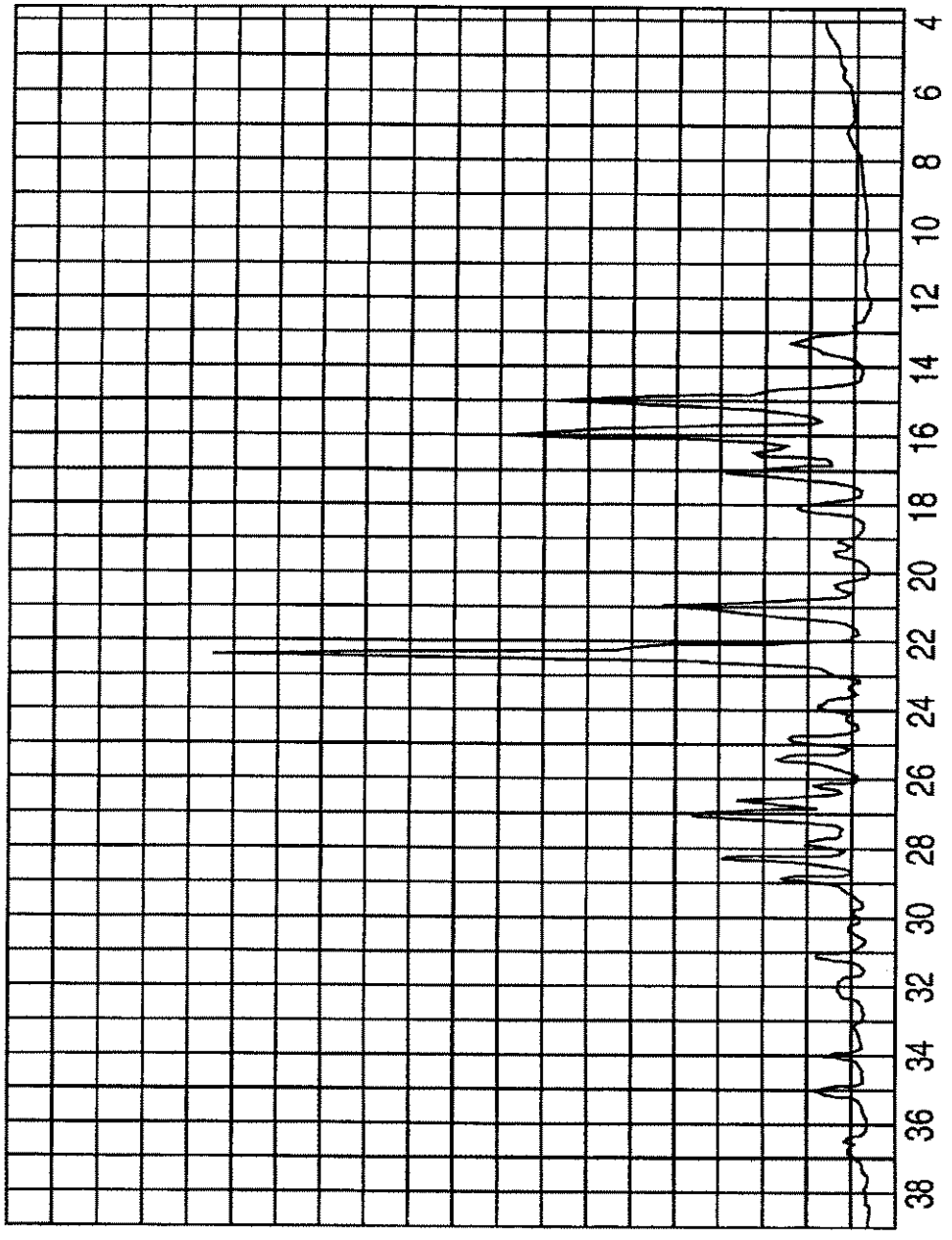

FIG. 14

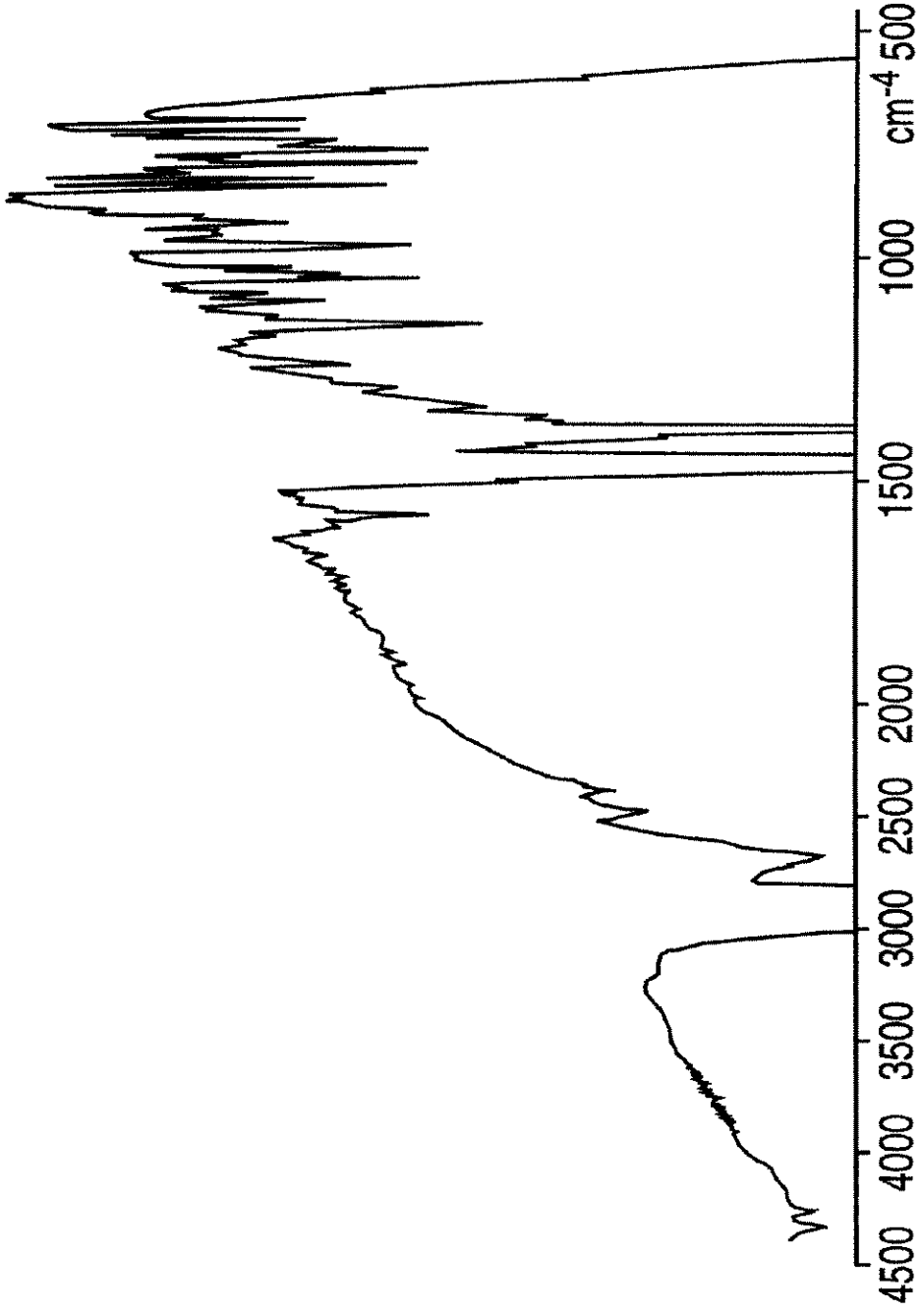

FIG. 15

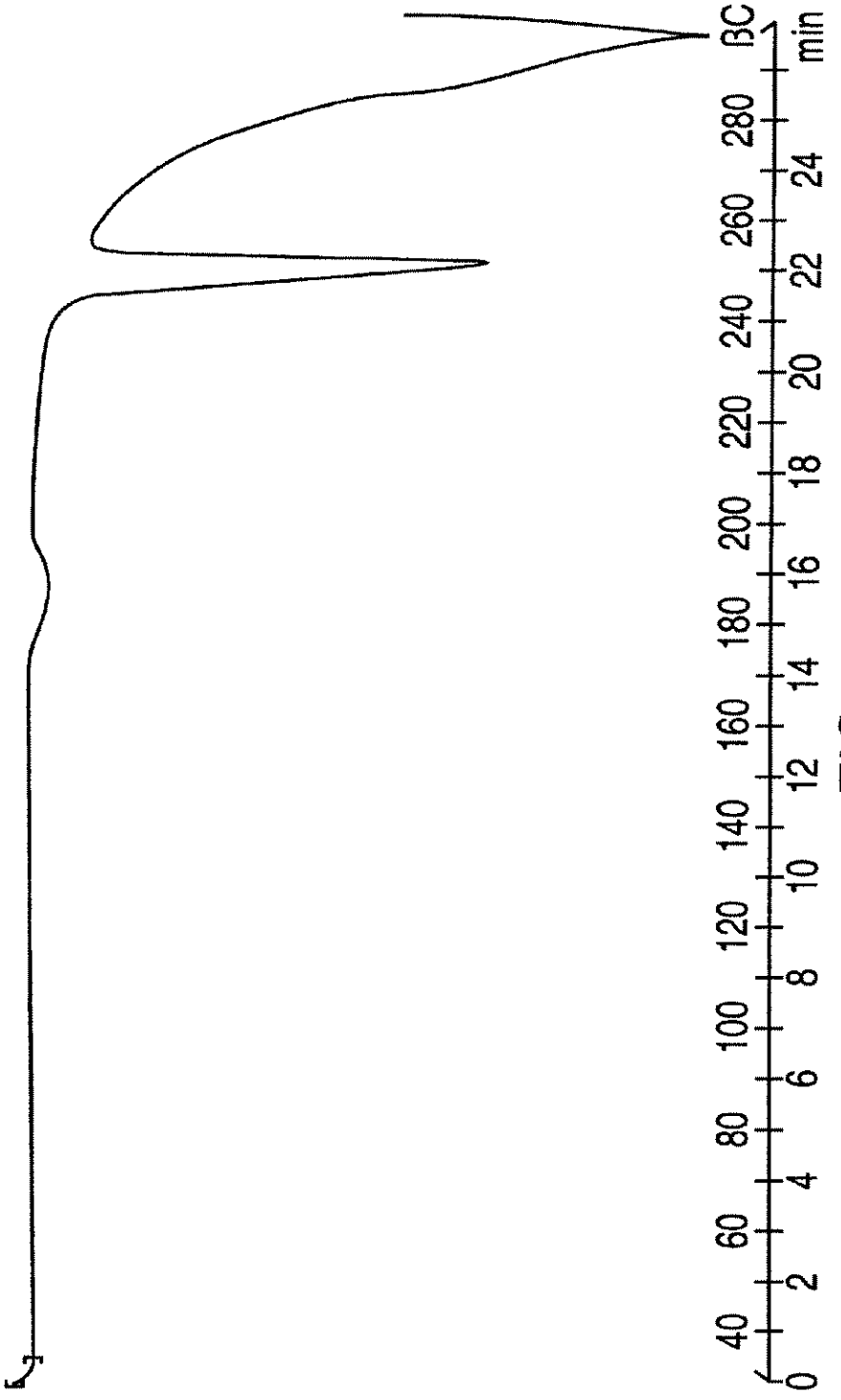
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FIG. 16

METHODS FOR PREPARATION OF SERTRALINE HYDROCHLORIDE POLYMORPHS

CROSS-REFERENCE TO RELATED APPLICATIONS

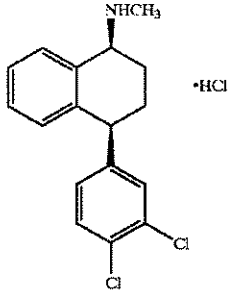
This application is a continuation-in-part of copending application Ser. No. 09/448,985 filed Nov. 24, 1999, the contents of which are incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to novel, reproducible methods for the preparation of crystalline forms of sertraline hydrochloride Forms III and V through X, as well as the preparation of an amorphous form of sertraline hydrochloride.

BACKGROUND OF THE INVENTION

Sertraline hydrochloride, (1S-cis)-4-(3,4 dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride, having the formula



is approved, under the trademark Zoloft®, by the U.S. Food and Drug Administration, for the treatment of depression, obsessive-compulsive disorder and panic disorder.

U.S. Pat. No. 4,536,518 ("the '518 patent") describes the preparation of sertraline hydrochloride with a melting point of 243–245° C., by treating an ethyl acetate/ether solution of the free base with gaseous hydrogen chloride. The solid state properties of the sertraline hydrochloride so produced are not otherwise disclosed.

According to U.S. Pat. No. 5,248,699 ("the '699 patent"), the sertraline hydrochloride produced by the method of the '518 patent has a crystalline form denominated "Form II." The '699 patent discloses four other polymorphs I, III, IV, and V, and characterizes them by single crystal x-ray analysis, powder x-ray