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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 February 2012 (02.02.2012)

PCT

(10) International Publication Number
WO 2012/014000 A1

(51) International Patent Classification:
C07D 401/14 (2006.01) *C07D 403/14* (2006.01)
C07D 401/00 (2006.01)

(21) International Application Number:
PCT/IB2010/001888

(22) International Filing Date:
30 July 2010 (30.07.2010)

(25) Filing Language: English

(26) Publication Language: English

(72) Inventor; and
(71) Applicant : **POTLURI, Ramesh, Babu** [IN/IN]; SMS Pharmaceuticals Limited, #417, Nilgiri, Aditya Enclave, Ameerpet, Hyderabad Andhra Pradesh, 500 033 Hyderabad (IN).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **TBV, Ramesh** [IN/IN]; Sy. No. 189 & 190, Gagillapur Village, Qutubullapur (Mo), Rangareddy (Dist), Andhra Pradesh, 500 043 Hyderabad (IN). **KOTHAPALLI, Hari, Prasad** [IN/IN]; Sy. No. 189 & 190, Gagillapur Village, Qutubullapur (Mo), Rangareddy (Dist), Andhra Pradesh, 500 043 Hyderabad (IN). **AWADESH, Narain, Singh** [IN/IN]; Sy. No. 189 & 190, Gagillapur Village, Qutubullapur (Mo), Rangareddy (Dist), Andhra Pradesh, 500 043 Hyderabad (IN). **VENKATA SUBRAMANIAN, Hariharakrishnan** [IN/IN]; Sy. No. 189 & 190, Gagillapur Village, Qutubullapur (Mo), Rangareddy (Dist), Andhra Pradesh, 500 043 Hyderabad (IN). **TADIMALLA, Venkata, Srihari** [IN/IN]; Sy. No. 189 & 190, Gagillapur Village, Qutubullapur (Mo), Rangareddy (Dist), Andhra Pradesh, 500 043 Hyderabad (IN).

(74) Agent: **VISHWANATH, Ramesh, Babu**; Vishwanath & Global Attorneys, # 42-839, 2nd Floor, Moghanaakash, Arcade, Moulali, 500040 Hyderabad (IN).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2012/014000 A1

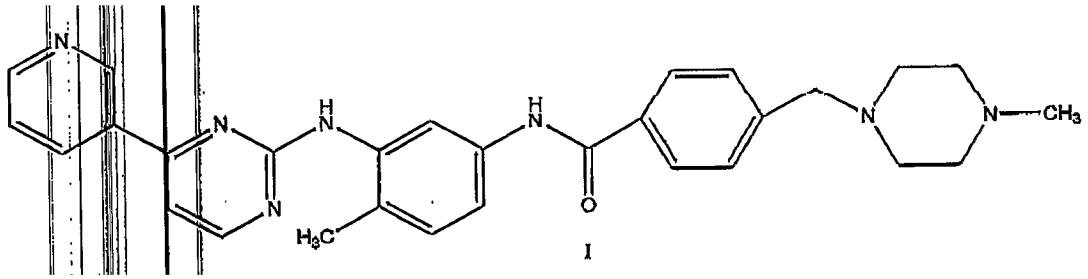
(54) **Title**: STABLE α-CRYSTAL FORM OF IMATINIB MESYLATE AND PREPARING PROCESS THEREOF

(57) **Abstract**: A stable, free flowing and non -hygroscopic α-crystalline form of 4-(4-methyl piperazin-1-yl methyl)-N-[4-methyl-3- (4-pyridin-3-yl)pyrimidin-2-yl amino)phenyl]-benzamide monomethanesulfonate (imatinib mesylate) is disclosed. A process for preparing the a-crystal polymorph of the said imatinib mesylate is also described.

