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Mitsubishi Tanabe Pharma Corp.,
Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica NV,
Janssen Research and Development, LLC,
and Cilag GmbH International

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

MITSUBISHI TANABE PHARMA
CORPORATION, JANSSEN
PHARMACEUTICALS, INC., JANSSEN
PHARMACEUTICA NV, JANSSEN
RESEARCH AND DEVELOPMENT, LLC, and
CILAG GMBH INTERNATIONAL,

Plaintiffs,

v.

APOTEX, INC. and APOTEX CORP.,

Defendants.

Civil Action No. _____

**COMPLAINT FOR PATENT
INFRINGEMENT**

(Filed Electronically)

Plaintiffs Mitsubishi Tanabe Pharma Corp. (“MTPC”), Janssen Pharmaceuticals, Inc. (“JPI”), Janssen Pharmaceutica NV (“JNV”), Janssen Research and Development, LLC (“JRD”), and Cilag GmbH International (“Cilag”) (collectively, “Plaintiffs”), by their attorneys, for their complaint against Apotex, Inc. and Apotex Corp. (collectively, “Apotex”) allege as follows:

NATURE OF THE ACTION

1. This is a civil action for infringement of United States Patent Nos. 7,943,582 (the “’582 patent”) and 8,513,202 (the “’202 patent”) (collectively, the “Patents-in-suit”) under the patent laws of the United States, 35 U.S.C. §100, *et seq.* This action arises from Apotex Corp.’s filing of Abbreviated New Drug Application (“ANDA”) No. 210449 (“the Apotex ANDA”) with the United States Food and Drug Administration (“FDA”) seeking approval to commercially market generic versions of JPI’s 100 mg and 300 mg INVOKANA[®] drug product (“the Apotex ANDA Product”) prior to the expiration of the Patents-in-suit.

THE PARTIES

2. MTPC is a corporation organized and existing under the laws of Japan, having an office and place of business at 3-2-10, Dosho-machi, Chuo-ku, Osaka 541-8505, Japan.

3. JPI is a corporation organized and existing under the laws of the State of Pennsylvania, having its principal place of business at 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560.

4. JNV is a corporation organized and existing under the laws of Belgium, having its principal place of business at Turnhoutseweg, 30, 2340 Beerse, Belgium.

5. JRD is a corporation organized and existing under the laws of the State of New Jersey, having its principal place of business at 920 Route 202, Raritan, New Jersey 08869.

6. Cilag is a company organized and existing under the laws of Switzerland, having its principal place of business at Gubelstrasse 34, 6300, Zug, Switzerland.

7. On information and belief, defendant Apotex, Inc. is a corporation organized and existing under the laws of Canada, having a principal place of business at 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9.

8. On information and belief, Apotex Corp. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 2400 North Commerce Parkway, Weston, Florida 33326.

THE PATENTS-IN-SUIT

9. On May 17, 2011, the United States Patent and Trademark Office (“USPTO”) duly and lawfully issued the ’582 patent, entitled “Crystalline form of 1-(β -D-glucopyransoyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate” to MTPC as assignee of inventors Sumihiro Nomura and Eiji Kawanishi. A copy of the ’582 patent is attached as Exhibit A.

10. JPI, JRD, and Cilag are exclusive licensees of the ’582 patent.

11. JNV is an exclusive sublicensee of the ’582 patent.

12. On August 20, 2013, the USPTO duly and lawfully issued the ’202 patent, entitled “Crystalline form of 1-(β -D-glucopyransoyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate” to MTPC as assignee of inventors Sumihiro Nomura and Eiji Kawanishi. A copy of the ’202 patent is attached as Exhibit B.

13. JPI, JRD, and Cilag are exclusive licensees of the ’202 patent.

14. JNV is an exclusive sublicensee of the ’202 patent.

THE INVOKANA[®] DRUG PRODUCT

15. JPI holds approved New Drug Application (“NDA”) No. 204042 for canagliflozin tablets, which are prescribed and sold under the trademark INVOKANA[®]. INVOKANA[®] is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

16. The claims of the Patents-in-suit cover, *inter alia*, certain polymorphic forms of canagliflozin.

17. Pursuant to 21 U.S.C. § 355(b)(1), and attendant FDA regulations, the ’582 and ’202 patents are listed in the FDA publication “Approved Drug Products with Therapeutic Equivalence Evaluations” (the “Orange Book”), with respect to INVOKANA[®].

JURISDICTION AND VENUE

18. This action arises under the patent laws of the United States, 35 U.S.C. §§ 100, *et seq.*, and this Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

19. On information and belief, Apotex Corp. is a subsidiary of Apotex, Inc. and is controlled and dominated by Apotex, Inc. On information and belief, Apotex, Inc. and Apotex Corp. operate as part of a single, integrated generic pharmaceutical manufacturer with Apotex, Inc. as the ultimate parent. Apotex’s website states that “Apotex Corp. is the US Company that markets the products of Apotex, Inc.” Apotex Press Release, <http://www.apotex.com/global/about/press/20110510.asp> (last visited July 9, 2017).

20. On information and belief, Apotex Corp. and Apotex, Inc. have been, and continue to be, joint and prime actors in the drafting, submission, approval, and maintenance of the Apotex ANDA.

21. This Court has personal jurisdiction over Apotex, Inc. because, *inter alia*, Apotex, Inc. has committed an act of patent infringement under 35 U.S.C. § 271(e)(2) and intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will lead to foreseeable harm and injury to Plaintiffs in New Jersey. For example, on information and belief, following approval of the Apotex ANDA, Apotex, Inc. will work in concert with Apotex Corp. to make, use, import, sell, and/or offer for sale the Apotex ANDA Product in the United States, including in New Jersey, prior to the expiration of the Patents-in-suit.

22. This Court also has personal jurisdiction over Apotex, Inc. because, *inter alia*, this action arises from actions of Apotex, Inc. directed toward New Jersey. For example, Apotex's counsel sent a letter dated June 5, 2017 to JPI, a corporation with its principal place of business in this Judicial District stating that Apotex Corp. had submitted ANDA No. 210449 seeking approval to commercially manufacture, use, import, offer for sale, and sell the Apotex ANDA Product prior to the expiration of the Patents-in-suit. On information and belief, if Apotex Corp. succeeds in obtaining FDA approval, Apotex, Inc. would work in concert with Apotex Corp. to sell its Apotex ANDA Product in New Jersey and other states, causing injury to Plaintiffs in New Jersey.

23. This Court also has personal jurisdiction over Apotex, Inc. because Apotex, Inc. has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, Apotex, Inc. regularly and continuously transacts business within New Jersey, including by making pharmaceutical products for sale in New Jersey and selling pharmaceutical products in New Jersey. On information and belief, Apotex, Inc. derives substantial revenue

from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey. For example, Apotex's website states it "has many submissions for U.S. regulatory review as well as being a leader for generic drug approvals."

About Apotex, <http://www.apotex.com/ca/en/about/video.asp> (last accessed July 9, 2017).

24. On information and belief, Apotex, Inc. has continuously placed its products into the stream of commerce for distribution and consumption in the State of New Jersey, and throughout the United States, and thus has engaged in the regular conduct of business within this Judicial District.

25. On information and belief, Apotex, Inc. derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

26. On information and belief, Apotex, Inc. has previously invoked, stipulated, and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

27. Apotex, Inc. has previously been sued in this Judicial District and has availed itself of New Jersey courts through the assertion of counterclaims in suits brought in New Jersey, including *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 17-3387 (D.N.J.) (not contesting personal jurisdiction and asserting counterclaims); *AstraZeneca AB, et al. v. Apotex Corp., et al.*, Civil Action No. 15-8492 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims); *Novartis Pharmaceuticals Corporation v. Apotex, Inc., et al.*, Civil Action No. 15-3634 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims).

28. In the alternative, this Court has jurisdiction over Apotex, Inc. because the requirements of Federal Rule of Civil Procedure 4(k)(2)(A) are met as (a) Plaintiffs' claims arise under federal law; (b) Apotex, Inc. is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Apotex, Inc. has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting an ANDA to the FDA and/or manufacturing and/or selling pharmaceutical products distributed throughout the United States, such that this Court's exercise of jurisdiction over Apotex, Inc. satisfies due process.

29. Venue is proper for Apotex, Inc. under 28 U.S.C. §§ 1391 and/or 1400(b), including because, *inter alia*, Apotex, Inc. is subject to personal jurisdiction in this Judicial District, as set forth above, has committed an act of infringement and will commit further acts of infringement in this Judicial District, as set forth in paragraphs 21-22 above, and/or continuously transacts business in this Judicial District, as set forth in paragraph 23 above.