diffraction, infra-red spectroscopy, and differential scanning calorimetry. The '699 patent reports that Form II is produced by rapid crystallization of sertraline hydrochloride from an organic solvent, including isopropyl alcohol, ethyl acetate or hexane, and generally describes methods for making sertraline hydrochloride Forms I–V. According to this patent, the preferential formation of Forms I, II or IV in an acidic solution consisting of isopropyl alcohol, hexane, acetone, methyl isobutyl ketone, glacial acetic acid or, preferably, ethyl acetate, depends on the rapidity of crystallization. Form I is described as being made by crystallizing sertraline hydrochloride in an acidic solution using an organic solvent such as those listed above. The crystallization of Form I is carried out at a temperature from about 20° C. to about the solvent reflux temperature, preferably from about 40° to 60° C. The only method described in this patent for making Forms II and IV is by the rapid crystallization of sertraline hydrochloride from an organic solvent such as those listed above. Slow crystallization or granulation of sertraline hydrochloride is said to produce Form I. Form III is described as being formed by heating Forms I, II or IV to temperatures above about 180° C. Granulating either of Forms II, III or IV in any of the solvents listed above at a temperature from about 40° C. to 60° C. is said to cause conversion to Form I. The only method described in this patent for making Form V is by sublimation of sertraline hydrochloride Form I at reduced pressure and at a temperature from about 180–190° C. However, in our hands attempts to repeat this procedure to obtain Form V have been unsuccessful.

