(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 February 2006 (02.02.2006)

PCT

(10) International Publication Number
WO 2006/012237 A2

(51) International Patent Classification:
A61K 31/496 (2006.01)

(21) International Application Number:
PCT/US2005/022327

(22) International Filing Date: 24 June 2005 (24.06.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/583,303 25 June 2004 (25.06.2004) US
11/166,465 23 June 2005 (23.06.2005) US

(71) Applicants *(for all designated States except US)*: **SHANGHAI INSTITUTE OF PHARMACEUTICAL INDUSTRY** [CN/CN]; NO. 98 He Hai Road New District, Changzhou City, Jiangsu Province (CN). **WATSON LABORATORIES, INC.** [US/US]; 577 Chipeta Way, Salt Lake City, UT 84108 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ZHANG, Qingwen** [CN/CN]; 1111 NO. 1 Zhong Shan Road, Shanghai 200437 (CN). **XU, Yan-Yan** [CN/CN]; 1111 NO. 1 Zhong Shan Road, Shanghai 200437 (CN). **SHI, Huilin** [CN/CN]; 1111 NO. 1 Zhong Shan Road, Shanghai 200437 (CN). **YIN, Xia** [CN/CN]; NO. 98 He Hai Road New District, Changzhou City, Jiangsu Province (CN). **XI, Xiaojin** [CN/CN]; NO. 98 He Hai Road New District, Changzhou City, Jiangsu Province (CN). **SU, Dianguo** [CN/CN]; NO. 98 He Hai Road New District, Changzhou City, Jiangsu Province (CN).

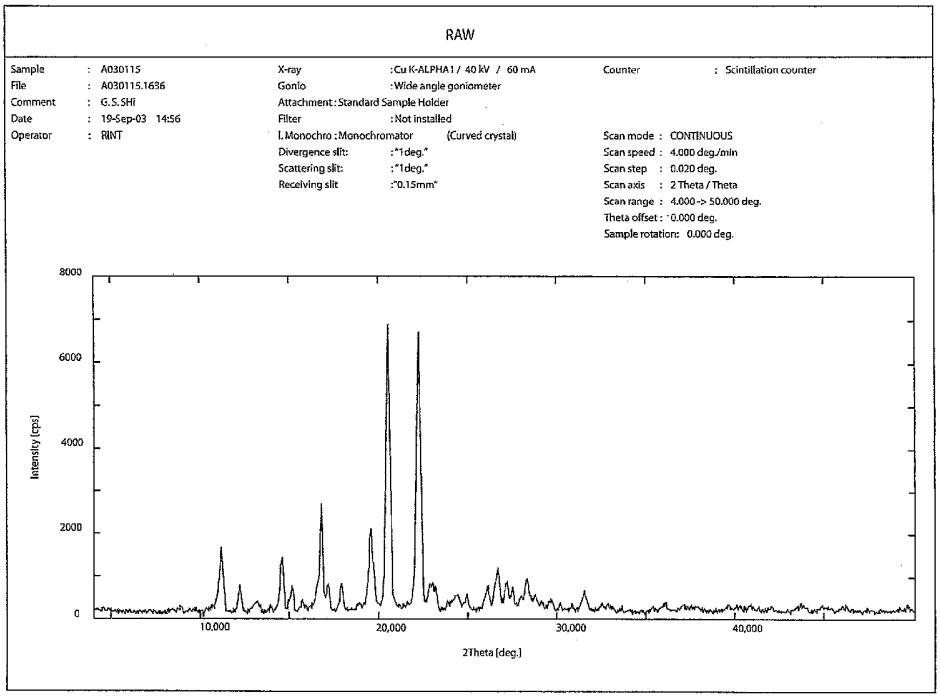
(74) Agent: **OSBORNE, David, W.**; Thorpe North & Western LLP, P.O. Box 1219, Sandy, UT 84091-1219 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,

[Continued on next page]

(54) Title: ARIPIPRAZOLE CRYSTALINE FORMS AND ASSOCIATED METHODS



(57) Abstract: A crystal form of anhydrous aripiprazole having good stability, which can be prepared by simple and economical processes, including such processes are disclosed and described. In one aspect, such a process may include dissolving aripiprazole in an appropriate solvent by heating, and then rapidly cooling with agitation of high speed, to cause the anhydrous aripiprazole of crystal a to swiftly and uniformly precipitate.

WO 2006/012237 A2

FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

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

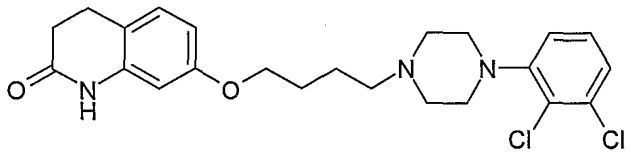
ARIPIPRAZOLE CRYSTALINE FORMS AND ASSOCIATED METHODS

FIELD OF THE INVENTION

The present invention is related to certain crystal forms of aripiprazole, and to methods for the production and use thereof. Accordingly, the present invention involves the fields of chemistry, medicine, and pharmaceutical sciences.

BACKGROUND OF THE INVENTION

Aripiprazole is the compound 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxyl]-3,4-dihydro-2(1*H*)-quinolinone, and is included as monograph no. 791 in The Merck Index (2001), which is incorporated herein by reference. The CAS registry number for aripiprazole is 129722—12—9, and its chemical structure is:



Aripiprazole is an atypical antipsychotic indicated for the treatment of schizophrenia and acute bipolar mania, including manic and mixed episodes associated with bipolar disorder. Examples of such uses may be found in U.S. Patent Nos. 4,734,416 and 5,006,528, which are incorporated herein by reference. Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.34, 0.8, 1.7, and 3.4 nM, respectively), moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha$_1$-adrenergic and histamine H_1 receptors (K_i values of 44, 15, 39, 57, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K_i=98 nM). The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D_2, 5-HT_{1A}, and 5-HT_{2A} may explain some of the other clinical effects of aripiprazole, e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha$_1$ receptors.

A number of specific aripiprazole crystal forms have been discovered, for example, those crystal forms disclosed in PCT Publication WO 03/026659, and U.S. Patent Application Publication No. 20040058935, each of which is incorporated herein by reference. However, the processes required for the production of such aripiprazole crystal forms are typically costly, time-consuming and energy-consuming, for example, requiring heating at 100°C for 18 hours, followed by a temperature of 120°C for 3 hours.