30. This Court has personal jurisdiction over Apotex Corp. because, *inter alia*, this action arises from actions of Apotex Corp. directed toward New Jersey. For example, Apotex's counsel sent a letter dated June 5, 2017 to JPI, a corporation with its principal place of business in this Judicial District stating that Apotex Corp. had submitted ANDA No. 210449 seeking approval to commercially manufacture, use, import, offer for sale, and sell the Apotex ANDA Product prior to the expiration of the Patents-in-suit.

31. The Court also has personal jurisdiction over Apotex Corp. because Apotex Corp. has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, Apotex Corp. regularly and continuously transacts business within New Jersey, including by selling pharmaceutical products in New Jersey. On information and belief, Apotex

Corp. derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey.

32. This Court has personal jurisdiction over Apotex Corp. because, *inter alia*, Apotex Corp. intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will lead to foreseeable harm and injury to Plaintiffs in New Jersey. For example, on information and belief, following approval of the Apotex ANDA, Apotex Corp. will work in concert with Apotex, Inc. to make, use, import, sell, and/or offer for sale the Apotex ANDA Product in the United States, including in New Jersey, prior to the expiration of the Patents-in-suit.

33. On information and belief, Apotex Corp. has continuously placed its products into the stream of commerce for distribution and consumption in the State of New Jersey and throughout the United States, and thus has engaged in the regular conduct of business within this Judicial District.

34. On information and belief, Apotex Corp. derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

35. On information and belief, Apotex Corp. has previously invoked, stipulated, and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

36. Apotex Corp. has previously been sued in this Judicial District and has availed itself of New Jersey courts through the assertion of counterclaims in suits brought in New Jersey, including *Celgene Corporation v. Hetero Labs Limited, et al.*, Civil Action No. 17-3387 (D.N.J.) (not contesting personal jurisdiction and asserting counterclaims); *AstraZeneca*

AB, et al. v. Apotex Corp., et al., Civil Action No. 15-8492 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims); *Novartis Pharmaceuticals Corporation v. Apotex, Inc., et al.*, Civil Action No. 15-3634 (D.N.J.) (not contesting personal jurisdiction or venue and asserting counterclaims).

37. Venue is proper for Apotex Corp. under 28 U.S.C. §§ 1391 and/or 1400(b). As set forth in paragraphs 21-22, Apotex Corp. has committed and will commit further acts of infringement in this Judicial District. In addition, Apotex Corp. does business in this Judicial District through a permanent and continuous presence in the State of New Jersey. For example, Apotex Corp. is registered with the State of New Jersey's Department of Health as a drug manufacturer and wholesaler under Registration No. 5003192 and continuously sells its products in this Judicial District. Upon information and belief, Apotex Corp. employs a salesforce that includes personnel that regularly and continuously work in this Judicial District and, if Apotex Corp. succeeds in obtaining FDA approval, Apotex Corp. will use its salesforce to sell the Apotex ANDA Product in the State of New Jersey.

APOTEX CORP.'S INFRINGING ANDA SUBMISSION

38. On or about June 6, 2017, JPI received from Apotex's counsel a letter, dated June 5, 2017 ("Apotex Letter"), stating that Apotex Corp. had submitted the Apotex ANDA to the FDA seeking approval to market the Apotex ANDA Product before the expiration of the Patents-in-suit. MTPC received the Apotex Letter on or about June 8, 2017.

39. Apotex specifically directed the Apotex Letter to JPI's headquarters in Raritan, New Jersey, within this Judicial District.

40. The Apotex ANDA Product is intended to be a generic version of INVOKANA[®].

41. The Apotex Letter alleges that the Apotex ANDA Product does not infringe the '582 patent or the '202 patent. Notwithstanding these allegations, on information and belief, discovery/testing will show that the Apotex ANDA Product infringes the Patents-in-suit.

42. This action is being commenced before the expiration of 45 days from the date MTPC and JPI received the Apotex Letter.

COUNT I
Infringement of U.S. Patent No. 7,943,582 by Apotex

43. Plaintiffs repeat and reallege paragraphs 1-42 above as if fully set forth herein.

44. By filing its ANDA No. 210449 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of the Apotex ANDA Product before the expiration of the '582 patent, Apotex Corp. committed an act of infringement under 35 U.S.C. § 271(e)(2).

45. On information and belief, discovery/testing will show that if Apotex commercially makes, uses, offers to sell, or sells the Apotex ANDA Product within the United States, or imports the Apotex ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '582 patent, it would further infringe at least claims 1, 6, and 7 of the '582 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

46. Apotex Corp. has had knowledge of the '582 patent since at least the date it submitted the Apotex ANDA. Apotex, Inc. will have knowledge of the '582 patent at least upon the date of service of this Complaint.

47. Plaintiffs will be irreparably harmed if Apotex is not enjoined from infringing the '582 patent. Plaintiffs do not have an adequate remedy at law.

COUNT II
Infringement of U.S. Patent No. 8,513,202 by Apotex

48. Plaintiffs repeat and reallege paragraphs 1-47 above as if fully set forth herein.

49. By filing its ANDA No. 210449 for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of the Apotex ANDA Product before the expiration of the '202 patent, Apotex Corp. committed an act of infringement under 35 U.S.C. § 271(e)(2).

50. On information and belief, discovery/testing will show that if Apotex commercially makes, uses, offers to sell, or sells the Apotex ANDA Product within the United States, or imports the Apotex ANDA Product into the United States, or induces or contributes to any such conduct during the term of the '202 patent, it would further infringe at least claims 1 and 3-5 of the '202 patent under 35 U.S.C. §§ 271(a), (b), and/or (c).

51. Apotex Corp. has had knowledge of the '202 patent since at least the date it submitted the Apotex ANDA. Apotex, Inc. will have knowledge of the '202 patent at least upon the date of service of this Complaint.

52. Plaintiffs will be irreparably harmed if Apotex is not enjoined from infringing the '202 patent. Plaintiffs do not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A Judgment that Apotex has infringed one or more claims of the '582 patent by filing ANDA No. 210449;

B. A Judgment that Apotex has infringed, and that Apotex's making, using, selling, offering to sell, or importing the Apotex ANDA Product would constitute infringement

of one or more claims of the '582 patent, and/or induce or contribute to infringement of one or more claims of the '582 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

C. A permanent injunction restraining and enjoining Apotex, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Apotex ANDA Product until after the expiration of the '582 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

D. An Order that the effective date of any approval of ANDA No. 210449 relating to the Apotex ANDA Product be a date that is not earlier than the expiration date of the '582 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

E. A Judgment that Apotex has infringed one or more claims of the '202 patent by filing ANDA No. 210449;

F. A Judgment that Apotex has infringed, and that Apotex's making, using, selling, offering to sell, or importing the Apotex ANDA Product would constitute infringement of one or more claims of the '202 patent, and/or induce or contribute to infringement of one or more claims of the '202 patent pursuant to 35 U.S.C. § 271(a), (b) and/or (c);

G. A permanent injunction restraining and enjoining Apotex and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the Apotex ANDA Product until after the expiration of the '202 patent, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

H. An Order that the effective date of any approval of ANDA No. 210449 relating to the Apotex ANDA Product be a date that is not earlier than the expiration date of the '202 patent as extended plus any other regulatory exclusivity to which Plaintiffs are or become entitled; and

I. Such other and further relief as the Court may deem just and proper.

Dated: July 19, 2017

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and Development, LLC, and Cilag
GmbH International*

CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matters captioned *Mitsubishi Tanabe Pharma Corporation, et al. v. Aurobindo Pharma USA, Inc., et al.*, Civil Action No. 17-5005 (FLW)(DEA) and *Mitsubishi Tanabe Pharma Corporation, et al. v. Princeton Pharmaceuticals, Inc., et al.*, Civil Action No. 17-5135 (FLW)(DEA) are related to the matter in controversy because the matter in controversy involves the same patents.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: July 19, 2017

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EXHIBIT A

US007943582B2

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

(10) **Patent No.:** **US 7,943,582 B2**
(45) **Date of Patent:** **May 17, 2011**

(54) **CRYSTALLINE FORM OF
1-(β -D-GLUCOPYRANSOYL)-4-METHYL-3-
[5-(4-FLUOROPHENYL)-2-
THIENYLMETHYL]BENZENE
HEMIHYDRATE**

(75) Inventors: **Sumihiro Nomura**, Osaka (JP); **Eiji Kawanishi**, Osaka (JP)

(73) Assignee: **Mitsubishi Tanabe Pharma Corporation**, Osaka-Shi (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 451 days.

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(21) Appl. No.: **11/987,670**

(22) Filed: **Dec. 3, 2007**

(65) Prior Publication Data

US 2008/0146515 A1 Jun. 19, 2008

Related U.S. Application Data

(60) Provisional application No. 60/868,426, filed on Dec. 4, 2006.

(30) Foreign Application Priority Data

Dec. 4, 2006 (JP) 2006-327019

(51) Int. Cl.