SUMMARY OF THE INVENTION

The present invention relates to a process for making sertraline hydrochloride Form V comprising the steps of: dissolving or suspending sertraline hydrochloride in a suitable solvent; removing the solvent; and drying to form sertraline hydrochloride Form V.

The present invention also relates to a process for making sertraline hydrochloride Form V comprising the steps of: dissolving or suspending sertraline base in a solvent; adding hydrogen chloride to the solvent to reduce the pH of the solution or suspension; and isolating sertraline hydrochloride Form V from the solution or suspension.

The present invention also relates to a process for making sertraline hydrochloride Form V comprising the step of drying sertraline hydrochloride Form VII.

The present invention also relates to a process for making sertraline hydrochloride Form V comprising the steps of: dissolving or suspending sertraline hydrochloride in water; adding a sufficient amount of hydrochloric acid or hydrogen chloride to facilitate precipitation of sertraline hydrochloride; removing the water; and isolating sertraline hydrochloride Form V.

The present invention also relates to a process for making sertraline hydrochloride Form VI comprising the steps of: dissolving sertraline base in a solvent; adding hydrochloric acid to the solvent; and isolating sertraline hydrochloride Form VI without further drying.

The present invention also relates to a process for making sertraline hydrochloride Form VI comprising the steps of: dissolving or suspending sertraline hydrochloride in ethanol or methanol; stirring for a time sufficient to induce the transformation of sertraline hydrochloride to sertraline hydrochloride Form VI; and isolating sertraline hydrochloride Form VI.

The present invention also relates to a process for making sertraline hydrochloride Form VIII comprising the steps of: suspending sertraline base in water; adding hydrogen chloride to the water; and filtrating the precipitate so obtained without further drying.

The present invention also relates to a process for making sertraline hydrochloride Form VIII comprising the steps of: suspending or dissolving sertraline hydrochloride ethanolate Form VI or sertraline hydrochloride Form II in water or a mixture of water and isopropyl alcohol; and isolating sertraline hydrochloride Form VIII.

The present invention also relates to a process for making sertraline hydrochloride Form III comprising the steps of: heating sertraline hydrochloride Form V or Form VI to a temperature sufficient, and for a time sufficient, to induce the transformation of sertraline hydrochloride Form V or Form

VI to sertraline hydrochloride Form III; and isolating sertraline hydrochloride Form III.

The present invention also relates to a process for making amorphous sertraline hydrochloride comprising the steps of: suspending or dissolving sertraline base in a non-polar organic solvent; adding gaseous hydrochloric acid; and isolating amorphous sertraline hydrochloride.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form V.

FIG. **2** is a characteristic x-ray powder diffraction spectrum of amorphous sertraline hydrochloride.

FIG. **3** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form V.

FIG. **4** is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form V.

FIG. **5** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form VI.

FIG. **6** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form VII.

FIG. **7** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form VIII.

FIG. **8** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form IX.

FIG. **9** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form VIII.

FIG. **10** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form IX.

FIG. **11** is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form VIII.

FIG. **12** is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form IX.

FIG. **13** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form VI.

FIG. **14** is a characteristic x-ray powder diffraction spectrum of sertraline hydrochloride Form X.

FIG. **15** is a characteristic infrared (IR) absorption spectrum of sertraline hydrochloride Form X.

FIG. **16** is a characteristic differential scanning calorimetric (DSC) thermogram of sertraline hydrochloride Form X.

DETAILED DESCRIPTION OF THE INVENTION

Form V

The present invention provides new processes for making sertraline hydrochloride Form V from sertraline hydrochloride, sertraline base or amorphous sertraline hydrochloride. The methods provided in the present invention are more commercially practicable than the sublimation-condensation method of U.S. Pat. No. 5,248,699, which we have not been able to reproduce. It has also surprisingly been found that, by the present method, Form V is formed even at different crystallization rates.

Where the present invention provides methods for the conversion of sertraline hydrochloride to sertraline hydrochloride Form V, in one embodiment sertraline hydrochloride is combined with a solvent. Suitable solvents include methanol, ethanol, 1-methoxy-2-propanol, trichloroethane, water, and mixtures thereof. If a mixture of isopropyl alcohol and water is used, it is preferably an about 6:1 mixture. Preferably the solvent is methanol, ethanol, or mixtures thereof, and most preferably the solvent is ethanol. Sertraline hydrochloride Form V is then isolated by allowing the solution to cool. One preferred method is to rapidly cool the solvent to 5° C. Another preferred method comprises seeding the solution with sertraline hydrochloride Form V crystals, followed by slow cooling to room temperature, followed by filtration and drying.

Alternatively, Form V may be obtained by forming a solution or suspension of sertraline hydrochloride in a suitable solvent and spray drying the solution or suspension. Preferred solvents include water and water/alcohol mixtures.

The present invention also provides methods for the conversion of sertraline hydrochloride to sertraline hydrochloride Form V wherein the solvate sertraline hydrochloride Form VI (described in more detail below) is an intermediate. In this embodiment of the present invention, sertraline hydrochloride is suspended or dissolved in either methanol or ethanol or mixtures thereof thereby forming sertraline hydrochloride Form VI. This intermediate sertraline hydrochloride Form VI is then dried, with or without a separate isolation step, to remove all solvent and sertraline hydrochloride Form V is isolated. Sertraline hydrochloride Form V can also be prepared by suspending or dissolving sertraline hydrochloride solvate Form VI in water.

Sertraline hydrochloride Form V can also be prepared by drying Form VII (described in more detail below). In this embodiment of the present invention, sertraline hydrochloride Form V is dried at 80° C. overnight thereby forming sertraline hydrochloride Form V.

The present invention also provides methods for the conversion of sertraline hydrochloride to sertraline hydrochloride Form V wherein the sertraline hydrochloride Form VIII (described in more detail below) is an intermediate. In this embodiment of the present invention, sertraline hydrochloride Form II is suspended or dissolved in water thereby forming sertraline hydrochloride Form VIII. This intermediate sertraline hydrochloride Form VIII is then dried, with or without a separate isolation step, to remove all solvent and sertraline hydrochloride Form V is isolated. Methods for the preparation of sertraline hydrochloride Form II are disclosed in copending applications serial Nos. 09/448,985 filed Nov. 24, 1999 and attorney docket number 1662/49107, filed May 22, 2000, the contents of which are hereby incorporated by reference.