Thus, simple and cost-effective processes to prepare aripiprazole crystal forms which are stable, and of low hygroscopicity, and suitable for dosage form preparation, continue to be sought.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides a crystal form of anhydrous aripiprazole having good stability, which can be prepared by simple and economical processes. Such an aripiprazole crystal form is hereinafter simply referred to as "anhydrous aripiprazole of crystal α", and may be characterized by the following physical and chemical properties:

(1) Melting point of from about 138.5 to about 140.5°C.

(2) Endothermic peak at about 141.1°C in Differential Scanning Calorimetry (DSC) (heating rate of 10°C /min).

(3) Strong absorption peaks at about 2946, 2812, 1677, 1627, 1595, 1577, 1447, 1378, 1241, 1198, 1173, 960, 857 and 778 cm^{-1} on the IR spectrum.

(4) Characteristic powder X-ray diffraction pattern with peaks at diffraction angles (2θ)= 10.98°, 14.30°, 16.54°, 19.28°, 20.32°, 22.02° and 26.60° (conditions for measure of X- ray diffraction: CuKα ray, tube voltage 40kv, tube current 60mA).

In addition to the above-mentioned anhydrous aripiprazole of crystal α, the present invention encompasses unexpectedly efficient processes for the preparation thereof. In one aspect, such a method may include dissolving aripiprazole in an appropriate solvent by heating, and then rapidly cooling with agitation at high speed, to cause the anhydrous aripiprazole of crystal α to swiftly and uniformly precipitate. The formed anhydrous aripiprazole of crystal α may then be filtered out of the solution and dried to eliminate solvent.

While a number of solvents may be used, in one aspect, the solvent used in the above-mentioned method may be a member selected from the group consisting essentially of lower alcohols (such as anhydrous ethanol), acetonitrile, toluene, or mixtures thereof.

The recrystallization concentration of aripiprazole contained in the mother solution may be adjusted within various ranges suitable for production of the present aripiprazole crystal form. However, in one aspect, the concentration of the recrystallization mother solution may be about 1g of aripiprazole dissolved in about 4–50 ml of solvent. Further, while the cooling rate for cooling the solution may be varied within certain ranges, in another aspect, the cooling rate may be in the range of about 3-60°C/min. Still further, the speed at which the solution is agitated during the cooling of the solution may be varied. However, in still another aspect, the agitation speed may be in the range of about 10-900 rpm.

Alternatively, the anhydrous aripiprazole of crystal α may be prepared by dissolving aripiprazole in a first solvent at a temperature range of from about room temperature to reflux temperature of the solvent, followed by adding a second solvent in which aripiprazole is less

soluble than in the first solvent, all during agitation, in order to rapidly and uniformly precipitate the anhydrous aripiprazole of crystal α. The formed anhydrous aripiprazole of crystal α may then be filtered out of the solution and dried to eliminate solvents.

A number of solvents may be used as the first solvent in which aripiprazole is more soluble than the second solvent. However, in one aspect, the first solvent may be a member selected from the group consisting essentially of tetrahydrofuran, ethyl acetate, dichloromethane, or mixtures thereof. Additionally, a number of solvents may be used as the second solvent in which aripiprazole is less soluble than in the first solvent. However, in one aspect, the second solvent may be a member selected from the group consisting essentially of hexane, heptane, or mixtures thereof. In another aspect, about 1g of aripiprazole may be dissolved in about 0.5–50 ml, preferably 1-30 ml, most preferably 2-10 ml of the first solvent, and in another aspect, about 1-10 ml of the second solvent may be added into every 1 ml of the first solvent, to ensure that aripiprazole is sufficiently precipitated. Further, while the solution may be agitated at a variety of speeds, in one aspect, the agitation speed may be in the range of about 10-900 rpm.

The present invention additionally encompasses methods of use for the anhydrous aripiprazole of crystal α disclosed herein. In one aspect, the compound may be combined with a pharmaceutically acceptable carrier to form a pharmaceutical composition. In some aspects, such a pharmaceutical composition may be administered as a treatment to a patient suffering from schizophrenia and/or acute bipolar mania, including manic and mixed episodes associated with bipolar disorder.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a representative powder X-ray diffraction pattern for anhydrous aripiprazole of crystal α.

Fig. 2 is peak search of a representative powder X-ray diffraction pattern for anhydrous aripiprazole of crystal α.

Fig. 3 is a representative infrared spectrum for anhydrous aripiprazole of crystal α (potassium bromide pellet).

DETAILED DESCRIPTION OF THE INVENTION

A. Definitions

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set forth below.

The singular forms "a," "an," and, "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an excipient" includes reference to one or

more of such excipients, and reference to "the drug" includes reference to one or more of such drugs.

As used herein, "subject" refers to a mammal that may benefit from the administration of a drug composition or method of this invention. Examples of subjects include humans, and may also include other animals such as horses, pigs, cattle, dogs, cats, rabbits, and aquatic mammals.

As used herein, the terms "formulation" and "composition" are used interchangeably and refer to a mixture of two or more compounds, elements, or molecules. In some aspects the terms "formulation" and "composition may be used to refer to a mixture of one or more active agents with a carrier or other excipients. The terms "drug," "pharmaceutical," "active agent," and "bioactive agent" are also used interchangeably to refer to a pharmacologically active substance or composition. These terms of art are well-known in the pharmaceutical and medicinal arts.

As used herein, "effective amount" of a substance, such as a carrier, adjuvant, excipient, reagent, reactant, solvent, etc., refers to a sufficient amount of such substance to perform an intended task and achieve an intended result. For example, an effective amount of a solvent may be an amount of solvent that is sufficient to dissolve an agent to a selected degree. Further, an effective amount of a carrier may be an amount that is sufficient to provide an intended composition when combined with a drug. Furthermore, an "effective amount" or a "therapeutically effective amount" of a drug refers to a non-toxic, but sufficient amount of the drug, to achieve therapeutic results in treating a condition for which the drug is known to be effective. It is understood that various biological factors may affect the ability of a substance to perform its intended task. Therefore, an "effective amount" or a "therapeutically effective amount" may be dependent in some instances on such biological factors. Further, while the achievement of therapeutic effects may be measured by a physician or other qualified medical personnel using evaluations known in the art, it is recognized that individual variation and response to treatments may make the achievement of therapeutic effects a somewhat subjective decision. The determination of an effective amount is well within the ordinary skill in the art of pharmaceutical sciences and medicine. See, for example, Meiner and Tonascia, "Clinical Trials: Design, Conduct, and Analysis," Monographs in Epidemiology and Biostatistics, Vol. 8 (1986), incorporated herein by reference.