STABLE α-CRYSTAL FORM OF IMATINIB MESYLATE AND PREPARING PROCESS THEREOF

Field of the invention:

The invention given herein pertains to stable, free flowing and non-hygroscopic α-crystal polymorph of methane sulfonic acid addition salt of 4-(4-methyl piperazin-1-yl methyl)-N-[4-methyl(3-(4-pyridin-3-yl) pyrimidin-2-yl amino)phenyl]-benzamide of formula-I and process for the preparation thereof.



I

Background of the invention:

Imatinib, sold by the Novartis as Gleevec™ is used for the treatment of chronic myeloid leukemia (CML), malignant gastro intestinal tumors and other solid tumors.

US patent no. 6894051 describes α and β crystalline forms of imatinib mesylate. The α crystalline described in that patent is described as hygroscopic and unstable and the process for the crystal involves a number of unit operations making it cumbersome.

WO 2004/106326, relating to H1 crystal of imatinib mesylate, makes use of chlorinated solvents, which are undesirable on account of its hazaradous properties.

WO 2005/095379 teaches preparation of α-polymorph of imatinib mesylate using sub molar equivalents (0.95 – 0.99) of methane sulfonic acid in an alkanol or a mixture of alkanol and alkanoic acid ester. The process requires seeding with α-crystals. The process is a little lengthy and inconsistent for repeatability. Use of mixed solvents of alkanol and alkanoic ester is not favourable as it leads to small amount of undesired form.

WO 2006/024863 describes a process which produces non-inform α-crystals requiring micronization. It is likely to result in non-uniform crystals.

US patent 2006/0223816 A1 describes formation of α-polymorph of imatinib mesylate using class III as well as class II solvents. Repeating this process it was observed that at temperatures close to 70-80°C, impurities formation were more and at <15°C filteration of addition salt took several hours. Additionally the initiation of α-crystals formation needed seeding by α-crystals.

US patent 2007/0197545 A1 describes formation of α-polymorph of imatinib methane sulfonate as well as forms I and II of imatinib di methane sulfonate salts.

The criticality of the mole ratio of base to acid in the formation of mono and di salt is studied in detail. The formation of α-polymorph is carried out in a mixture of ethyl alcohol and an alkanol selected from C_1-C_4 alkanol. Mixture of solvents is not desirable for an individual process. It was observed in our hand that any solvent which has solubility in water or tends to be hygroscopic gave inconsistent result in the formation of pure α-crystal polymorph.

Considering the fact that the methods described in the preceding paragraph have limits in terms of simplicity and consistency in the formation of the required polymorphic crystals, it was decided to develop a simple methodology, which will give the α-polymorph in stable form.

Summary of the invention

The present application describes a simple, facile and industrially operational methodology in order to achieve consistent results in terms of yield and quality of the required crystalline polymorph. This invention yields a stable, free flowing and non-hygroscopic α-crystal polymorph substantially free of β-crystal polymorph.

In one embodiment of the invention a free flowing, stable and non-hygroscopic α-polymorph is obtained by conducting salt formation in a water immiscible or partially miscible organic solvent or a mixture there of.

In another embodiment of the invention a free flowing, stable and non-hygroscopic α-polymorph is formed by performing the reaction in a alkanoic acid ester or a alkanone.

In yet another embodiment of the present invention, the formation of α-polymorph is achieved by using C_{1-4} alkanoic acid ester, an alkanone or a mixture of C_{1-4} alkanoic acid ester and an alkanone there of.

In a further embodiment of the present invention, the selective formation of α-polymorph is achieved by mixing a suspension or a partially soluble solution of imatinib base with a solution of methane sulfonic acid under stirring.

In one more further embodiment of the present invention by conducting the salt formation at 20-80^{o}C.

The ideal solvents, which give consistent formation of free flowing, stable and non-hygroscopic α-polymorph is achieved by conducting salt formation in a solvent selected from the group methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, methyl propionate, ethyl propionate, methyl

butanoate, ethyl butanoate or a mixture there of, acetone, ethyl methyl ketone, methyl iso butyl ketone or a mixture there of or a mixture of an alkanoic acid ester and an alkanone.