The present invention also provides methods for the conversion of sertraline base to sertraline hydrochloride Form V. In one such embodiment, sertraline base is added to at least one solvent, and hydrogen chloride gas is bubbled through the solution. Suitable solvents include methanol, ethanol, water, ethyl acetate, isopropyl alcohol, ether, hexane, and toluene, and mixtures thereof. Alternatively, an appropriate amount of hydrogen chloride gas dissolved in a suitable solvent and then combined with the sertraline base solution. As used herein, "hydrogen chloride" includes both gaseous hydrogen chloride and aqueous hydrogen chloride (i.e. hydrochloric acid). Sertraline hydrochloride Form V is isolated by allowing precipitation to occur from about 0° C. to about 60° C. followed by filtration and drying. Preferred solvents include methanol, ethanol, hexane, isopropyl alcohol, or mixtures thereof. In a variation of this method, sertraline base is added to a suitable solvent and the resulting solution is added to a hydrochloric acid solution of pH 0–4; preferably the pH of the solution is about 1.

Alternatively, sertraline base is added to a solvent. The solution is heated and concentrated hydrochloric acid is added. Water may also be added. The solvent may be partially removed by distillation. Sertraline hydrochloride Form V is isolated by allowing the mixture to cool to room temperature and remain at room temperature overnight,

followed by filtration and drying. Suitable solvents for use in this method include methanol, ethanol, water, hexane, isopropyl alcohol, and ethyl acetate, and mixtures thereof.

Alternatively, sertraline base may be combined with a solvent selected from the group consisting of methanol, ethanol and a mixture thereof. A saturated solution of hydrogen chloride gas in isopropyl alcohol is added to induce formation of sertraline hydrochloride Form V. Sertraline hydrochloride Form V is isolated by allowing the solution to stand at room temperature overnight, followed by filtration and drying of the precipitate.

Form V may also be obtained by forming a suspension of sertraline base and hydrochloric acid in water or a water/ethanol mixture and spray drying the suspension. In this embodiment of the present invention, the solution or suspension of sertraline base and hydrochloric acid is sprayed into a heated chamber. The temperature of the chamber is such that the solvent is removed thus forming sertraline hydrochloride Form V.

Sertraline base for use in the processes of the present invention may be produced by dissolving sertraline mandelate in ethyl acetate followed by neutralization of the sertraline mandelate with aqueous sodium hydroxide. The organic phase is separated from the aqueous phase and dried using magnesium sulfate. The solvent is removed under reduced pressure to produce sertraline base as an oil. Methods for making sertraline base are set forth in U.S. Pat. Nos. 4,536,518 and 5,248,699, the contents of which are incorporated herein by reference.

Where the present invention provides methods for the conversion of amorphous sertraline hydrochloride to sertraline hydrochloride Form V, amorphous sertraline hydrochloride is kept in a closed container, such as a bag, and warmed to about 40° C. to about 80° C. or is stored at room temperature for a period between a few hours and several days depending on the temperature.

The sertraline hydrochloride Form V that results from practicing the invention as exemplified herein can be characterized by its powder X-ray diffraction pattern. FIG. **1** is a representative pattern of sertraline hydrochloride Form V. The principal peaks observed are at about 5.2°±0.2, 10.4°±0.2, 11.0°±0.2, 14.3°±0.2, 16.5°±0.2, 17.3°±0.2, 18.4°±0.2, 19.1°±0.2, 19.7°±0.2, 20.9°±0.2, 22.0°±0.2, 23.2°±0.2, 23.6°±0.2, 25.5°±0.2, 26.0°±0.2, and 29.1°±0.2 degrees 2 theta.

Three experiments were performed in order to repeat the procedure described in U.S. Pat. No. 5,248,699 for preparing Form V by sublimation. Two experiments were performed by sublimating a sample of Form I under 30 mm Hg vacuum and temperature between 170–190° C. A third experiment was performed by sublimating a sample of Form I under high vacuum (0.1 mm Hg) and temperature between 180–195° C.

The three samples of sertraline hydrochloride prepared by sublimation were analyzed by powder x-ray diffraction. In all cases, the typical broad featureless pattern without sharp peaks typical of amorphous materials was obtained. FIG. **2** is one such pattern.

In conclusion, sertraline hydrochloride could not be obtained by following the procedure set forth in U.S. Pat. No. 5,248,699 for preparing Form V by sublimation of Form I.

The IR spectrum of sertraline hydrochloride Form V produced by the present process is characterized by the following bands: 773 cm^{-1}, 822 cm^{-1}, 1012 cm^{-1}, 1032 cm^{-1}, 1054 cm^{-1}, 1133 cm^{-1}, 1328 cm^{-1}, 1562 cm^{-1}, and 1590 cm^{-1}, as shown in FIG. **4**.

The sertraline hydrochloride Form V of the present process is further characterized by the DSC thermogram data, for example, as disclosed in FIG. **3**. The DSC thermogram is characterized by a small endotherm (~3 Joule per gram) at about 210° C., believed to be a solid-solid transformation (based upon observation under a hot stage microscope) to Form III, and a melting peak 251° C.

Form VI

Sertraline hydrochloride Form VI is a solvated crystal form of sertraline hydrochloride. Sertraline hydrochloride Form VI may be an ethanolate, wherein ethanol is incorporated into the crystal structure of Form VI. Alternatively, sertraline hydrochloride Form VI may be a methanolate, wherein methanol is incorporated into the crystal structure of sertraline hydrochloride Form VI. All sertraline hydrochloride Form VI solvates have identical powder x-ray diffraction patterns. Therefore, when referring to sertraline hydrochloride Form VI all sertraline hydrochloride Form VI solvates, such as sertraline hydrochloride Form VI ethanolate and sertraline hydrochloride Form VI methanolate, are necessarily included.

To form the novel crystalline form sertraline hydrochloride Form VI, sertraline base is added to the appropriate solvent. Which solvent is appropriate will depend on which solvate is to be formed, e.g. ethanol (to form the ethanolate) and methanol (to form the methanolate). Hydrogen chloride gas is then bubbled through the solution. Sertraline hydrochloride Form VI is isolated by allowing precipitation to occur, followed by filtration. The DSC thermogram of Form VI crystallized from ethanol displays a desolvation peak at 95° C. (see FIG. **13**) and loses 11.2% weight (by TGA); Form VI crystallized from methanol loses 8.3 % weight (by TGA) upon desolvation. Form VI crystallized from ethanol is an ethanolate, and more specifically is a monoethanolate. Form VI crystallized from methanol is a methanolate, and more specifically is a monomethanolate.

The present invention also provides new processes for making sertraline hydrochloride solvate Form VI by reslurry of other sertraline hydrochloride crystalline forms. In the conversion of sertraline hydrochloride to sertraline hydrochloride ethanolate Form VI, sertraline hydrochloride is dissolved in the appropriate solvent and stirred for about 18–36 hours; 24 hours is preferred. Sertraline hydrochloride solvate Form VI is isolated by a suitable method, such as filtration. Sertraline hydrochloride Forms I, II, III IV, V and X are suitable for use as starting materials in this process.