As used herein, "pharmaceutically acceptable carrier," and "carrier" may be used interchangeably, and refer to any inert and pharmaceutically acceptable material that has substantially no biological activity, and makes up a substantial part of the formulation. The carrier may be polymeric, such as an adhesive, or non-polymeric and is generally admixed with other components of the composition (e.g., drug, binders, fillers, penetration enhancers, anti-irritants, emollients, lubricants, etc., as needed) to comprise the formulation.

The term "admixed" means that the drug and/or enhancer can be dissolved, dispersed, or suspended in the carrier. In some cases, the drug may be uniformly admixed in the carrier.

As used herein, a plurality of items, structural elements, compositional elements, and/or materials may be presented in a common list for convenience. However, these lists should be construed as though each member of the list is individually identified as a separate and unique member. Thus, no individual member of such list should be construed as a de facto equivalent of any other member of the same list solely based on their presentation in a common group without indications to the contrary.

Concentrations, amounts, and other numerical data may be expressed or presented herein in a range format. It is to be understood that such a range format is used merely for convenience and brevity and thus should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. As an illustration, a numerical range of "about 1 to about 5" should be interpreted to include not only the explicitly recited values of about 1 to about 5, but also include individual values and sub-ranges within the indicated range. Thus, included in this numerical range are individual values such as 2, 3, and 4 and sub-ranges such as from 1-3, from 2-4, and from 3-5, etc.
This same principle applies to ranges reciting only one numerical value. Furthermore, such an interpretation should apply regardless of the breadth of the range or the characteristics being described.

B. The Invention

In the present invention, aripiprazole may be dissolved in an appropriate solvent, and then the anhydrous aripiprazole of crystal α may be swiftly and uniformly precipitated using one of various methods. In one aspect, precipitation may be effected with rapid cooling and agitation of the above-mentioned aripiprazole solution. In another aspect, precipitation may be caused by adding a second solvent, in which aripiprazole is less soluble than in the first solvent used to create the aripiprazole solution, to the above-mentioned aripiprazole solution. In either case, once precipitation is complete, the aripiprazole precipitate may be filtered out of solution and dried to eliminate the solvent to give anhydrous aripiprazole of crystal α which is stable, low hygroscopic, and suitable for dosage form preparation. The processes can be easily conducted with less consumption of time and energy than that required by other known methods such as those disclosed in WO 03/026659.

Aripiprazole used as starting material to prepare anhydrous aripiprazole of crystal α may be synthesized according to processes disclosed in U.S. Patent Nos. 4,734,416 and 5,006,528, and Chinese Patent Application CN1504461A, which are all incorporated herein by reference. Aripiprazole used as starting material to prepare anhydrous aripiprazole of crystal α may be of any

type or form. For example, the aripiprazole may be in either purified form or crude form, and may be of any crystal form, such as type I, type II, B, C, D, E, F, G and any combination thereof as described in WO 03/026659 which is incorporated herein by reference.

The solvents used as either the first or second solvent may be selected from a variety of solvents known to dissolve aripiprazoles, with the only proviso that the second solvent must be a substance in which aripiprazole is less soluble than in the first solvent. In other words, the first solvent must be a material that exerts a greater solvent action on aripiprazoles than the second solvent. In any case, examples of suitable solvents include without limitation, lower alcohols (e.g. anhydrous ethanol), acetonitrile, toluene, tetrahydrofuran, ethyl acetate, dichloromethane, hexane, heptane, and mixtures thereof.

In a first method, the aripiprazole solution is cooled in order to precipitate the anhydrous aripiprazole of crystal α. While the cooling rate may be a variety of rates which will suitably yield the desired anhydrous aripiprazole of crystal α, in one aspect, the cooling rate may be about 3-60°C/min. In another aspect, the rate may be about 5-40°C/min. In a further aspect, the rate may be about 10-30°C/min. In yet another aspect, the rate may be about 20-40°C/min.

Prior to or while the aripiprazole solution is being cooled, it may in some embodiments be agitated in a manner suitable to aid, or accelerate the mixing and/or precipitation of the desired anhydrous aripiprazole of crystal α. While varying speed of agitation may be applied to the solution, in one aspect, the solution may be agitated at a speed of about 10-900 rpm. In another aspect, the agitation speed may be about 20-700 rpm. In a further aspect, the agitation speed may be about 50-550 rpm. In yet another aspect, the speed may be about 60-900 rpm.

In any of the methods of the present invention, the mother aripiprazole solution may be prepared to present a suitable aripiprazole concentration to suitably effect crystallization and formation of the desired anhydrous aripiprazole of crystal α. Various concentrations can be used. The concentration of the crystallization mother solution may be about 1g of aripiprazole dissolved in about 4–50 ml of solvent, more preferably about 1g of aripiprazole may be dissolved in about 6-30 ml of solvent, and most preferably about 1 g of aripiprazole may be dissolved in about 8-12 ml of solvent.

In a second method of the present invention, precipitation of the desired anhydrous aripiprazole of crystal α is effected by the addition of a second solvent to the aripiprazole solution. As discussed above, the second solvent is a material in which aripiprazole is less soluble than in the first solvent used to make the aripiprazole solution. While any suitable solvents may be used, in one aspect, the first solvent (i.e. greater solvent action on aripiprazole) may be a member selected from the group consisting essentially of tetrahydrofuran, ethylacetate, dichloromethane, or mixtures thereof, and the second solvent (i.e. lesser solvent action on aripiprazole than the first solvent) may

be a member selected from the group consisting essentially of hexane, heptane, or mixtures thereof. In another aspect, the first solvent may be tetrahydrofuran and the second solvent may be hexane.

The temperature at which the aripiprazole is dissolved in the first solvent may range from room temperature to reflux temperature of the solvent. However, in one aspect, the temperature may be from about 23°C to about 100°C. In another aspect, the temperature may be from about 30°C to about 90°C. In yet another aspect, the temperature may be from about 40°C to about 100°C.