A61K 31/7034 (2006.01)

C07H 7/04 (2006.01)

(52) U.S. Cl. **514/23**; 536/1.11

(58) Field of Classification Search None
See application file for complete search history.

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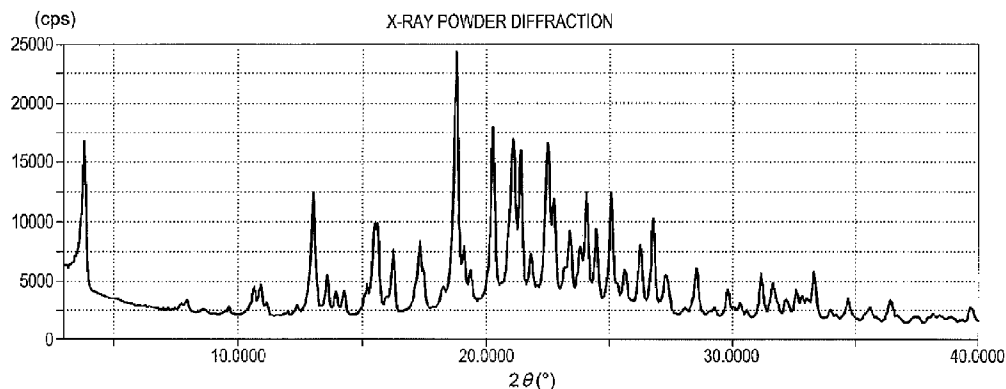
Primary Examiner — Eric S Olson

(74) *Attorney, Agent, or Firm* — Birch, Stewart, Kolasch & Birch, LLP

(57) ABSTRACT

A novel crystal form of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate, and having favorable characteristics, is characterized by its x-ray powder diffraction pattern and/or by its infra-red spectrum.

7 Claims, 2 Drawing Sheets



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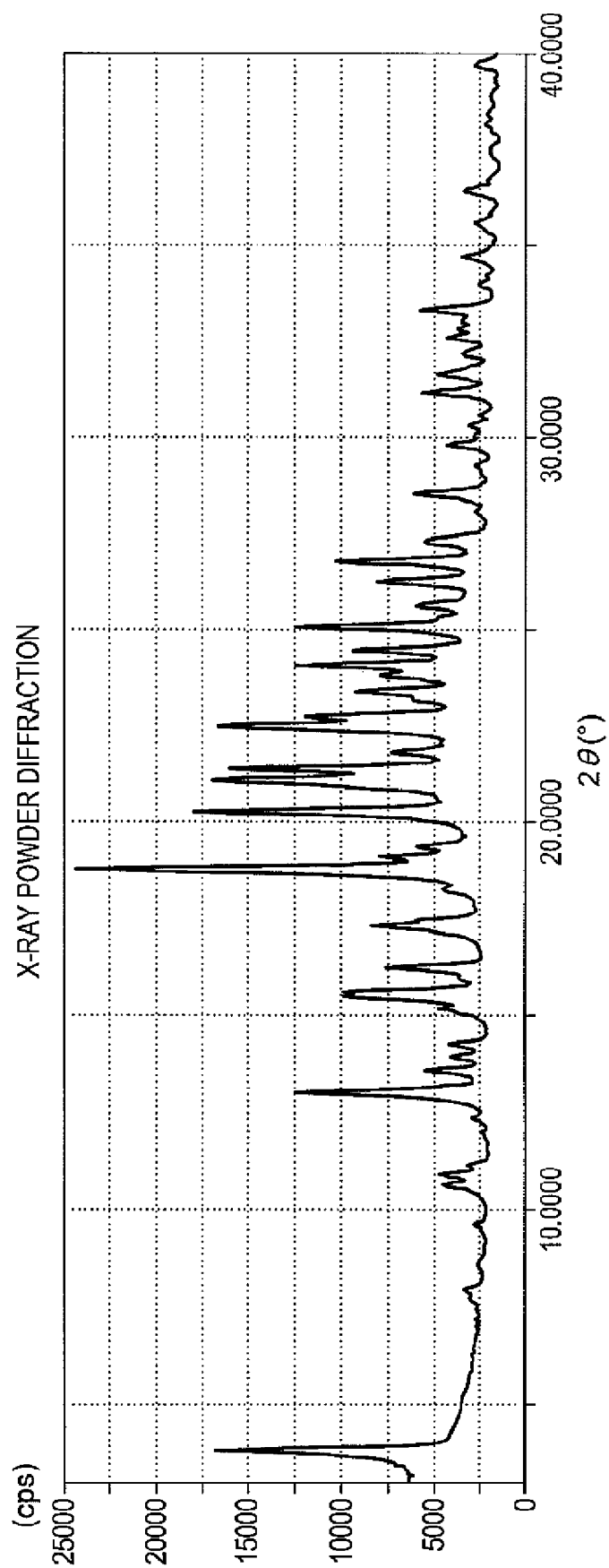


FIG.1

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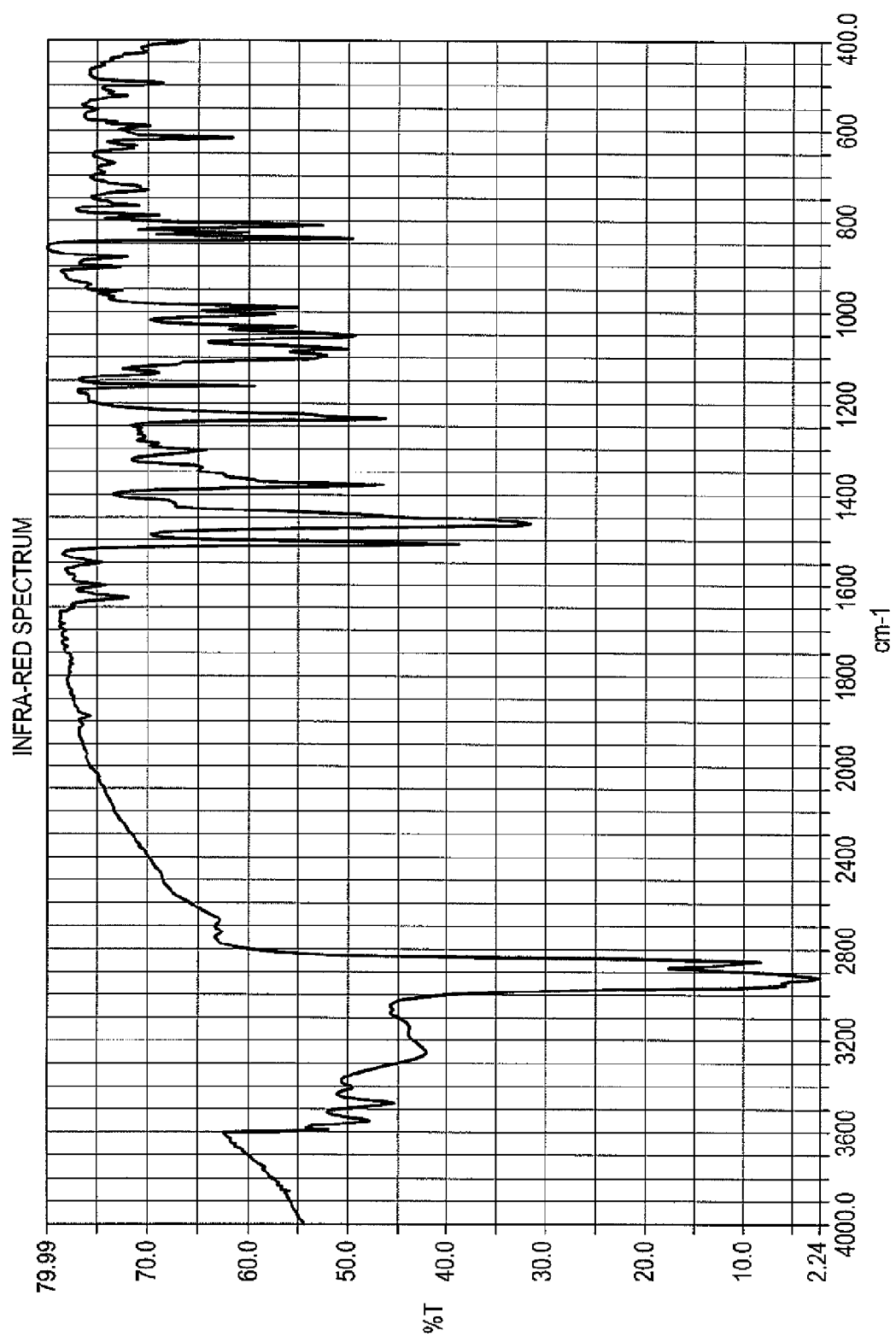


FIG.2

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CRYSTALLINE FORM OF
1-(β -D-GLUCOPYRANSOYL)-4-METHYL-3-
[5-(4-FLUOROPHENYL)-2-
THIENYLMETHYL]BENZENE
HEMIHYDRATE

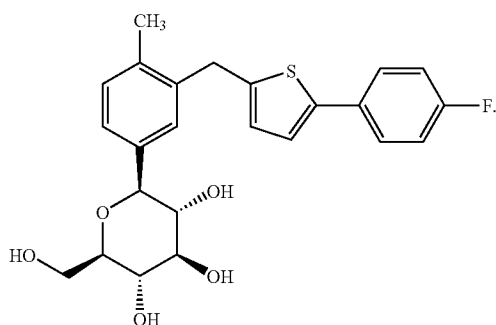
BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a crystalline form of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate useful as an inhibitor of sodium-dependent glucose transporter, to methods for its preparation and isolation, to pharmaceutical compositions which include the compound and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment.