The sertraline hydrochloride Form VI so isolated is a solvate and exhibits the powder x-ray diffraction pattern of FIG. **5**, comprising peaks at 7.3°±0.2, 12.1°±0.2, 12.7°±0.2, 14.0°±0.2, 15.6°±0.2, 17.6°±0.2, 20.1°±0.2, 20.6°±0.2, 21.9°±0.2, 22.7°±0.2, 23.0°±0.2, 23.8°±0.2, 24.3°±0.2, 25.4°±0.2, and 26.3°±0.2 degrees two-theta. Drying of the precipitated sertraline hydrochloride Form VI at 50–60° C. overnight yields sertraline hydrochloride Form V.

Form VII

It has also been discovered that a new crystalline form of sertraline hydrochloride, designated Form VII, may be obtained by suspending or dissolving Form V in water, and filtrating the suspension after one day without further drying.

In another embodiment of the invention, sertraline hydrochloride Form VII is made from sertraline hydrochloride Form VI. Sertraline hydrochloride Form VI is dispersed in water and the mixture is heated to facilitate the dissolution of sertraline hydrochloride Form VI. The solution may be heated to between about 30° C. and about 90° C., preferably to about 80° C. The pH is then lowered, preferably to about

pH 1, and the mixture is allowed to cool to room temperature and stirred until the reaction is complete. Preferably the reaction is stirred for two hours at room temperature. Sertraline hydrochloride Form VII is isolated by filtration and washing with water.

As shown in FIG. 6, sertraline hydrochloride Form VII is characterized by two unique strong x-ray powder diffraction peaks at 4.0°±0.2, and 20.0 degrees two-theta and medium intensity peaks at 8.0°±0.2, 11.6°±0.2, 12.0°±0.2, 13.8°±0.2, 16.5°±0.2, 22.8°±0.2, 24.1°±0.2, 25.0°±0.2, 26.6°±0.2, 30.7°±0.2, 34.7°±0.2 2 two-theta. The TGA curve shows a loss on drying of about 45%.

Forms VIII and IX

Additional new crystalline forms of sertraline hydrochloride, Forms VIII and IX, have also been discovered. Sertraline hydrochloride hydrate Form VIII may be produced by suspending sertraline base in water and heating, followed by acidification and filtration. Form IX is obtained by drying of Form VIII. Preferably the sertraline base is suspended in water, the suspension heated to a temperature between about 30° C. and about 80° C. Hydrogen chloride is added to reduce the pH, preferably to between about 1 to about 4, and the resulting solution is cooled to room temperature.

The present invention also provides new processes for making sertraline hydrochloride Form VIII from sertraline hydrochloride ethanolate Form VI. In one embodiment of the present invention, a slurry of sertraline hydrochloride ethanolate Form VI in water or a mixture of water and isopropyl alcohol is stirred, preferably for about one hour. The slurry is then filtered and washed with water and sertraline hydrochloride hydrate Form VIII is isolated.

The present invention also provides precesses of making sertraline hydrochloride Form VIII from sertraline hydrochloride Form II. In the conversion of sertraline hydrochloride Form II to sertraline hydrochloride Form VIII, sertraline hydrochloride Form II is suspended in water or a mixture of water and isopropyl alcohol and stirred, preferably overnight, and sertraline hydrochloride hydrate Form VIII is isolated by filtration.

Sertraline hydrochloride Form VIII is characterized by x-ray powder diffraction peaks at 4.7°±0.2, 11.8°±0.2, 16.3°±0.2, 17.8°±0.2, 19.6°±0.2, 23.2°±0.2, 24.2°±0.2, 25.1°±0.2, and 26.0°±0.2 two-theta, as described in FIG. 7.

The DSC thermogram for Form VIII is characterized by a strong endotherm below 100° C., small endothermic and exothermic events at about 220° C. and a melting peak at 247° C. as described in FIG. 9.

The TGA curve shows a loss on drying step of about 20% below 100° C.

The IR spectrum of Form VIII is characterized by the following bands: 740 cm^{-1}, 779 cm^{-1}, 822 cm^{-1}, 887 cm^{-1}, 915 cm^{-1}, 1031 cm^{-1}, 1053 cm^{-1}, 1110 cm^{-1}, 1134 cm^{-1}, 1153 cm^{-1}, 1217 cm^{-1}, 1307 cm^{-1}, and 1377 cm^{-1}, as described in FIG. 11.

Sertraline hydrochloride Form IX is characterized by x-ray powder diffraction peaks at 5.1°±0.2, 14.2°±0.2, 15.8°±0.2, 16.8°±0.2, 19.2°±0.2, 19.7°±0.2, 22.4°±0.2, 23.2°±0.2, 25.3°±0.2 and 26.1°±0.2 two-theta, as described in FIG. 8.

The IR spectrum of Form IX is characterized by the following bands: 701 cm^{-1}, 715 cm^{-1}, 741 cm^{-1}, 758 cm^{-1}, 780 cm^{-1}, 816 cm^{-1}, 823 cm^{-1}, 1030 cm^{-1}, 1053 cm^{-1}, 1078 cm^{-1}, 1110 cm^{-1}, 1204 cm^{-1}, 1217 cm^{-1}, 1307 cm^{-1}, and 1350 cm^{-1}, as described in FIG. 12.

Form X

It has further been discovered that another crystalline form of sertraline hydrochloride, denominated Form X may be obtained by suspending sertraline hydrochloride in benzyl alcohol, and heating to facilitate dissolution. The solution is cooled and the precipitate filtered, washed with benzyl alcohol and dried, to yield sertraline hydrochloride Form X.

The Form X produced in this manner is characterized by a powder x-ray diffraction pattern having its principal peaks at 15.0°±0.2, 16.0° 16.5°±0.2 17.0°±0.2, 18.1°±0.2, 21.0°±0.2, 22.4°±0.2, 24.9°±0.2, 25.4°±0.2, 26.2°±0.2, 27.1°±0.2, 28.4°±0.2, and 29.0°±0.2 degrees two-theta as described in FIG. 14.

The IR spectrum of Form X is characterized by the following bands: 742 cm^{-1}, 776 cm^{-1}, 806 cm^{-1}, 824 cm^{-1}, 1002 cm^{-1}, 1017 cm^{-1}, 1028 cm^{-1}, 1060 cm^{-1}, 1079 cm^{-1}, 1135 cm^{-1}, 1218 cm^{-1}, 1314 cm^{-1}, 1336 cm^{-1}, and 1560 cm^{-1} as described in FIG. 15.

The DSC of Form X shows a small endotherm at about 190° C. followed by a melting endotherm at about 250° C. (see FIG. 16).

Form III

The present invention provides new processes for making sertraline hydrochloride Form III from sertraline hydrochloride Forms V and VI. In the conversion of sertraline hydrochloride Form V to sertraline hydrochloride Form III, Form V is heated to a temperature between about 150° C. and about 180° C. for about 3 hours to about 2 days to induce the formation of sertraline hydrochloride Form III. Heating for 24 hours is preferred. The reaction may be stirred. The method of the present invention has the advantage of using no solvent.