The concentration of the initial aripiprazole solution may be varied according to the first solvent used, and the desired volumes. The concentration may be about 1g of aripiprazole dissolved in about 0.5–50 ml of solvent. More preferably, the concentration may be about 1g of aripiprazole in about 1-30 ml of solvent. Most preferably, the concentration may be about 1g of aripiprazole in 2-10 ml of solvent. Additionally, the amount of second solvent added to the solution may also vary. Generally, about 1-10 ml of the second solvent may be added into every 1 ml of the first solvent. However, in one aspect, the amount of second solvent may be from about 2-8 ml. In a further aspect, the amount may be about 4-9 ml.

The prepared anhydrous aripiprazole of crystal α may in some aspects be characterized by the following physical and chemical properties:

(1) Melting point of about 138.5 to about 140.5°C.

(2) Endothermic peak at about 141.166°C in Differential Scanning Calorimetry (DSC) (heating rate of 10°C/min).

(3) Strong absorption bands at 2946, 2812, 1677, 1627, 1595, 1577, 1447, 1378, 1241, 1198, 1173, 960, 857 and 778 cm^{-1} on the IR spectrum.

(4) Characteristic powder X-ray diffraction pattern with peaks at diffraction angles (2θ) = 10.98°, 14.30°, 16.54°, 19.28°, 20.32°, 22.02° and 26.60° (conditions for measure of X- ray diffraction: CuKα ray, tube voltage 40kv, tube current 60mA)

When the crystal of the present invention is measured by X-ray diffraction, measurement error may occur in peaks to some extent depending on a measure apparatus or measurement conditions. Therefore, measurement error should be considered in identifying crystal structure.

The prepared anhydrous aripiprazole of crystal α is of low moisture absorption and high stability. After being stored at 25°C and 92.5% relative humidity (RH) for 10 days, the water content is not more than about 0.1% determined with Karl Fischer method. When it is sealed in a pouch of aluminum foil and stored at 40°C and 75% RH for 6 months, its appearance, melting point, the water content and content shows no apparent change. When it is sealed in a pouch of aluminum foil and stored at 25°C and 60% RH for 12 months, its appearance, melting point, the water content and assay shows no apparent change.

The prepared anhydrous aripiprazole of crystal α can be used to produce aripiprazole compositions, such as granules, tablets, capsules, suspensions, elixirs, syrups, liquids, etc. using methodology and ingredients well known to those of ordinary skill in the art. For example, after being screened, aripiprazole of crystal α can be blended uniformly with supplement materials, such as carriers (e.g., lactose, pregelatized starch and starch, etc.,), disintegrating agents (e.g., cornstarch, low-substituted hydroxypropyl cellulose or PVP, and added binders (e.g., microcrystalline astragalus, membranaceus malatas, or gelatin, or hydroxypropyl methyl cellulose), to prepare a pliable composition that can be used to establish the above-mentioned dosage formulation types. Those of ordinary skill in the art will recognize a number of other adjuvants and additives that can be suitably used in order to prepare formulations with specific properties or characteristics. Furthermore, the anhydrous aripiprazole of crystal α can be combined with other drugs or bioactive agents in order to provide combinatory therapies. Those of ordinary skill in the art will recognize a number of specific drugs indicated for mental disorders or conditions which can be suitably combined with the anhydrous aripiprazole of crystal α of the present invention in order to provide advanced therapies.

In a release medium of pH 4.5, the release of a solid aripiprazole preparation produced from aripiprazole of crystal α is more than 85% after 30 min. After it is stored at 25°C and 92.5% RH for 10 days, the appearance, relative substances, release and content of the solid aripiprazole preparation shows no apparent change. When it is sealed in a pouch of aluminum foil and stored at 40°C and 75% RH for 6 months, the appearance, release and content of the solid aripiprazole preparation shows no apparent change. When it is sealed in a pouch of aluminum foil and stored at 25°C and 60% RH for 12 months, the appearance, relative substances, release and content of the solid aripiprazole preparation shows no apparent change.

The present invention also includes the use of aripiprazole compositions for administration to a subject to treat or prevent a condition for which aripiprazole is effective. Examples of such conditions include various psychotic disorders, such as schizophrenia or acute bipolar mania, including manic and mixed episodes associated with bipolar disorder.

In addition to the foregoing, the present invention additionally encompasses the use of an anhydrous aripiprazole of crystal α for the manufacture of a medicament that can be used in treating or preventing a condition for which aripiprazole is effective.

EXAMPLES

Reference Example 1

The mixture of 30g of 7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]-2-butenyloxy]-3,4-dihydro-1*H*-quinoline-2-one and 3g of 5% palladium on carbon is charged into 600ml of tetrahydrofuran. Hydrogenation is processed at room temperature and under 4 bar pressure of

hydrogen until starting materials disappear.

After the catalyst is removed by filtration, the filtration is concentrated. The residue is dissolved in anhydrous ethanol at reflux temperature, and 8.4g of oxalic acid dihydrate is then charged. Being filtered, washed and dried, 29.8g of 7-[4-[4-(2,3-dichlorophenyl)piperazine-1-yl]-butoxyl]-3,4-dihydro-1*H*-quinoline-2-one (aripiprizole) oxalate is obtained, which melting point is 202-204°C (decomposed).

The above oxalate is basified to become the base with aqueous sodium hydroxide, extracted with dichloromethane, and concentrated in vacuo to obtain 26g of crude aripiprizole.

26g of crude aripiprizole product obtained above is recrystallized from 312 ml of anhydrous ethanol, treated with activated carbon, and then filtered when hot. The filtration is allowed to stand still to precipitate at room temperature. Being filtered, washed and dried at 75°C under vacuum, 22g (yield 85%) of purified aripiprizole of crystal β is obtained, which melts at 147-148°C, exhibits an endothermic peak at about 150.666°C and 149.939°C in Differential Scanning Calorimetry (DSC) spectrum (heating rate of 10°C/min).

Reference Example 2

The mixture of 29.8g of 7-(4-bromobutoxy)-3,4-dihydro-1*H*-quinoline-2-one, 22.5g of sodium iodide and 380ml of acetonitrile is refluxed for 30min, and then 24.6g of 1-(2,3-dichlorophenyl)piperazine and 15.2g of triethylamine is charged, refluxed for other 3 hours, and concentrated in vacuo. The residue is dissolved in dichloromethane, washed with water, dried with sodium sulfate anhydrous, and then concentrated in vacuo. The residue is dissolved in anhydrous ethanol at reflux temperature, and 12.6g of oxalic acid dihydrate is then charged. Being filtered, washed and dried, 41g of 7-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]-butoxyl]-3,4-dihydro-1*H*-quinoline-2-one (aripiprizole) oxalate is obtained.