2. Description of the Related Art

WO 2005/012326 pamphlet discloses a class of compounds that are inhibitors of sodium-dependent glucose transporter (SGLT) and thus of therapeutic use for treatment of diabetes, obesity, diabetic complications, and the like. There is described in WO 2005/012326 pamphlet 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene of formula (I):



In general, for commercial use it is important that a product should have good handling qualities. Additionally, there is a need to produce the product in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

And it is desirable that the product should be in a form that is readily filterable and easily dried.

Additionally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

But there have been difficulties in obtaining a crystal form of the compound of formula (I) from organic solvents.

It has now been discovered that the compound of formula (I) hemihydrate can be produced in a crystalline form in a manner reproducible on a commercial scale.

SUMMARY OF THE INVENTION

The present invention provides a crystalline form of hemihydrate of the compound of formula (I) as a novel material, in particular in pharmaceutically acceptable form.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1:

X-ray powder diffraction pattern of the crystalline of hemihydrate of the compound of formula (I).

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FIG. 2:

Infra-red spectrum of the crystalline of hemihydrate of the compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The inventors of the present invention have found that the compounds of formula (I) can be crystallized from a water-containing solvent and the crystalline form of hemihydrate of the compounds (I) have good handling qualities and characteristics.

Accordingly, the present invention is directed to:

1. A crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.
2. A crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene characterized by a powder x-ray diffraction pattern comprising the following 2 θ values measured using CuK α radiation: 4.36 $\pm$ 0.2, 13.54 $\pm$ 0.2, 16.00 $\pm$ 0.2, 19.32 $\pm$ 0.2, 20.80 $\pm$ 0.2.
3. A crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same X-ray powder diffraction pattern as set out in FIG. 1.
4. A crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same IR spectrum, as set out in FIG. 2.
5. A process for the preparation of a crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, which comprises forming a solution of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.
6. A pharmaceutical composition comprising an effective amount of a crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and a pharmaceutically acceptable carrier.
7. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.

As discussed, the present invention includes a certain solid state crystalline form. Several methods for characterizing such forms exist, and the invention should not be limited by the methods chosen or the instrumentation used in characterizing the compounds of the present invention. For example, with regard to x-ray diffraction patterns, the diffraction peak intensities in the experimental patterns can vary, as is known in the art, primarily due to preferred orientation (non-random orientation of the crystals) in the prepared sample. As such, the scope of the present invention must be considered in light of the variability of characterization that is appreciated by those skilled in the art.

X-Ray Powder Diffraction

The crystalline form of the present invention (I) is characterized by its X-ray powder diffraction pattern. The X-ray diffraction pattern of the crystalline of hemihydrate of the compound (I) was measured on an X-ray diffractometer

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(RINT-TTR III, Rigaku, Tokyo, Japan) with measured using CuK_α radiation. Methodology of X-ray powder diffraction is as follows:

Scanning rate: 2.00 degree/minute.

Target: CuK_α .

Voltage: 50 kV.

Current: 300 mA.

Scan range: from 3 to 40.0 degree.

Sampling width: 0.0200 degree.

Infra-Red Spectrum

The infra-red spectrum of the crystalline form of the present invention in mineral oil comprises the following main peaks: 1626, 1600, 1549, and 1507 cm^{-1} .

The infra-red spectrum of crystalline compound (I) hemihydrate is shown in the accompanying drawing in which the ordinate is the transmittance in % and the abscissa is the wavenumber in cm^{-1} .

Thermogravimetric Analysis

The crystalline form of the present invention has been observed to exist in a hemihydrate form. The theoretical water content of the crystalline of the present invention is 1.98%. The thermogravimetric analysis for the crystalline of the present invention shows a mass loss of 1.705%.

Methodology of thermogravimetric analysis is as follows: about 8 mg of compound (I) hemihydrate is weighed and transferred in an aluminum cell holder for TG-50 (Shimadzu, Japan), and then, the thermogravimetric (TG) thermal curve of crystalline compound (I) hemihydrate is determined at a heat rate of 5°C./minute . Typical measuring range is from ambient to 150°C .

The present invention also provides a process for producing the crystalline form of hemihydrate of the compound (I) which comprises forming a solution of compound (I) and precipitating the crystalline form from solution.

Typically, the crystalline of hemihydrate of the compound (I) may be obtained from a mixture of the compound of formula (I), a good solvent and water, optionally containing a poor solvent.

Sometimes some impurities may act as crystallization inhibitors, and impurities need to be removed using a conventional manner, such as silica gel column chromatography. However, the crystalline of hemihydrate of the compound of formula (I) can even be obtained from relatively impure compound (I).

The present invention also provides a pharmaceutical composition comprising the crystalline of hemihydrate of the compound (I) and a pharmaceutically acceptable carrier.

The crystalline compound of the present invention possesses activity as inhibitors of sodium-dependent glucose transporters, and show excellent blood glucose lowering effect.

The crystalline form of the present invention are expected to be useful in the treatment, prevention or delaying the progression or onset of diabetes mellitus (type 1 and type 2 diabetes mellitus, etc.), diabetic complications (such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy), postprandial hyperglycemia, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, atherosclerosis, or hypertension.

The crystalline form of the present invention or a pharmaceutically acceptable salt thereof may be administered either orally or parenterally, and can be used in the form of a suitable pharmaceutical preparation. Suitable pharmaceutical preparations for oral administration include, for example, solid preparations such as tablets, granules, capsules, and powders,

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or solution preparations, suspension preparations, emulsion preparations, and the like. Suitable pharmaceutical preparations for parenteral administration include, for example, suppositories; injection preparations or intravenous drip preparations, using distilled water for injection, physiological saline solution or aqueous glucose solution; and inhalant preparations.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, from about 0.01 mg/kg to about 100 mg/kg body weight (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be given at a dosage of from about 0.01 mg/kg/day to about 100 mg/kg/day (preferably from about 0.01 mg/kg/day to about 50 mg/kg/day and more preferably from about 0.01 mg/kg/day to about 30 mg/kg/day). The method of treating a disorder described in the present invention may also be carried out using a pharmaceutical composition comprising the crystalline form as defined herein and a pharmaceutical acceptable carrier. The dosage form will contain from about 0.01 mg/kg to about 100 mg/kg (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be constituted into any form suitable for the mode of administration selected. The dosages, however, may be varied depending upon administration routes, the requirement of the subjects, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

The crystalline form of the present invention may be used, if necessary, in combination with one or more of other anti-diabetic agents, antihyperglycemic agents and/or agents for treatment of other diseases. The present compounds and these other agents may be administered in the same dosage form, or in a separate oral dosage form or by injection.

The dosage of those agents may vary according to, for example, ages, body weight, conditions of patients, administration routes, and dosage forms.

These pharmaceutical compositions may be orally administered to mammalian species including human beings, apes, and dogs, in the dosage form of, for example, tablet, capsule, granule or powder, or parenterally administered in the form of injection preparation, or intranasally, or in the form of transdermal patch.

The crystalline form of hemihydrate of the compound of formula (I) can be prepared from a mixture of the compound (I), a good solvent and water, optionally containing a poor solvent.

Examples of good solvents which have been found suitable include ketones (e.g., acetone, 2-butanone), esters (e.g., ethyl acetate, methyl acetate), alcohols (e.g., methanol, ethanol, i-propanol), and a mixture of these solvents. Examples of poor solvents include alkanes (e.g., hexane, heptane), aromatic hydrocarbons (e.g., benzene, toluene), ethers (e.g., diethyl ether, dimethyl ether, diisopropyl ether) and a mixture of these solvents.

One preferred preparation of the crystalline form of hemihydrate of the compound of formula (I) typically involves dissolving in a good solvent (e.g., ketones or esters) crude or amorphous compound of formula (I) prepared in accordance with the procedures described in WO 2005/012326 pamphlet, and adding water and a poor solvent (e.g., alkanes or ethers) to the resulting solution, followed by filtration.