The formation of α-crystal polymorph is carried out, preferably, in an alkanoic acid ester or an alkanone or a mixture there of under stirring at a temperature of 20-80^{o}C.

Detailed description of the invention

It has been observed that a free flowing, stable and non-hygroscopic α-crystal polymorph with consistent particle size, is formed, by conducting the salt formation in an alkanoic acid ester, a mixture of alkanoic acid esters, an alkanone, a mixture of alkanones and a mixture of alkanoic acid ester and a alkanone under stirring at a temperature of 0-80^{o}C.

In one embodiment of the invention the salt formation is preferably carried out in an alkanoic acid ester R^1-COOR^2 where R^1 is methyl, ethyl & propyl and R^2 is methyl, ethyl, propyl and butyl or mixtures there of, an alkanone R^1 CO R^2 where R^1 is methyl, ethyl and isobutyl and R^2 is methyl or mixture there of and a mixture of an alkanoic acid ester and an alkanone.

It is preferable to use to an alkanoic acid ester, a mixture of alkanoic acid ester, an alkanone, a mixture of alkanone and a mixture of an alkanoic acid ester and an alkanone.

It is more preferable to use an alkanoic acid ester or an alkanone. It is most preferable to use an alkanoic acid ester.

The suitable solvents are methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate or a mixture there of, or acetone, methyl ethyl ketone, methyl iso butyl ketone or mixtures there or mixture of an alkanoic acid ester and an alkanone.

It is more preferable to use an alkanoic acid ester or an alkanone or a mixture of an alkanoic acid ester and an alkanone.

It is most preferable to use an industrially available alkanoic acid ester.

In another embodiment of the present invent, the salt formation is carried at a temperature of 10-80^{o}C.

It is preferable to use a temperature of 15-80^{o}C.

It is more preferable to use a temperature of 20-70^{o}C.

It is most preferable to use temperature between 50-60^{o}C.

In yet another embodiment of the present invention, the mole ratio methane sulfonic acid to that of imatinib base is preferably 0.95 to 1.0.

It is more preferable to use a mole ratio of 0.98 to 1.0.

It is most preferable to use equi molar ratio of methane sulfonic acid and base.

It is preferable to use a 10-40 volumes of solvent. It will be more preferable to use 15-30 volumes of solvent.

It is preferable to conduct the salt formation at 15 to 80^{O}C. It is more preferable to form salt at 25 to 70^{O}C.

It is most preferable to form α-polymorph crystals of imatinib mesylate at 30 to 65^{O}C.

As per the findings of this applicants the preferable solvents are ethyl acetate and butyl acetate.

Formation of α-polymorph is achieved by adding a solution of methane sulfonic acid in an organic solvent to a partially soluble suspension of imatinib base in the same organic solvent under stirring at a temperature of 30 to 75^{O}C, preferably at 50-60^{O}C. The addition of the methane sulfonic acid may be preferably done in

1 - 6 hrs and more preferably 1 - 2 hrs. The maintenance, after completion of addition, preferably, is 1-2 hrs and more preferably 1 – 1.5 hrs.

The process is very simple, easily operational resulting in the formation of stable, free flowing, non-hygroscopic α-polymorphic crystals of imatinib methane sulfonate. Additionally the preferential α-polymorph crystal formation takes place without seeding by α-crystals.

The solvents used in this invention include methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, methyl propionate, ethyl propionate, methyl butanoate, ethyl butanoate and mixtures there of.

The process reported herein is quite rugged since it can be performed at wide range of temperatures preferably 20-80^{o}C, more preferably 25-75^{o}C and mot preferably 30-70^{o}C. The mole ratio of acid to base is 1 : 1, wherein, one can achieve selective formation of α-polymorph, which is easily filtered and dried.

The process gives, a free flowing, non-hygroscopic and stable α-polymorph substantially free of β-polymorph in at least 88.5% yield and at least 95% yield. By proper choice of conditions, such as solvent and temperature, HPLC purity of 99.5 and above can be obtained.