Amorphous Sertraline Hydrochloride

In an embodiment of the present invention, amorphous sertraline is made by dissolving sertraline hydrochloride in water or a water/alcohol mixture and drying the solution by the spray dryer technique. Amorphous sertraline hydrochloride may also be made by sublimation of sertraline hydrochloride.

The amorphous sertraline hydrochloride produced by methods of the present invention is characterized by a powder x-ray diffraction pattern having the typical broad featureless pattern without sharp peaks typical of amorphous materials. FIG. 2 is one such pattern.

Pharmaceutical Compositions Containing Sertraline Hydrochloride Polymorphs

In accordance with the present invention, these new crystalline forms of sertraline hydrochloride and known forms of sertraline hydrochloride prepared by the new methods disclosed herein may be prepared as pharmaceutical compositions that are particularly useful for the treatment of depression, obsessive-compulsive disorder and panic disorder. Such compositions comprise one of the new crystalline forms of sertraline hydrochloride with pharmaceutically acceptable carriers and/or excipients known to one of skill in the art.

For example, these compositions may be prepared as medicaments to be administered orally, parenterally, rectally, transdermally, bucally, or nasally. Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or gelatin capsules, sub-lingual tablets, syrups and suspensions. Suitable forms of parenteral administration include an aqueous or non-aqueous solution or emulsion, while for rectal administration suitable forms for administration include suppositories with hydrophilic or hydrophobic vehicle. For topical administration the invention provides suitable transdermal delivery systems known in the art, and for nasal delivery there are provided suitable aerosol delivery systems known in the art.

Experimental

The powder X-ray diffraction patterns were obtained by methods known in the art using a Philips X-ray powder diffractometer, Goniometer model 1050/70 at a scanning speed of 2° per minute, with a Cu radiation of λ=1.5418 §.

The differential scanning calorimeter thermograms were obtained by methods known in the art using a DSC Mettler 821 Star°. The weight of the samples was less than 5 mg. The temperature range of scans was 30° C.–300° C. at a rate of 10° C./min. Samples were purged with nitrogen gas at a flow rate of 40 mL/min. Standard 40 μm aluminum crucibles were used having lids with three small holes.

The infrared spectra were obtained by methods known in the art using a Perkin Elmer FT-IR Paragon 1000 spectrometer. Samples were analyzed in Nujol mulls. Spectra were obtained at 4 cm^{-1} resolution and 16 scans each.

EXAMPLES

The present invention will now be further explained in the following examples. However, the present invention should not be construed as limited thereby. One of ordinary skill in the art will understand how to vary the exemplified preparations to obtain the desired results.

Example 1

Preparation of Sertraline Base

Sertraline mandelate (5 g) was stirred at room temperature with 50 mL ethyl acetate. Aqueous sodium hydroxide was added dropwise until the sertraline mandelate was completely neutralized. The phases were separated and the organic phase was dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure resulting sertraline base as an oil (3.2 g).

Example 2

Preparation of Sertraline Hydrochloride Form VI and Form V

Sertraline base (25 g) was dissolved in methanol (125 mL) at room temperature. The solution was acidified with hydrogen chloride gas until pH 1.5 was reached. (Precipitation occurred during acidification.) The temperature rose to approximately 40° C. The slurry was allowed to cool to room temperature and stirred for about 2 hours. The solid was separated by filtration to give sertraline hydrochloride methanolate Form VI. Drying the product overnight gave sertraline hydrochloride Form V.

Example 3

Preparation of Sertraline Hydrochloride Form VI and Form V

Sertraline base (3.2 g) was dissolved in absolute ethanol (32 mL) at room temperature and then hydrogen chloride gas was bubbled in until pH 0.5 was reached. The temperature rose to 40° C. The slurry was allowed to cool to room temperature and stirred for about 16 hours. The solid was separated by filtration, and washed with ethanol (3×2 mL). FIG. **5** sets forth the X-ray diffraction pattern of the product (sertraline hydrochloride ethanolate Form VI) so obtained. Drying overnight at 50–60° C. of that product yielded 2.95 g (82%) of sertraline hydrochloride Form V.

Example 4

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was dissolved in absolute ethanol (15 mL) at room temperature. A saturated solution of hydrogen chloride in isopropyl alcohol was added dropwise to reach a pH of 1.3. The resulting slurry was stirred at room temperature overnight. The solid was separated by filtration and dried overnight at 50–60° C. yielding 2.75 g (81. 8%) sertraline hydrochloride Form V.

Example 5

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was dissolved in absolute ethanol (15.5 mL) at room temperature and then the solution was cooled to approximately 0° C. Hydrogen chloride gas was bubbled until pH 0.5 was reached. The temperature rose to approximately 7° C. Precipitation occurred and the slurry was stirred at about 10° C. for 2 hours. The solid was isolated by filtration, washed with ethanol and dried at approximately 50° C. The dried material (2.87 g, yield 82.7%) was sertraline hydrochloride Form V.

Example 6

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was stirred with 35 mL water. The slurry was heated at ~70° C. and, while maintaining this temperature, concentrated hydrochloric acid was added until pH 1 was reached. During acidification, almost complete dissolution was observed followed by precipitation. The mixture was cooled to room temperature and stirred for 2 hours. The solid was isolated by filtration, washed with water and dried overnight at 50–60° C., yielding 3.23 g (96%) sertraline hydrochloride Form V.

Example 7

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3 g) was dissolved in 10 mL absolute ethanol at 40° C. The solution was heated to 50–60° C. and concentrated hydrochloric acid 32% (1.2 mL) was added until pH ~1.3 was reached. Water (12 mL) was added. The resulting clear solution was concentrated to half its volume and was allowed to cool naturally to room temperature. The solid was isolated by filtration, washed with water and dried overnight at 50–60° C., yielding 3.18 g (94.65%) sertraline hydrochloride Form V.

Example 8

Preparation of Sertraline Hydrochloride Form V

Sertraline base (3.7 g) was dissolved in 18.5 mL absolute ethanol and the solution was heated to 60° C. Hydrogen chloride gas was bubbled through the ethanol solution until pH ~0.5 was reached. The mixture was cooled to room temperature and the stirring was continued for 2 hours. The solid obtained after filtration, washing with ethanol and drying at 50° C. was sertraline hydrochloride Form V (3.16 g, yield 76%).

Example 9

Preparation of Sertraline Hydrochloride Form V

Sertraline free base was dissolved in ethanol absolute and the solution was acidified with hydrogen chloride gas to about pH 3. Precipitation occurs and the slurry was stirred at room temperature for 2 hours. The resulting solid was filtered, washed with ethanol and dried to yield sertraline hydrochloride Form V.