In case that a good solvent is soluble in water, a poor solvent needs not be used and water may be added to the

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solution of the compound of formula (I) in the good solvent so the solubility of the compound of formula (I) can be decreased in the solution.

In case that a poor solvent is used, water is preferably used in amount of 1 to 10 molar equivalents to the compound of formula (I), the good solvent is preferably used in amount of 10 to 100 times of volume of water, and the poor solvent is preferably used in amount of 0.1 to 10 times of volume of the good solvent.

The precise conditions under which the crystalline of hemihydrate of the compound (I) is formed may be empirically determined.

Under these conditions, crystallization can preferably be carried out at a lowered, ambient or elevated temperature.

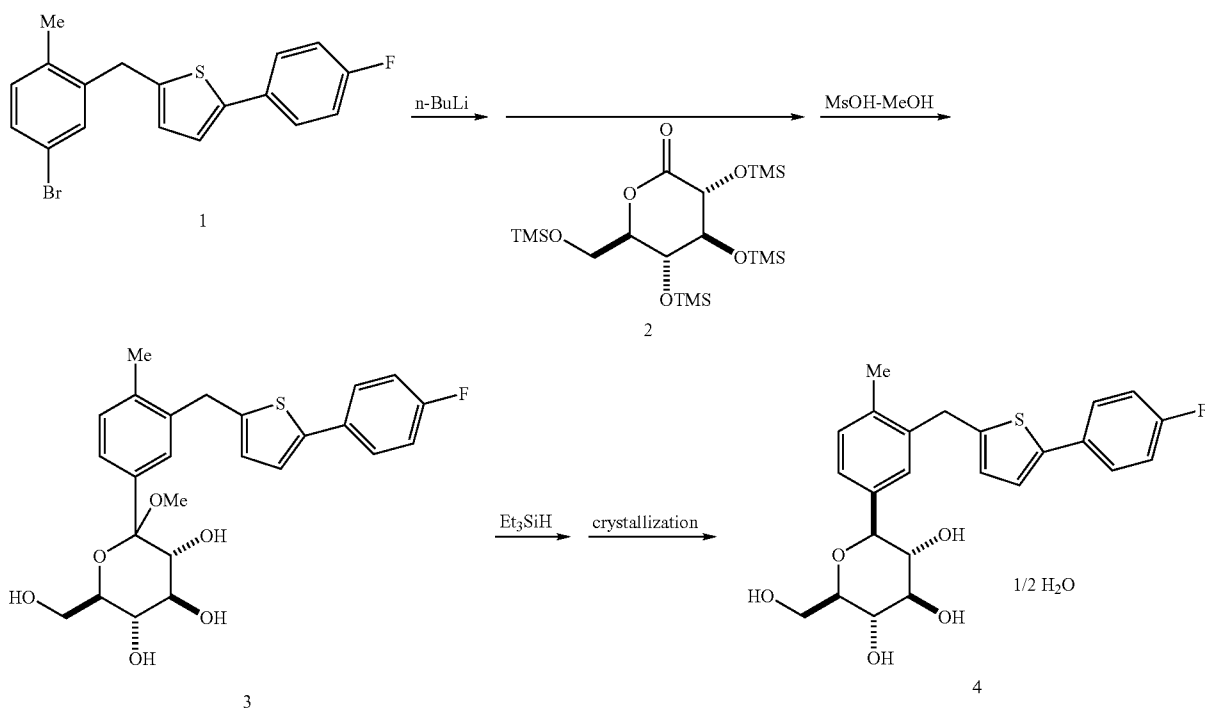
The crystalline form of hemihydrate of the compound of formula (I) is significantly easier to isolate than amorphous form of the compound and can be filtered from the crystallization medium after cooling, and washed and dried. Also, the crystalline form of the present invention is more stable than the amorphous form of the compound of formula (I).

EXAMPLES

Example 1

Crystalline 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate

1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene was prepared in a similar manner as described in WO 2005/012326.



(1) To a solution of 5-bromo-1-[5-(4-fluorophenyl)-2-thienylmethyl]-2-methylbenzene (1, 28.9 g) in tetrahydrofuran (480 ml) and toluene (480 ml) was added n-butyllithium (1.6M hexane solution, 50.0 ml) dropwise at -67 to -70°C .

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under argon atmosphere, and the mixture was stirred for 20 minutes at the same temperature. Thereto was added a solution of 2 (34.0 g) in toluene (240 ml) dropwise at the same temperature, and the mixture was further stirred for 1 hour at the same temperature. Subsequently, thereto was added a solution of methanesulfonic acid (21.0 g) in methanol (480 ml) dropwise, and the resulting mixture was allowed to warm to room temperature and stirred for 17 hours. The mixture was cooled under ice—water cooling, and thereto was added a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate, and the combined organic layer was washed with brine and dried over magnesium sulfate. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was triturated with toluene (100 ml)—hexane (400 ml) to give 1-(1-methoxyglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene (3) (31.6 g). APCI-Mass m/z 492 ($M+NH_4$).

(2) A solution of 3 (63.1 g) and triethylsilane (46.4 g) in dichloromethane (660 ml) was cooled by dry ice-acetone bath under argon atmosphere, and thereto was added dropwise boron trifluoride•ethyl ether complex (50.0 ml), and the mixture was stirred at the same temperature. The mixture was allowed to warm to 0°C . and stirred for 2 hours. At the same temperature, a saturated aqueous sodium hydrogen carbonate solution (800 ml) was added, and the mixture was stirred for 30 minutes. The organic solvent was evaporated under reduced pressure, and the residue was poured into water and extracted with ethyl acetate twice. The organic layer was washed with water twice, dried over magnesium sulfate and treated with activated carbon. The insoluble was filtered off

and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (300 ml), and thereto were added diethyl ether (600 ml) and H_2O (6 ml). The mixture was stirred at room temperature overnight, and the

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precipitate was collected, washed with ethyl acetate-diethyl ether (1:4) and dried under reduced pressure at room temperature to give 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (33.5 g) as colorless crystals. mp 98-100° C. APCI-Mass m/Z 462 (M+NH₄). ¹H-NMR (DMSO-d₆) δ 2.26 (3H, s), 3.13-3.28 (4H, m), 3.44 (1H, m), 3.69 (1H, m), 3.96 (1H, d, J=9.3 Hz), 4.10, 4.15 (each 1H, d, J=16.0 Hz), 4.43 (1H, t, J=5.8 Hz), 4.72 (1H, d, J=5.6 Hz), 4.92 (2H, d, J=4.8 Hz), 6.80 (1H, d, J=3.5 Hz), 7.11-7.15 (2H, m), 7.18-7.25 (3H, m), 7.28 (1H, d, J=3.5 Hz), 7.59 (2H, dd, J=8.8, 5.4 Hz). Anal. Calcd. for C₂₄H₂₅FO₅S.0.5H₂O: C, 63.56; H, 5.78; F, 4.19; S, 7.07. Found: C, 63.52; H, 5.72; F, 4.08; S, 7.00.

Example 2

An amorphous powder of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene (1.62 g) was dissolved in acetone (15 ml), and thereto were added H₂O (30 ml) and a crystalline seed. The mixture was stirred at room temperature for 18 hours, and the precipitate was collected, washed with acetone—H₂O (1:4, 30 ml) and dried under reduced pressure at room temperature to give 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (1.52 g) as colorless crystals. mp 97-100° C.

The invention claimed is:

1. A crystalline form of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate.

2. A crystalline form of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1, having a powder x-ray diffraction pattern comprising the following 2 θ values measured using CuK α radiation: 4.36 $\pm$ 0.2, 13.54 $\pm$ 0.2, 16.00 $\pm$ 0.2, 19.32 $\pm$ 0.2, and 20.80 $\pm$ 0.2.

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3. A crystalline form of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1, having substantially the same X-ray diffraction pattern as set out in FIG. 1.

4. A crystalline form of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1, having substantially the same IR spectrum, as set out in FIG. 2.

5. A process for the preparation of a crystalline form of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1, which comprises forming a solution of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.

6. A pharmaceutical composition comprising an effective amount of a crystalline form of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1 and a pharmaceutically acceptable carrier.

7. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline form of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1 to a subject in need thereof.

* * * * *

EXHIBIT B

US008513202B2

(12) **United States Patent**
Nomura et al.(10) **Patent No.:** **US 8,513,202 B2**
(45) **Date of Patent:** ***Aug. 20, 2013**(54) **CRYSTALLINE FORM OF**
1-(β-D-GLUCOPYRANOSYL)-4-METHYL-
3-[5-(4-FLUOROPHENYL)-2-THIENYL-
METHYL]BENZENE HEMIHYDRATE(75) Inventors: **Sumihiro Nomura**, Osaka (JP); **Eiji Kawanishi**, Osaka (JP)(73) Assignee: **Mitsubishi Tanabe Pharma Corporation**, Osaka-Shi (JP)(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.(21) Appl. No.: **13/103,557**(22) Filed: **May 9, 2011**(65) **Prior Publication Data**

US 2011/0212905 A1 Sep. 1, 2011

Related U.S. Application Data

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(60) Provisional application No. 60/868,426, filed on Dec. 4, 2006.