The identification of α-crystal polymorph has been confirmed by studying their IR, DSC and XRD.

Figure i gives IR spectra,

figure ii gives the DSC and figure iii gives the XRD.

Thus the applicants have developed a rugged method for the formation of α-crystal polymorph, which has excellent physical properties such as easy filterability, drying properties, stability and non-hygroscopic nature.

Examples:

The following examples illustrate this invention. This should not be misctued in limiting the application of this invention in any way. The person skilled in the art may vary the parameters within the scope this invention.

Example 1

To a suspension of imatinib base (99 g, 0.2 mole), stirred at 40-60°C in methyl acetate (2 lts), was added a solution of methane sulfonic acid (19.22 g, 0.2 mole) in methyl acetate (100 ml) during 1.5 – 2hrs. After the addition, the reaction mixture

was stirred at that temperature for 1-2 hr and filtered. The solid was washed with the same solvent and dried under vacuum at 40-50°C.

The yield is 90% and HPLC purity is 99.5%.

Example 2

To a suspension of imatinib base (99 g, 0.2 mole), stirred at 40-60°C in ethyl acetate (2 lts), was added a solution of methane sulfonic acid (19.22 g, 0.2 mole) in ethyl acetate (100 ml) during 1.5 – 2hrs. After the addition, the reaction mixture was stirred at that temperature for 1-2 hr and filtered.

The solid was washed with the same solvent and dried under vacuum at 40-50°C.

The yield is 95% and HPLC purity is 99.85%.

Example 3

To a suspension of imatinib base (99 g, 0.2 mole), stirred at 40-60°C in propyl acetate (2 lts), was added a solution of methane sulfonic acid (19.22 g, 0.2 mole) in propyl acetate (100 ml) during 1.5 – 2hrs. After the addition, the reaction mixture was stirred at that temperature for 1-2 hr and filtered. The solid was washed with the same solvent and dried under vacuum at 40-50°C.

The yield is 89% and HPLC purity is 99.5%.

Example 4

To a suspension of imatinib base (99 g, 0.2 mole), stirred at 40-60°C in butyl acetate (2 lts), was added a solution of methane sulfonic acid (19.22 g, 0.2 mole) in butyl acetate (100 ml) during 1.5 – 2hrs. After the addition, the reaction mixture was stirred at that temperature for 1-2 hr and filtered. The solid was washed with the same solvent and dried under vacuum at 40-50°C.

The yield is 91% and HPLC purity is 99.5%.

Example 5

To a suspension of imatinib base (99 g, 0.2 mole), stirred at 40-60°C in isopropyl acetate (2 lts), was added a solution of methane sulfonic acid (19.22 g, 0.2 mole) in isopropyl acetate (100 ml) during 1.5 – 2hrs. After the addition, the reaction mixture was stirred at that temperature for 1-2 hr and filtered. The solid was washed with the same solvent and dried under vacuum at 40-50°C.

The yield is 90% and HPLC purity is 99.4%.

Example 6

To a suspension of imatinib base (99 g, 0.2 mole), stirred at 40-60°C in methyl propionate (2 lts), was added a solution of methane sulfonic acid (19.22 g, 0.2

mole) in methyl propionate (100 ml) during 1.5 – 2hrs. After the addition, the reaction mixture was stirred at that temperature for 1-2 hr and filtered. The solid was washed with the same solvent and dried under vacuum at 40-50°C.

The yield is 88.5% and HPLC purity is 98.8%.

Example 7

To a suspension of imatinib base (99 g, 0.2 mole), stirred at 40-60°C in ethyl propionate (2 lts), was added a solution of methane sulfonic acid (19.22 g, 0.2 mole) in ethyl propionate (100 ml) during 1.5 – 2hrs. After the addition, the reaction mixture was stirred at that temperature for 1-2 hr and filtered. The solid was washed with the same solvent and dried under vacuum at 40-50°C.