The above oxalate is basified to become the base with aqueous sodium hydroxide, extracted with dichloromethane, and in vacuo. 36g of crude aripiprazole is obtained.

Example 3

10g of purified aripiprizole of crystal β, prepared in reference Example 1, is dissolved in 120ml of anhydrous ethanol at reflux temperature (ratio of 12ml/g). The solution is immediately placed in an ice water bath, and agitated at a speed of 180 rpm to aid precipitation. Precipitation commences after 30 seconds, while the temperature of the recrystallization mother solution is 67°C. The solution is continuously agitated for other 30 minutes, then filtered, washed and dried at 75°C under vacuum. 9.7g of aripiprizole of crystal α is obtained (yield 97%).

Melting point: 139-140°C.

An endothermic peak at about 141.166°C in Differential Scanning Calorimetry (DSC) spectrum (heating rate of 10°C /min).

Strong absorption peaks at about 2946, 2812, 1677, 1627, 1595, 1577, 1447, 1378, 1241, 1198, 1173, 960, 857 and 778 cm^{-1} on the IR spectrum (potassium bromide pellet)

Powder X-ray diffraction spectrum is determined using a copper radiation source. Peaks at diffraction angles (2θ) and d spacing whose relative intensity (I/I_0) is more than 10%, are displayed in the table below:

Characteristic powder X-ray diffraction pattern of anhydrous aripiprazole of crystal α (conditions for measure of X- ray diffraction: CuKα ray, tube voltage 40kv, tube current 60mA) are shown in Table 1.

Table 1: Powder X-ray diffraction of anhydrous aripiprazole of crystal α

2θ	d spacing	relative intensity (I/I_0)
11.020	8.0221	24
14.360	6.1629	21
16.580	5.3424	37
16.940	5.2296	12
17.700	5.0068	11
19.340	4.5857	30
20.360	4.3582	100
22.080	4.0225	96
22.700	3.9140	12
26.640	3.3434	17
27.120	3.2853	12
28.280	3.1531	13

Example 4

10g of crude aripiprazole, as prepared in reference Example 2, is dissolved in 120ml of anhydrous ethanol at reflux temperature (ratio of 12ml/g), treated with activated carbon, and then filtered when hot. The filtrate is refluxed till it becomes clear, and immediately placed in ice water bath, agitated at a speed of 160rpm/min to cause precipitation. Precipitation begins after 30 seconds, while the temperature of the recrystallization mother solution is 66°C. The solution is continuously stirred for other 30 min in the ice water bath, and then filtered, washed and dried at 75°C under vacuum. 9.3g of aripiprazole of crystal α is obtained (yield 93%).

Example 5

10g of purified aripiprazole is dissolved in 120 ml of anhydrous ethanol at reflux temperature (ratio of 12ml/g), and then evaporated at atmospheric pressure to remove 40 ml of anhydrous ethanol. The concentrated solution is immediately placed in ice water bath, and agitated at a speed of 150 rpm/min to cause precipitation. Precipitation begins after 12 seconds, while the temperature of the recrystallization mother solution is 71°C. The solution is continuously stirred

for other 30 min in the ice water bath, then filtered, washed and dried at 75°C under vacuum. 9.7g of aripiprazole of crystal α is obtained (yield 97%).

Example 6

10g of purified aripiprazole is dissolved in 120 ml of anhydrous ethanol at reflux temperature (ratio of 12 ml/g), and then evaporated at atmospheric pressure to remove anhydrous ethanol until ~~it~~ precipitation occurs, when 40 ml of ethanol has been removed. The resultant suspension is immediately placed in an ice water bath and agitated at a speed of 60 rpm/min to cause further precipitation. The solution is continuously stirred for other 30 min in the ice water bath, then filtered, washed and dried at 75°C under vacuum. 9.9g of anhydrous aripiprazole of crystal α is obtained (yield 99%).

Example 7

2g of purified aripiprazole is dissolved in 8ml of heated tetrahydrofuran (4 ml/g), and 12 ml of hexane (6 ml/g) is then charged into the solution. Precipitation begins soon after the solution is refluxed with agitation at a speed of 90 rpm/min. The suspension is then continuously stirred for another 30 min, filtered, washed, and dried at 75°C. 1.8g of anhydrous aripiprazole of crystal α is obtained (yield 90%).

Example 8

Anhydrous aripiprazole of crystal α is subjected to sizing by passing through a sieve of 100 mesh, and then admixed with one or more of the following carriers, pregelatinized starch, microcrystalline cellulose, lactose, low-substituted hydroxypropyl cellulose or PVP. 2% aqueous hydroxypropyl methyl cellulose is added to the mixture to prepare a soft material which is then passed through a sieve of 20 mesh to prepare wet granules. The mixture is then dried at 50°C, and sieved through a 20 mesh sieve to granulate, and finally obtain a granulated aripiprazole crystal α composition, or formulation. To the composition, magnesium stearate is added and uniformly mixed. A quantity of the composition suitable for making a tablet is then pressed in order to form an aripiprazole tablet.

Tablets of 10 mg and 15mg aripiprazole are formed, each having 183mg total weight.

It is to be understood that the above-described compositions and methods of application are only illustrative of preferred embodiments of the present invention. Numerous modifications and alternative arrangements may be devised by those skilled in the art without departing from the spirit and scope of the present invention and the appended claims are intended to cover such modifications and arrangements. Thus, while the present invention has been described above with particularity and detail in connection with what is presently deemed to be the most practical and preferred embodiments of the invention, it will be apparent to those of ordinary skill in the art that numerous modifications, including, but not limited to, variations in size, materials, shape, form,

function and manner of operation, assembly and use may be made without departing from the principles and concepts set forth herein.

CLAIMS

What is claimed is:

1. An aripiprazole compound in a crystal form that is characterized by:

a) a melting point of from about 138.5 to about 140.5°C;

b) an endothermic peak at about 141.1°C in Differential Scanning Calorimetry (DSC) using a heating rate of 10°C /min;

c) absorption peaks at about 2946, 2812, 1677, 1627, 1595, 1577, 1447, 1378, 1241, 1198, 1173, 960, 857 and 778 cm^{-1} on an IR spectrum; and

d) a characteristic powder X-ray diffraction pattern with peaks at diffraction angles (2θ) =10.98°, 14.30°, 16.54°, 19.28°, 20.32°, 22.02° and 26.60° using a CuKα ray, with a tube voltage of 40kv, and a tube current of 60mA.