Example 10

Preparation of Sertraline Hydrochloride Form V

Sertraline free base (13.3 g) was dissolved in absolute ethanol (60 mL) and was added dropwise over one hour to ethanol (20 mL) containing hydrogen chloride (17.5 g) at 35° C. with precipitation. After 2 hours, the solid was filtrated, washed with ethanol and dried at about 80° C. to yield sertraline hydrochloride Form V (12.9 g, yield 87%).

Example 11

Preparation of Sertraline Hydrochloride Form V

Anhydrous sertraline hydrochloride (2 g) was stirred with 14 mL absolute ethanol and heated to reflux to obtain a clear solution. The solution was seeded with sertraline hydrochloride Form V and cooled naturally to room temperature. Massive precipitation was observed at about 50° C. The slurry was stirred at room temperature during 2 hours. The solid was filtered, washed with ethanol (3 mL) and dried overnight at 50–60° C. yielding 1.71 g (85.5%) of sertraline hydrochloride Form V.

Example 12

Preparation of Sertraline Hydrochloride Form V

Sertraline hydrochloride ethanolate (Form VI) (40 g) in 400 mL water was heated to 80° C. and complete dissolution was obtained. The pH was adjusted to approximately one with hydrochloric acid and the solution was naturally cooled to room temperature and stirred for 2 hours. The solid was filtered and dried at 50° C. for approximately 16 hours, yielding sertraline hydrochloride Form V.

Example 13

Preparation of Sertraline Hydrochloride Form V

Sertraline hydrochloride ethanolate (Form VI) (2 g) was mechanically stirred with ethanol (0.5 mL) at room temperature for 40 hours. The resulting solid was sertraline hydrochloride Form V.

Table 1 sets forth a summary of additional experiments conducted generally following procedures described above.

TABLE 1

PREPARATION OF SERTRALINE HCL - FORM V

Exp't	Method of Crystallization	XRD	Yield (%)
	SERTRALINE BASE AS STARTING MATERIAL		
A	Methanol/HCl gas	V	78.7
B	Methanol/HCl gas	V	69
C	Methanol/HCl aqueous	V	87.8
D	Ethanol/HCl gas	V	80.9
E	Water/HCl aqueous	V	96
F	Hexane/Isopropyl alcohol/HCl gas	V	89.9
G	Methanol/HCl aqueous/water	V	89
H	Isopropyl alcohol/HCl aqueous/water	V	78
I	Ethanol/HCl aqueous/evaporation of ethanol	V	96.1
J	Ethyl acetate/HCl aqueous/water/evaporation of ethyl acetate	V	96.1
K	Ethanol/isopropyl alcohol/HCl gas	V	81.8
L	Methanol/isopropyl alcohol/HCl gas	V	82.4

TABLE 1-continued

PREPARATION OF SERTRALINE HCL - FORM V

Exp't	Method of Crystallization	XRD	Yield (%)
	SERTRALINE HCl AS STARTING MATERIAL		
M	Methanol (Form I and amorphous)	V	60
N	Ethanol (Form V)	V	85.5
O	Isopropyl alcohol/water (Form V)	V	28

PXRD = powder x-ray diffraction.

Example 14

Preparation of Sertraline Hydrochloride Form VII

1.003 g Sertraline hydrochloride Form V was stirred for 24 hours at room temperature in 20 mL water (HPLC grade). At the end of the stirring the mixture looked like a jelly suspension. The suspension was filtrated and the compound obtained was kept at cold conditions (4° C.) until analyzed by x-ray diffraction.

Example 15

Preparation of Sertraline Hydrochloride Form VII from Sertraline Hydrochloride Form VI

A solution of sertraline hydrochloride ethanolate (Form VI) (40 g) in water (400 mL) was heated at 80° C. and complete dissolution of sertraline hydrochloride ethanolate (Form VI) was obtained. The pH was adjusted to about 1 and the solution was allowed to cool to room temperature and then stirred for 2 additional hours. The solid was isolated by filtration and washed with water to yield sertraline hydrochloride Form VII.

Sertraline hydrochloride Form VII dried overnight at 80° C. forms sertraline hydrochloride Form V.

Example 16

Preparation of Sertraline Hydrochloride Forms VIII and IX from Sertraline Base

Sertraline base (2.7 g) was suspended in 27 mL of water. This mixture was heated to 80° C. and treated with hydrochloric acid until about pH 1 was reached. A clear solution was obtained, which on cooling gave a precipitate. After 2 hours stirring at room temperature the solid was isolated by filtration. This solid was characterized by powder x-ray diffraction (see FIG. **3**, Form VIII). Drying for 24 hours at ~50° C. yielded 2.32 g (76.8%) of sertraline hydrochloride Form IX, characterized by powder x-ray diffraction, infrared absorption, differential scanning calorimetry, and thermal gravimetric analysis as set forth above and depicted in FIGS. **8**, **10**, and **12**.

Example 17

Preparation of Sertraline Hydrochloride Form VIII

Sertraline hydrochloride ethanolate (Form VI) (40 g) was stirred with water (80 mL) for 1 hour at room temperature. The slurry was filtrated and washed with water to yield sertraline hydrochloride hydrate Form VIII.

Example 18

Preparation of Sertraline Hydrochloride Form VIII from Sertraline Hydrochloride Form II

Sertraline hydrochloride Form 11 (0.4 g) and water (8 mL) were stirred at room temperature over night. The solid was filtrated to yield sertraline hydrochloride hydrate Form VIII.

Example 19

Preparation of Sertraline Hydrochloride Form X

In a 0.1 liter three-necked bottom round flask equipped with a mechanical stirrer, a condenser and a thermometer, 30 mL benzyl alcohol is added to 10 g sertraline hydrochloride. The suspension is heated to 100° C. when a clear solution is obtained. The solution is cooled 2 hours to 25° C. and the precipitate is filtered and washed with benzyl alcohol. After drying under vacuum at 80° C. for 24 hours, 6.2 g of sertraline hydrochloride Form X is obtained (yield 62%). The sertraline hydrochloride Form X was characterized by powder x-ray diffraction and infrared absorption analysis as set forth above and in FIG. **14** and FIG. **15**.

Example 20

Preparation of Sertraline Hydrochloride Ethanolate Form VI by Reslurry of Form I

Sertraline hydrochloride Form I (1 g) and absolute ethanol (20 mL) were stirred at room temperature for 24 hours. Filtration of the mixture yielded sertraline hydrochloride ethanolate-Form VI.

Example 21

Preparation of Sertraline Hydrochloride Ethanolate Form VI by Reslurry of Form II

Sertraline hydrochloride Form II (1 g) and absolute ethanol (20 mL) were stirred at room temperature for 24 hours. Filtration of the mixture yielded sertraline hydrochloride ethanolate Form VI.

Example 22

Preparation of Sertraline Hydrochloride Ethanolate Form VI by Reslurry of Form V

Sertraline hydrochloride Form V (1 g) and ethanol absolute (20 mL) were stirred at room temperature for 24 hrs. Filtration of the mixture yielded sertraline hydrochloride ethanolate Form VI.