(30) **Foreign Application Priority Data**

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C07H 7/04 (2006.01)(52) **U.S. Cl.**
CPC **A61K 31/7034** (2013.01); **C07H 7/04** (2013.01)
USPC **514/23**; 536/122(58) **Field of Classification Search**
None
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**

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(57) **ABSTRACT**

A novel crystal form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate, and having favorable characteristics, is characterized by its x-ray powder diffraction pattern and/or by its infra-red spectrum.

5 Claims, 2 Drawing Sheets

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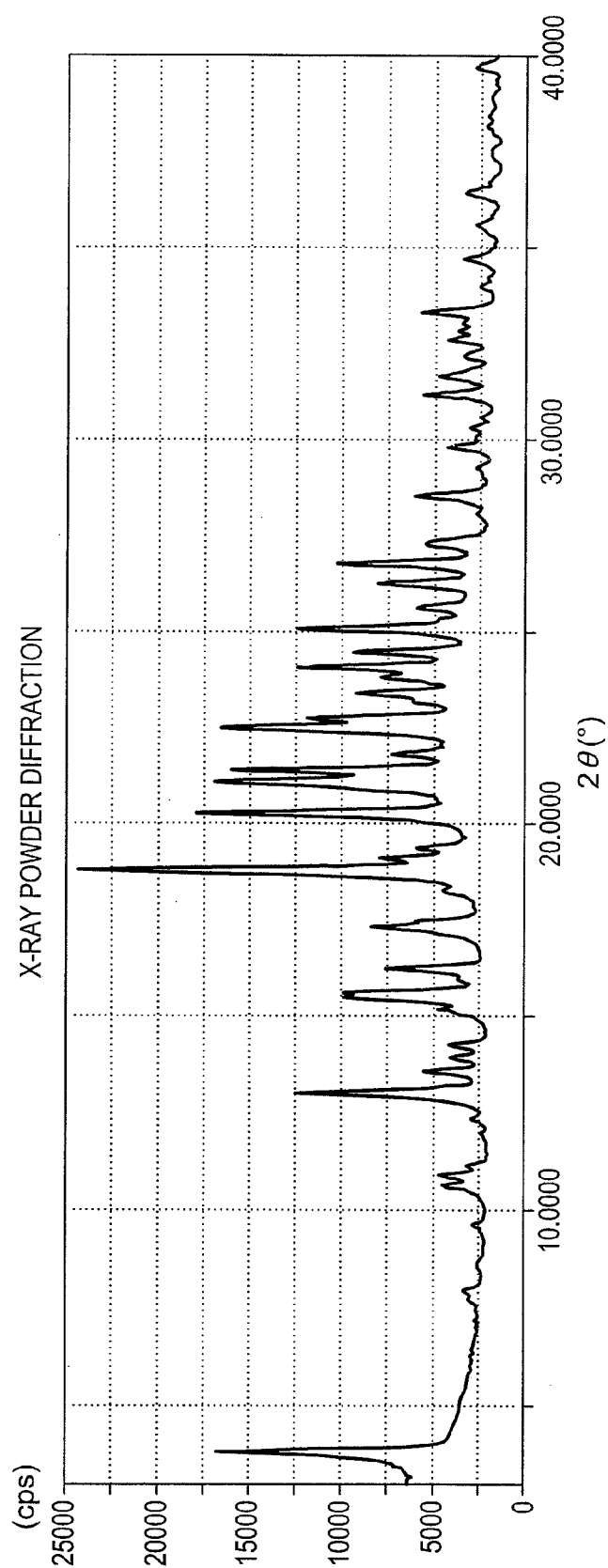


FIG.1

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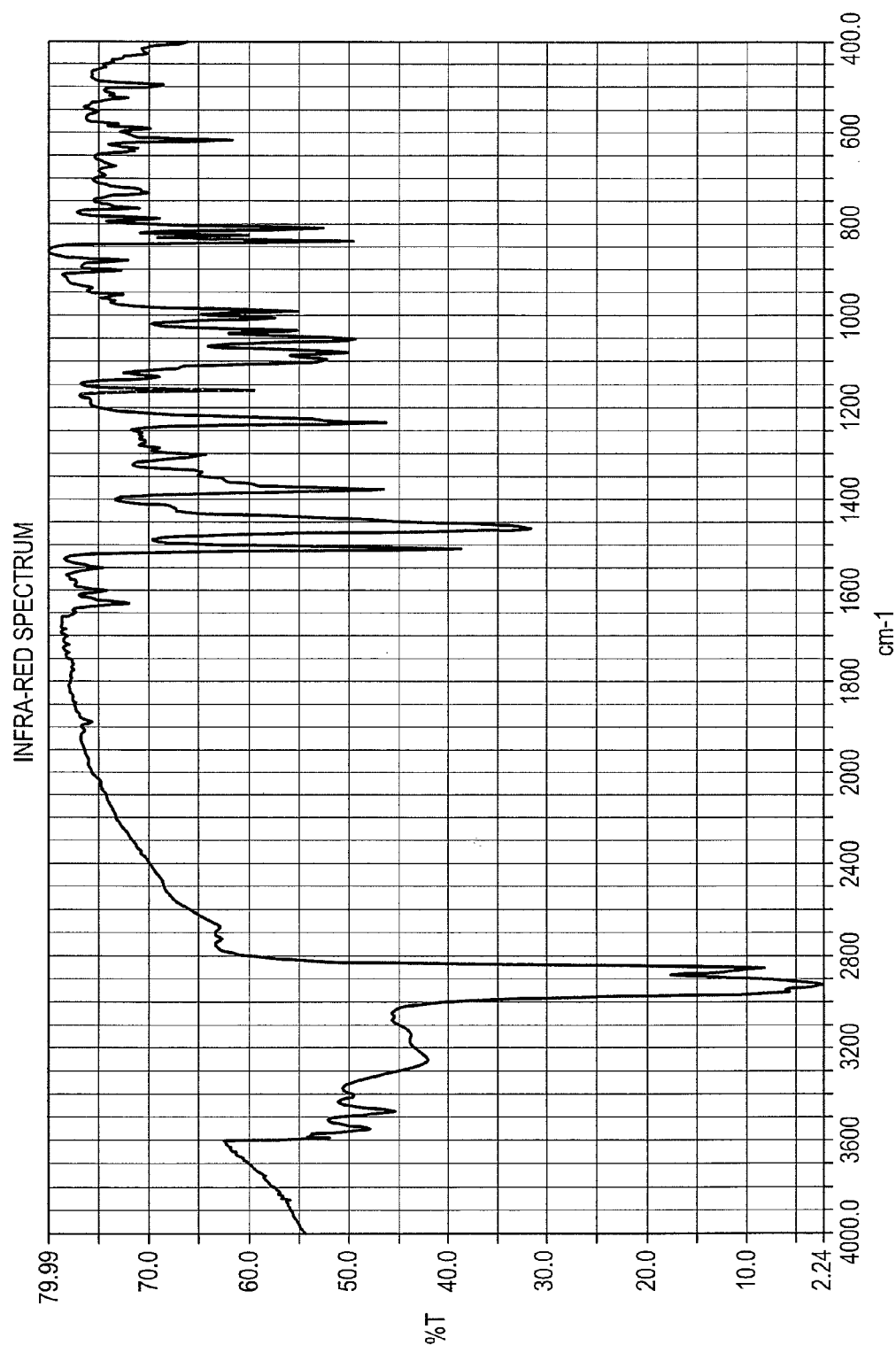


FIG.2

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1

**CRYSTALLINE FORM OF
1-(β -D-GLUCOPYRANOSYL)-4-METHYL-3-
[5-(4-FLUOROPHENYL)-2-THIENYL-
METHYL]BENZENE HEMIHYDRATE**

This application is a Continuation of U.S. application Ser. No. 11/987,670 filed Dec. 3, 2007, which issued as U.S. Pat. No. 7,943,582 on May 17, 2011, which claims the benefit of priority under 35 U.S.C. §119(e) of U.S. Application No. 60/868,426, filed Dec. 4, 2006. U.S. application Ser. No. 11/987,670 also claims the benefit of priority of JP 2006-327019, filed Dec. 4, 2006. The entire content of each of the above-identified applications is hereby incorporated by reference.