2. The aripiprazole compound of claim 1, further characterized by a water content of less than about 0.1% moisture after storage at about 25°C and 92.5% relative humidity for about 10 days.

3. The aripiprazole compound of claim 1, further characterized by no apparent change in appearance, melting point, or water content when sealed in a pouch of aluminum foil and stored at about 40°C and 75% relative humidity for about 6 months.

4. The aripiprazole compound of claim 1, further characterized by no apparent change in appearance, melting point, or water content when sealed in a pouch of aluminum foil and stored at about 25°C and 60% relative humidity for about 12 months.

5. A pharmaceutical composition comprising:
a pharmaceutically acceptable carrier; and
a therapeutically effective amount of an aripiprazole compound as recited in claim 1 in combination with the carrier.

6. The composition of claim 5, wherein the composition is formulated as a dosage formulation selected from the group consisting of granules, tablets, capsules, suspensions, elixirs, and syrups.

7. The composition of claim 6, wherein the dosage formulation is a tablet.

8. The composition of claim 5, wherein about 85% or more of the aripiprazole in the composition is released within about 30 minutes of dispensing the composition into an aqueous release medium having a pH of about 4.5.

9. The composition of claim 5, wherein the composition shows no apparent change in appearance, relative substances, release rate, or content after storage at about 25°C and 92.5% RH for about 10 days.

10. The composition of claim 5, wherein the composition shows no apparent change in appearance, relative substances, release rate, or content when sealed in a pouch of aluminum foil and stored at about 40°C and 75% RH for about 6 months.

11. The composition of claim 5, wherein the composition shows no apparent change in appearance, relative substances, release rate, or content when sealed in a pouch of aluminum foil and stored at 25°C and 60% RH for about 12 months.

12. A process for preparing an aripiprazole compound as recited claim 1, comprising:

a) forming a heated aripiprazole solution having an aripiprazole concentration of about 1 g of aripiprazole in about 4-50 ml of solvent;

b) cooling the aripiprazole solution at a rate of about 3-60°C/min while agitating at a speed of about 10-900 rpm; and

c) harvesting crystals of the aripiprazole compound from the solution.

13. The process of claim 12, wherein the aripiprazole concentration in the aripiprazole solution is about 1 g of aripiprazole in about 6-30 ml of solvent.

14. The process of claim 13, wherein the aripiprazole concentration in the aripiprazole solution is about 1 g of aripiprazole in about 8-12 ml of solvent.

15. The process of claim 12, wherein the solvent is a member selected from the group consisting essentially of: lower alcohols, acetonitrile, toluene, or mixtures thereof.

16. The process of claim 15, wherein the lower alcohol is anhydrous ethanol.

17. The process of claim 12, wherein the cooling rate is about 5-40°C/min.

18. The process of claim 17, wherein the cooling rate is about 10-30°C/min.

19. The process of claim 18, wherein the cooling rate is about 20-40°C/min.

20. The process of claim 12, wherein the agitation speed is about 20-700 rpm.

21. The process of claim 20, wherein the agitation speed is about 50-550 rpm.

22. The process of claim 12, wherein crystals of the aripiprazole compound are harvested from the aripiprazole solution by filtration.

23. A process for preparing an aripiprazole compound as recited in claim 1, comprising:

a) forming an aripiprazole solution by dissolving aripiprazole in a first solvent at a temperature of from about room temperature to reflux temperature;

b) adding a second solvent in which the aripiprazole is less soluble than in the first solvent to the solution; and

c) harvesting crystals of the aripiprazole compound from the solution.

24. The process of claim 23, further comprising agitating the solution prior to harvesting the crystals of the aripiprazole compound.

25. The method of claim 23, wherein the first solvent is a member selected from the group consisting essentially of: tetrahydrofuran, ethyl acetate, dichloromethane, or mixtures thereof.

26. The method of claim 25, wherein the first solvent is tetrahydrofuran.

27. The method of claim 23, wherein the second solvent is a member selected from the group consisting essentially of: hexane, heptane, or mixtures thereof.

28. The method of claim 27, wherein the second solvent is hexane.

29. The method of claim 23, wherein the aripiprazole is dissolved in an amount of about 1 g for every 0.5–50 ml of the first solvent.

30. The method of claim 29, wherein the aripiprazole is dissolved in an amount of about 1 g for every 1-30 ml of the first solvent.

31. The method of claim 30, wherein the aripiprazole is dissolved in an amount of about 1 g for every 2-10 ml of the first solvent.

32. The method of claim 23, wherein the second solvent is added to the aripiprazole solution in an amount of about 1-10 ml for every 1 ml of the first solvent.

33. The method of claim 24, wherein the solution is agitated at a speed of about 10-900 rpm.

34. Use of an aripiprazole compound as recited in claim 1 for the manufacture of a medicament that can be administered to a subject in order to treat or prevent a condition for which aripiprazole is effective.

35. The use of claim 34, wherein the condition for which aripiprazole is effective is schizophrenia.

36. The use of claim 34, wherein the condition for which aripiprazole is effective is bipolar disorder.

37. An aripiprazole crystalline compound made by a process comprising:

a) forming a heated aripiprazole solution having an aripiprazole concentration of about 1 g of aripiprazole to about 8-12 ml of solvent;

b) cooling the aripiprazole solution at a rate of about 20-40°C/min while agitating at a speed of about 50-550 rpm; and

c) filtering the solution in order to harvesting crystals of the aripiprazole compound.

38. An aripiprazole crystalline compound made by a process comprising:

a) forming an aripiprazole solution having an aripiprazole concentration of about 1 g of aripiprazole to about 2-10 ml of tetrahydrofuran at a temperature of from about room temperature to reflux temperature;

b) adding a hexane to the solution in an amount of about 1-10 ml for every 1 ml of tetrahydrofuran; and

c) filtering the solution in order to harvesting crystals of the aripiprazole compound.