Example 23

Preparation of Amorphous Sertraline Hydrochloride

Sertraline free base (10 g) was dissolved in ethyl acetate (690 mL). At room temperature, ether (690 mL) was added to the sertraline ethyl acetate solution and the solution was acidified with HCl gas to about pH 0.5. The resulting gelatinous suspension was stirred at room temperature over night. Filtration and air drying of the suspension yielded amorphous sertraline hydrochloride (9.39 g, yield 83.8%).

Example 24

Preparation of Sertraline Hydrochloride Form III from Form V

Sertraline hydrochloride Form V was heated at 150° C. in a reactor under mechanical stirring for 24 hrs. The resulting material obtained was sertraline hydrochloride Form III.

Example 25

Preparation of Sertraline Hydrochloride Form III from Form VI

Sertraline hydrochloride form VI was heated to 180° C. for 24 hours. The dried material is sertraline hydrochloride Form III.

Example 26

Preparation of Sertraline Hydrochloride Form III from Form V

Sertraline hydrochloride Form V was heated at a temperature >180° C. for 24 hours. The resulting material was sertraline hydrochloride Form III.

Example 27

Preparation of Amorphous Sertraline Hydrochloride

Sertraline hydrochloride Form V (10 g) was dissolved in water (2L) and this solution was dried by the spray dryer technique. The material obtained in this way is Sertraline hydrochloride amorphous.

Example 28

Preparation of Amorphous Sertraline Hydrochloride by Sublimation

Sertraline hydrochloride Form I was sublimated at 190–200° C., at a vacuum of 30–0.1 mm Hg, using a laboratory-type sublimator. The resulting material was amorphous sertraline hydrochloride.

A similar procedure starting from Form V also gave amorphous sertraline hydrochloride.

Example 29

Preparation of Sertraline Hydrochloride Form V from Amorphous Sertraline Hydrochloride

Sertraline hydrochloride amorphous was heated to 80° C. for 24 hours. The resulting product was sertraline hydrochloride Form V.

It should be understood that some modification, alteration and substitution is anticipated and expected from those skilled in the art without departing from the teachings of the invention. Accordingly, it is appropriate that the following claims be construed broadly and in a manner consistent with the scope and spirit of the invention.

What is claimed is:

1. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) dissolving or suspending sertraline hydrochloride in a suitable solvent;

(b) removing the solvent; and

(c) drying to form sertraline hydrochloride Form V.

2. The process of claim **1**, wherein the solvent is selected from the group consisting of methanol, ethanol, water, 1-methoxy-2-propanol, trichloroethane, and isopropyl alcohol, and mixtures thereof.

3. The process of claim **2**, wherein the solvent is water.

4. The process of claim **3**, wherein the step of drying to form sertraline hydrochloride Form V is achieved by spray drying.

5. The process of claim **1**, further comprising the step of seeding the solution with sertraline hydrochloride Form V.

6. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) dissolving or suspending sertraline base in a solvent;

(b) adding hydrogen chloride gas to the solvent to reduce the pH of the solution or suspension; and

(c) isolating sertraline hydrochloride Form V from the solution or suspension.

7. The process of claim 6 wherein the pH of the solution or suspension of sertraline base and hydrogen chloride is about 0 to about 4.

8. The process of claim 6 wherein the solvent is selected from the group consisting of methanol, ethanol, water, ethyl acetate, isopropyl alcohol, ether, hexane, and toluene, and mixtures thereof.

9. The process of claim 8 wherein the solvent is ether.

10. The process of claim 8 wherein the solvent is water.

11. The process of claim 10 wherein the step of isolating sertraline hydrochloride Form V is done by spray drying the solution or suspension.

12. A process for making sertraline hydrochloride Form V comprising the step of drying sertraline hydrochloride Form VII at about 80° C.

13. A process for making sertraline hydrochloride Form V comprising the steps of:

(a) dissolving or suspending sertraline hydrochloride in water;

(b) adding a sufficient amount of hydrogen chloride to facilitate precipitation of sertraline hydrochloride;

(c) removing the water; and

(d) isolating sertraline hydrochloride Form V.

14. A process for making sertraline hydrochloride Form VI comprising the steps of:

(a) dissolving sertraline base in a solvent;

(b) adding hydrogen chloride to the solvent; and

(c) isolating sertraline hydrochloride Form VI without further drying.

15. The process of claim 14 wherein the isolation step comprises precipitation of sertraline hydrochloride Form VI followed by filtration.

16. The process of claim 14 wherein the solvent is at least one solvent selected from the group consisting of ethanol, methanol, or mixtures of methanol or ethanol with water.

17. A process for making sertraline hydrochloride Form VI comprising the steps of:

(a) suspending sertraline hydrochloride Form I, II or V in ethanol or methanol;

(b) stirring for a time sufficient to induce the transformation of sertraline hydrochloride to sertraline hydrochloride Form VI; and

(c) isolating sertraline hydrochloride Form VI.

18. A process for making sertraline hydrochloride Form VIII comprising the steps of:

(a) suspending sertraline base in water;

(b) adding hydrogen chloride to the water; and

(c) filtrating the precipitate so obtained without further drying.

19. A process for making sertraline hydrochloride Form VIII comprising the steps of:

(a) suspending or dissolving sertraline hydrochloride ethanolate Form VI or sertraline hydrochloride Form II in water or a mixture of water and isopropyl alcohol; and

(b) isolating sertraline hydrochloride Form VIII.

20. A process for making sertraline hydrochloride Form III comprising the steps of:

(a) heating sertraline hydrochloride Form V or Form VI to a temperature sufficient, and for a time sufficient, to induce the transformation of sertraline hydrochloride Form V or Form VI to sertraline hydrochloride Form III; and

(b) isolating sertraline hydrochloride Form III.

21. The process of claim 20 wherein the temperature is between about 150° C. and about 180° C.

22. A process for making amorphous sertraline hydrochloride comprising the steps of:

(a) suspending or dissolving sertraline base in a solvent selected from the group consisting of ether, toluene and t-butyl-methyl ether, and mixtures thereof;

(b) adding hydrogen chloride gas; and

(c) isolating amorphous sertraline hydrochloride.

23. The process of claim 2, wherein the solvent is 1-methoxy-2-propanol.

24. A process for making sertraline hydrochloride Form V comprising the steps of :

(a) dissolving or suspending sertraline base in a solvent;

(b) adding hydrochloric acid to the solvent to reduce the pH of the solution or suspension; and

(c) isolating sertraline hydrochloride Form V form the solution or suspension.

25. The process of claim 24, wherein the pH of the solution or suspension of sertraline base and hydrogen chloride is about 0 to about 4.

26. The process of claim 24 wherein the solvent is selected from the group consisting of methanol, ethanol, water, ethyl acetate, isopropyl alcohol, ether, hexane, and toluene, and mixtures thereof.

27. The process of claim 26 wherein the solvent is ether.

28. The process of claim 26 wherein the solvent is water.

29. The process of claim 28 wherein the step of isolating sertraline hydrocloride Form V is done by spray drying the solution or suspension.

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