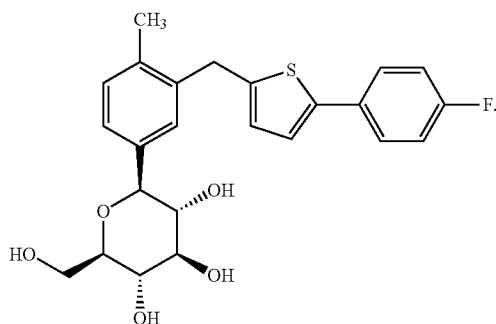
BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a crystalline form of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate useful as an inhibitor of sodium-dependent glucose transporter, to methods for its preparation and isolation, to pharmaceutical compositions which include the compound and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment.

2. Description of the Related Art

WO 2005/012326 pamphlet discloses a class of compounds that are inhibitors of sodium-dependent glucose transporter (SGLT) and thus of therapeutic use for treatment of diabetes, obesity, diabetic complications, and the like. There is described in WO 2005/012326 pamphlet 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene of formula (I):



In general, for commercial use it is important that a product should have good handling qualities. Additionally, there is a need to produce the product in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

And it is desirable that the product should be in a form that is readily filterable and easily dried. Additionally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

But there have been difficulties in obtaining a crystal form of the compound of formula (I) from organic solvents.

It has now been discovered that the compound of formula (I) hemihydrate can be produced in a crystalline form in a manner reproducible on a commercial scale.

2

SUMMARY OF THE INVENTION

The present invention provides a crystalline form of hemihydrate of the compound of formula (I) as a novel material, in particular in pharmaceutically acceptable form.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1:

X-ray powder diffraction pattern of the crystalline of hemihydrate of the compound of formula (I).

FIG. 2:

Infra-red spectrum of the crystalline of hemihydrate of the compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The inventors of the present invention have found that the compounds of formula (I) can be crystallized from a water-containing solvent and the crystalline form of hemihydrate of the compounds (I) have good handling qualities and characteristics.

Accordingly, the present invention is directed to:

1. A crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.
2. A crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene characterized by a powder x-ray diffraction pattern comprising the following 2 θ values measured using CuK α radiation: 4.36 $\pm$ 0.2, 13.54 $\pm$ 0.2, 16.00 $\pm$ 0.2, 19.32 $\pm$ 0.2, 20.80 $\pm$ 0.2.
3. A crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same X-ray powder diffraction pattern as set out in FIG. 1.
4. A crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, having substantially the same IR spectrum, as set out in FIG. 2.
5. A process for the preparation of a crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene, which comprises forming a solution of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.
6. A pharmaceutical composition comprising an effective amount of a crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and a pharmaceutically acceptable carrier.
7. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline of hemihydrate of 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene.

As discussed, the present invention includes a certain solid state crystalline form. Several methods for characterizing such forms exist, and the invention should not be limited by the methods chosen or the instrumentation used in characterizing the compounds of the present invention. For example, with regard to x-ray diffraction patterns, the diffraction peak intensities in the experimental patterns can vary, as is known in the art, primarily due to preferred orientation (non-random

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orientation of the crystals) in the prepared sample. As such, the scope of the present invention must be considered in light of the variability of characterization that is appreciated by those skilled in the art.

X-Ray Powder Diffraction

The crystalline form of the present invention (I) is characterized by its X-ray powder diffraction pattern. The X-ray diffraction pattern of the crystalline of hemihydrate of the compound (I) was measured on an X-ray diffractometer (RINT-TTR III, Rigaku, Tokyo, Japan) with measured using $\text{CuK}\alpha$ radiation. Methodology of X-ray powder diffraction is as follows:

Scanning rate: 2.00 degree/minute.

Target: $\text{CuK}\alpha$.

Voltage: 50 kV.

Current: 300 mA.

Scan range: from 3 to 40.0 degree.

Sampling width: 0.0200 degree.

Infra-Red Spectrum

The infra-red spectrum of the crystalline form of the present invention in mineral oil comprises the following main peaks: 1626, 1600, 1549, and 1507 cm^{-1} .

The infra-red spectrum of crystalline compound (I) hemihydrate is shown in the accompanying drawing in which the ordinate is the transmittance in % and the abscissa is the wavenumber in cm^{-1} .

Thermogravimetric Analysis

The crystalline form of the present invention has been observed to exist in a hemihydrate form. The theoretical water content of the crystalline of the present invention is 1.98%. The thermogravimetric analysis for the crystalline of the present invention shows a mass loss of 1.705%.

Methodology of thermogravimetric analysis is as follows: about 8 mg of compound (I) hemihydrate is weighed and transferred in an aluminum cell holder for TG-50 (Shimadzu, Japan), and then, the thermogravimetric (TG) thermal curve of crystalline compound (I) hemihydrate is determined at a heat rate of 5°C./minute . Typical measuring range is from ambient to 150°C .

The present invention also provides a process for producing the crystalline form of hemihydrate of the compound (I) which comprises forming a solution of compound (I) and precipitating the crystalline form from solution.

Typically, the crystalline of hemihydrate of the compound (I) may be obtained from a mixture of the compound of formula (I), a good solvent and water, optionally containing a poor solvent.

Sometimes some impurities may act as crystallization inhibitors, and impurities need to be removed using a conventional manner, such as silica gel column chromatography. However, the crystalline of hemihydrate of the compound of formula (I) can even be obtained from relatively impure compound (I).

The present invention also provides a pharmaceutical composition comprising the crystalline of hemihydrate of the compound (I) and a pharmaceutically acceptable carrier.

The crystalline compound of the present invention possesses activity as inhibitors of sodium-dependent glucose transporters, and show excellent blood glucose lowering effect.

The crystalline form of the present invention are expected to be useful in the treatment, prevention or delaying the progression or onset of diabetes mellitus (type 1 and type 2 diabetes mellitus, etc.), diabetic complications (such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy), postprandial hyperglycemia, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia,

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elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, atherosclerosis, or hypertension.

The crystalline form of the present invention or a pharmaceutically acceptable salt thereof may be administered either orally or parenterally, and can be used in the form of a suitable pharmaceutical preparation. Suitable pharmaceutical preparations for oral administration include, for example, solid preparations such as tablets, granules, capsules, and powders, or solution preparations, suspension preparations, emulsion preparations, and the like. Suitable pharmaceutical preparations for parenteral administration include, for example, suppositories; injection preparations or intravenous drip preparations, using distilled water for injection, physiological saline solution or aqueous glucose solution; and inhalant preparations.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, from about 0.01 mg/kg to about 100 mg/kg body weight (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be given at a dosage of from about 0.01 mg/kg/day to about 100 mg/kg/day (preferably from about 0.01 mg/kg/day to about 50 mg/kg/day and more preferably from about 0.01 mg/kg/day to about 30 mg/kg/day). The method of treating a disorder described in the present invention may also be carried out using a pharmaceutical composition comprising the crystalline form as defined herein and a pharmaceutical acceptable carrier. The dosage form will contain from about 0.01 mg/kg to about 100 mg/kg (preferably from about 0.01 mg/kg to about 50 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) of the active ingredient, and may be constituted into any form suitable for the mode of administration selected. The dosages, however, may be varied depending upon administration routes, the requirement of the subjects, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

The crystalline form of the present invention may be used, if necessary, in combination with one or more of other anti-diabetic agents, antihyperglycemic agents and/or agents for treatment of other diseases. The present compounds and these other agents may be administered in the same dosage form, or in a separate oral dosage form or by injection.

The dosage of those agents may vary according to, for example, ages, body weight, conditions of patients, administration routes, and dosage forms.

These pharmaceutical compositions may be orally administered to mammalian species including human beings, apes, and dogs, in the dosage form of, for example, tablet, capsule, granule or powder, or parenterally administered in the form of injection preparation, or intranasally, or in the form of transdermal patch.

The crystalline form of hemihydrate of the compound of formula (I) can be prepared from a mixture of the compound (I), a good solvent and water, optionally containing a poor solvent.

Examples of good solvents which have been found suitable include ketones (e.g., acetone, 2-butanone), esters (e.g., ethyl acetate, methyl acetate), alcohols (e.g., methanol, ethanol, i-propanol), and a mixture of these solvents. Examples of poor solvents include alkanes (e.g., hexane, heptane), aromatic hydrocarbons (e.g., benzene, toluene), ethers (e.g., diethyl ether, dimethyl ether, diisopropyl ether) and a mixture of these solvents.

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One preferred preparation of the crystalline form of hemihydrate of the compound of formula (I) typically involves dissolving in a good solvent (e.g., ketones or esters) crude or amorphous compound of formula (I) prepared in accordance with the procedures described in WO 2005/012326 pamphlet, and adding water and a poor solvent (e.g., alkanes or ethers) to the resulting solution, followed by filtration.