1/3

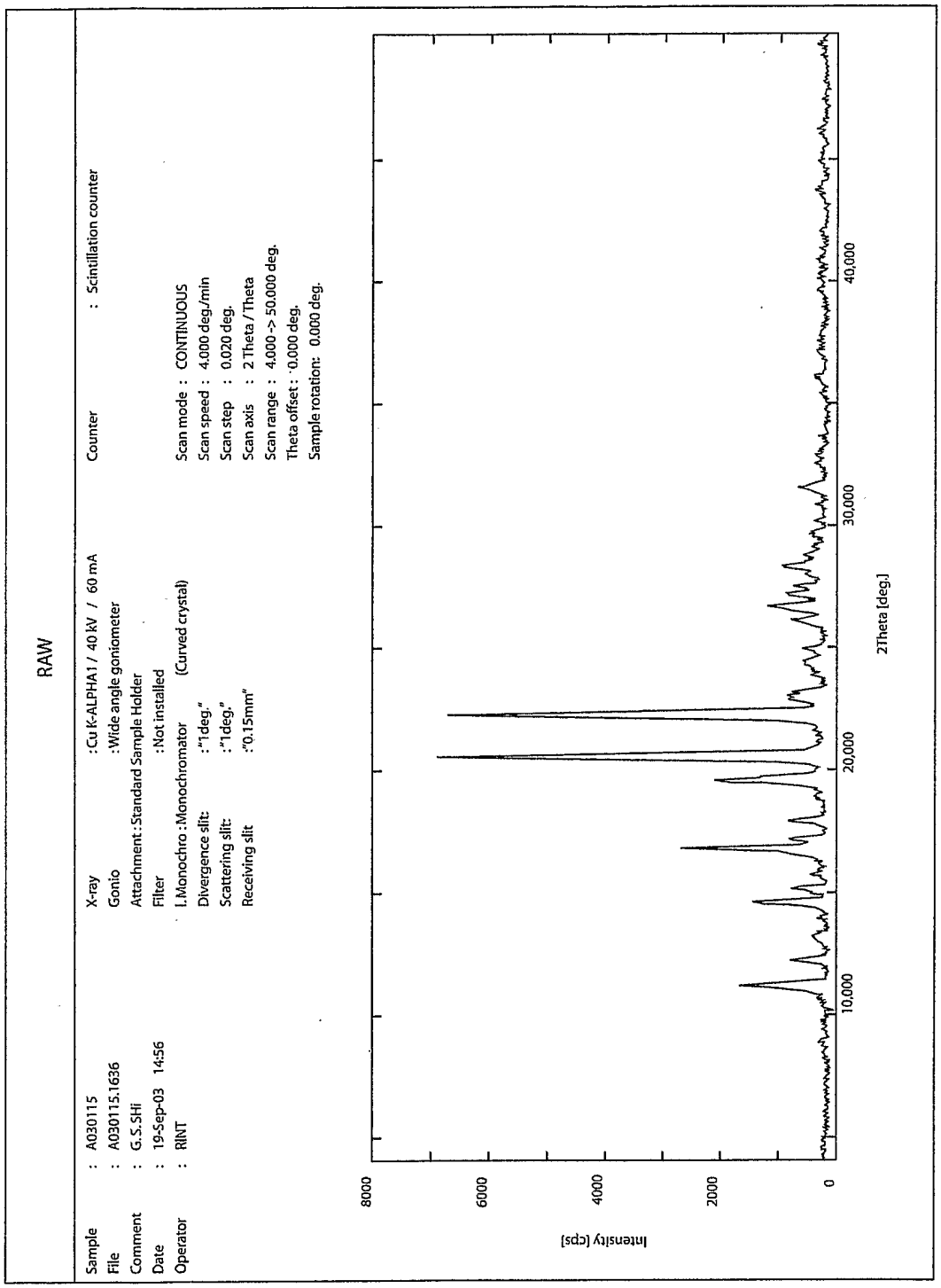
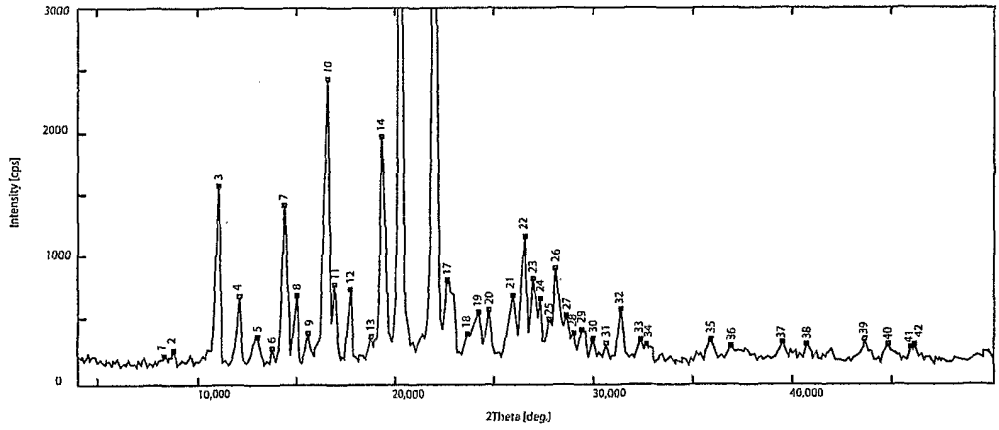

RAW
Sample : A030115
File : A030115.1636
Comment : G.S.SHI
Date : 19-Sep-03 14:56
Operator : RINT
X-ray :Cu K-ALPHA1 / 40 kV / 60 mA
Gonio :Wide angle goniometer
Attachment :Standard Sample Holder
Filter :Not installed
I.Monochro :Monochromator (Curved crystal)
Divergence slit: :"1deg."
Scattering slit: :"1deg."
Receiving slit :"0.15mm"
Counter : Scintillation counter
Scan mode : CONTINUOUS
Scan speed : 4.000 deg./min
Scan step : 0.020 deg.
Scan axis : 2 Theta / Theta
Scan range : 4.000 -> 50.000 deg.
Theta offset : 0.000 deg.
Sample rotation: 0.000 deg.
Intensity [cps]
8000
6000
4000
2000
0
10,000
20,000
30,000
40,000
2Theta [deg.]

Fig. 1

Peack search

Sample : A030115 [Smoothing] mode : Savitzk-Golay's Points : 11
File : A030115.1636 [B.G. elimination]
Comment : G.S.SHI [Ka2 elimination]
Date : 19-Sep-03 14:56 [Peak search
Operator : RINT Typical width : 0.10
Minimum height : 100.000



Peack search

Sample : A030115 File : A030115.1636 Comment : G.S.SHI
Date : 19-Sep-03 14:55 Operator : RINT

Peack No.	2 Theta	FWHM	d-value	Intensity	I/Io
1	8.280	*****	10.6696	211	3
2	8.740	*****	10.1091	254	4
3	11.020	0.165	8.0221	1568	24
4	12.040	0.165	7.3447	686	10
5	12.960	0.141	6.8253	354	5
6	13.740	*****	6.4396	268	4
7	14.360	0.212	6.1629	1406	21
8	14.940	0.165	5.9249	694	10
9	15.500	0.141	5.7121	396	6
10	16.580	0.165	5.3424	2436	37
11	16.940	0.165	5.2296	766	12
12	17.700	0.188	5.0068	736	11
13	18.720	0.141	4.7362	345	5
14	19.340	0.188	4.5857	1971	30
15	20.390	0.165	4.3582	6644	100
16	22.080	0.165	4.0225	6393	96
17	22.700	*****	3.9140	812	12
18	23.720	0.141	3.7479	371	6
19	24.280	*****	3.6628	541	8
20	24.800	*****	3.5871	568	9
21	26.000	0.282	3.4242	686	10
22	26.640	0.235	3.3434	1160	17
23	27.120	*****	3.2853	827	12
24	27.460	0.165	3.2454	658	10
25	27.940	0.141	3.1907	475	7
26	28.200	0.165	3.1631	895	13
27	28.800	*****	3.0974	524	8
28	29.100	0.110	3.0661	373	6
29	29.580	0.141	3.0174	399	6
30	30.160		2.9607	330	5

Peak No.	2 Theta	FWHM	d-value	Intensity	I/Io
31	30.840	0.141	2.8970	291	4
32	31.840	0.212	2.8342	565	9
33	32.560	0.165	2.7477	319	5
34	32.850	0.110	2.7233	288	4
35	32.860	*****	2.4860	327	5
	36.100				
36		*****	2.4187	272	4
37	37.140	0.188	2.2685	291	4
38	39.700	0.212	2.2057	286	4
39	40.880	0.188	2.0688	321	5
40	43.720	0.194	2.0197	277	4
	44.040				
41		0.094	1.9714	271	4
42	46.000	0.118	1.9633	274	4
	46.200				

Fig. 2

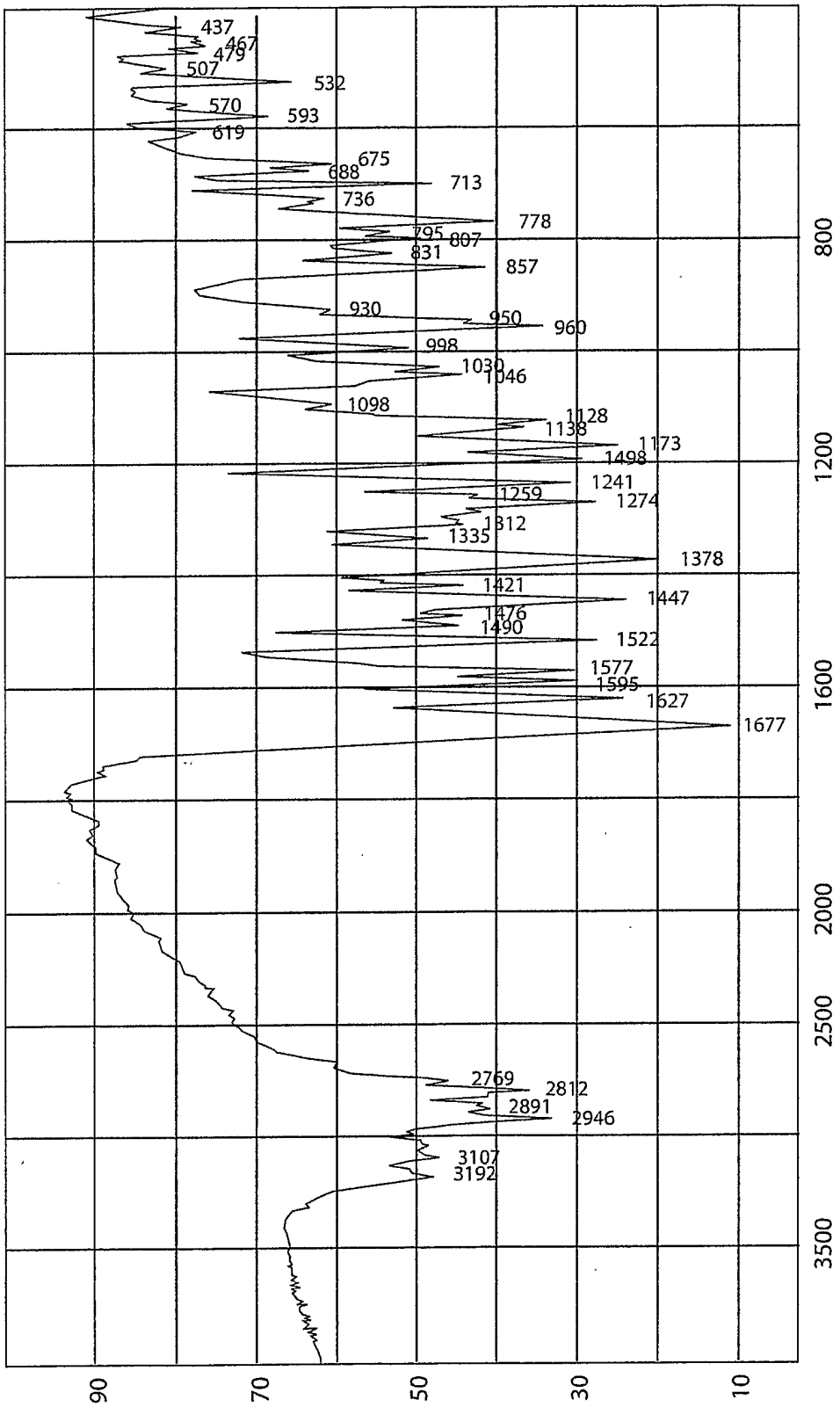

437
467
479
507
532
570
593
619
675
688
713
736
778
795
807
831
857
930
950
960
998
1030
1046
1098
1128
1138
1173
1498
1241
1259
1274
1312
1335
1378
1421
1447
1476
1490
1522
1577
1595
1627
1677
2769
2812
2891
2946
3107
3192
800
1200
1600
2000
2500
3500
90
70
50
30
10

Fig. 3