In case that a good solvent is soluble in water, a poor solvent needs not be used and water may be added to the solution of the compound of formula (I) in the good solvent so the solubility of the compound of formula (I) can be decreased in the solution.

In case that a poor solvent is used, water is preferably used in amount of 1 to 10 molar equivalents to the compound of formula (I), the good solvent is preferably used in amount of 10 to 100 times of volume of water, and the poor solvent is preferably used in amount of 0.1 to 10 times of volume of the good solvent.

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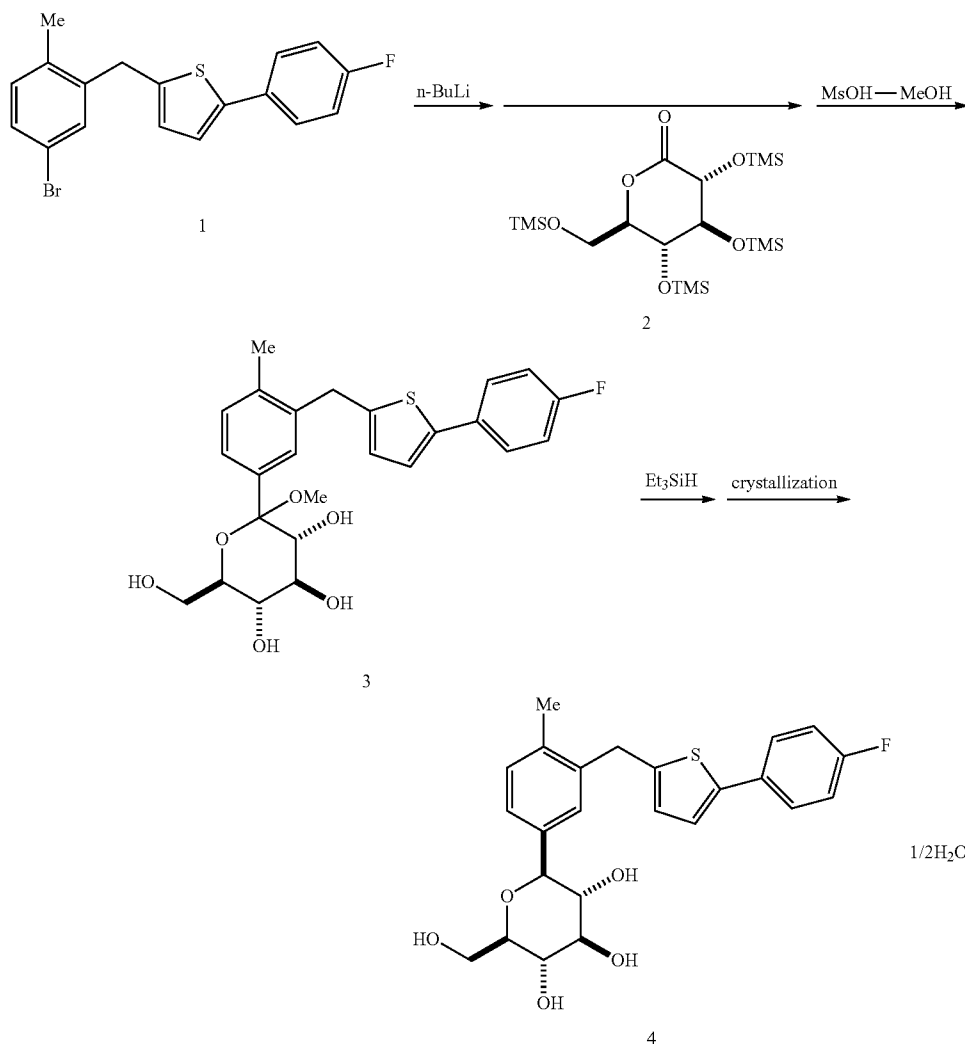
The crystalline form of hemihydrate of the compound of formula (I) is significantly easier to isolate than amorphous form of the compound and can be filtered from the crystallization medium after cooling, and washed and dried. Also, the crystalline form of the present invention is more stable than the amorphous form of the compound of formula (I).

EXAMPLES

Example 1

Crystalline 1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate

1-(β -D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene was prepared in a similar manner as described in WO 2005/012326.



The precise conditions under which the crystalline of hemihydrate of the compound (I) is formed may be empirically determined.

Under these conditions, crystallization can preferably be carried out at a lowered, ambient or elevated temperature.

(1) To a solution of 5-bromo-1-[5-(4-fluorophenyl)-2-thienylmethyl]-2-methylbenzene (1, 28.9 g) in tetrahydrofuran (480 ml) and toluene (480 ml) was added n-butyllithium (1.6M hexane solution, 50.0 ml) dropwise at -67 to -70° C. under argon atmosphere, and the mixture was stirred for 20

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minutes at the same temperature. Thereto was added a solution of 2 (34.0 g) in toluene (240 ml) dropwise at the same temperature, and the mixture was further stirred for 1 hour at the same temperature. Subsequently, thereto was added a solution of methanesulfonic acid (21.0 g) in methanol (480 ml) dropwise, and the resulting mixture was allowed to warm to room temperature and stirred for 17 hours. The mixture was cooled under ice—water cooling, and thereto was added a saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate, and the combined organic layer was washed with brine and dried over magnesium sulfate. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was triturated with toluene (100 ml)—hexane (400 ml) to give 1-(1-methoxyglucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]-benzene (3) (31.6 g). APCI-Mass m/Z 492 (M+NH₄).

(2) A solution of 3 (63.1 g) and triethylsilane (46.4 g) in dichloromethane (660 ml) was cooled by dry ice—acetone bath under argon atmosphere, and thereto was added dropwise boron trifluoride.ethyl ether complex (50.0 ml), and the mixture was stirred at the same temperature. The mixture was allowed to warm to 0° C. and stirred for 2 hours. At the same temperature, a saturated aqueous sodium hydrogen carbonate solution (800 ml) was added, and the mixture was stirred for 30 minutes. The organic solvent was evaporated under reduced pressure, and the residue was poured into water and extracted with ethyl acetate twice. The organic layer was washed with water twice, dried over magnesium sulfate and treated with activated carbon. The insoluble was filtered off and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (300 ml), and thereto were added diethyl ether (600 ml) and H₂O (6 ml). The mixture was stirred at room temperature overnight, and the precipitate was collected, washed with ethyl acetate—diethyl ether (1:4) and dried under reduced pressure at room temperature to give 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (33.5 g) as colorless crystals. mp 98-100° C. APCI-Mass m/Z 462 (M+NH₄). ¹H-NMR (DMSO-d₆) δ 2.26 (3H, s), 3.13-3.28 (4H, m), 3.44 (1H, m), 3.69 (1H, m), 3.96 (1H, d, J=9.3 Hz), 4.10, 4.15 (each 1H, d, J=16.0 Hz), 4.43 (1H, t, J=5.8 Hz), 4.72 (1H, d, J=5.6 Hz), 4.92 (2H, d, J=4.8 Hz), 6.80 (1H, d, J=3.5 Hz), 7.11-7.15 (2H, m), 7.18-7.25 (3H, m), 7.28 (1H, d, J=3.5 Hz), 7.59 (2H, dd, J=8.8, 5.4 Hz). Anal. Calcd. for C₂₄H₂₅FO₅S.0.5H₂O: C, 63.56; H, 5.78; F, 4.19; S, 7.07. Found: C, 63.52; H, 5.72; F, 4.08; S, 7.00.

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Example 2

An amorphous powder of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene (1.62 g) was dissolved in acetone (15 ml), and thereto were added H₂O (30 ml) and a crystalline seed. The mixture was stirred at room temperature for 18 hours, and the precipitate was collected, washed with acetone—H₂O (1:4, 30 ml) and dried under reduced pressure at room temperature to give 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate (1.52 g) as colorless crystals. mp 97-100° C.

The invention claimed is:

1. A crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate having an infra-red spectrum in mineral oil comprising the following main peaks: 1626, 1600, 1549, and 1507 cm⁻¹.

2. A process for the preparation of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1, which comprises forming a solution of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene and crystallizing said hemihydrate from the solution by precipitation or recrystallization.

3. A pharmaceutical composition comprising an effective amount of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1 and a pharmaceutically acceptable carrier.

4. A method for treatment or delaying the progression or onset of diabetes mellitus, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids, elevated blood levels of glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis, or hypertension, which comprises administering a therapeutically effective amount of a crystalline form of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene hemihydrate of claim 1 to a subject in need thereof.

5. A method for inhibiting a sodium-dependent glucose transporter in a mammal in need thereof, comprising administering to said mammal a therapeutically effective amount of the crystalline form of hemihydrate of 1-(β-D-glucopyranosyl)-4-methyl-3-[5-(4-fluorophenyl)-2-thienylmethyl]benzene of claim 1.

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