The yield is 89% and HPLC purity is 99.3%.

CLAIMS:

We claim

1. A process for the preparation of substantially pure α-polymorph of imatinib mesylate by adding a solution of methane sulfonic acid, dissolved in an organic solvent, preferably alkanoic acid ester to a stirred suspension or sparingly soluble suspension of imatinib base in the same organic solvent, preferably alkanoic acid ester.

2. A claim, as claimed in claim 1, wherein the alkanoic acid ester is methyl acetate, ethyl acetate, propyl acetate, iropropyl acetate, butyl acetate, methyl propionate, ethyl propionate, propyl propionate, isopropyl propionate, methyl butanoate, ethyl butanoate or a mixture there of

3. A claim, as claimed in claim 2, wherein the alkanoic acid ester is methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate or mixture there of

4. A claim, as claimed in claims 2 and 3, where in the alkanoic acid ester is methyl acetate, ethyl acetate or their mixture.

5. A claim, as claimed in claim 1, wherein the addition of methane sulfonic acid to imatinib base is carried out at 20-80^{O}C, preferably at 50-60^{O}C.

6. A claim, as claimed in claim 1, wherein the crystals of imatinib mesylate formed are substantially pure α-polymorph, >99.5%.

7. A claim, as claimed in claims 1 and 6, wherein the crystals of imatinib mesylate formed are substantially pure α-polymorph, which shows in an X-ray diffraction diagram lines having a relative line intensity, as compared to the most intense line in the diagram, of about 20% or more at the following angles of refraction 2theta: 4.9^{O}, 10.5^{O}, 14.9^{O}, 16.5^{O}, 17.7^{O}, 18.2^{O}, 18.7^{O}, 19.2^{O}, 21.4^{O}, 21.7^{O}, 22.7^{O}, 23.2^{O}, 23.8^{O}, 25.0^{O} and 28.6^{O}.

8. A claim, as claimed in claims 1 and 6, wherein the crystals of imatinib mesylate formed are substantially pure α-polymorph, which has a melting range of 223 – 226 °C in differential scanning calorimetry (DSC) thermogram.

9. A claim, as claimed in claims 1 and 6, wherein the crystals of imatinib mesylate formed are substantially pure α-polymorph, which has the IR spectrum absorption bands using a KBr pellets at 3033, 2924, 2824, 2707, 1660, 1575, 1527, 1447, 1317, 1220, 1163, 1036, 807 and 554 cm^{-1}.

10. A claim, as claimed in claim 1, wherein α-polymorph is formed in not less that 85% yield and preferably not less than 95% yield.

11. A claim, as claimed in claim 1, wherein the HPLC purity of α-polymorph is not less than 99% and preferably not less than 99.5%.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2010/001888

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D401/-, C07D403/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases: WPI; EPODOC; CNPAT; CNKI; CAplus (STN); REGISTRY (STN); CASREACT(STN); Keywords: imatinib, mesylate, methyl, piperazino, benzoylamido, pyridyl, pyrimidine, methansulfonic, methylsulfonic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 20060223816 A1 (CHEMAGIS LTD.), 05 Oct. 2006 (05.10.2006), see paragraphs [0020]-[0022] and [0030]-[0032], claim 6.	1-11
Y	WO 2005095379 A2 (INSTYTUT FARMACEUTYCZNY), 13 Oct. 2005 (13.10.2005), see lines 1-23 in page 8, lines 18-22 in page 10.	1-11
A	WO 2009151899 A2 (DR. REDDY'S LABORATORIES LTD. et al.), 17 Dec. 2009 (17.12.2009), see lines 10-20 in page 4.	1-11

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 Apr. 2011(08.04.2011)	**05 May 2011 (05.05.2011)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer WEN, Guoyong Telephone No. (86-10)82245644

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2010/001888

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
US 20060223816 A1	05.10.2006	FR 2900655 A1	09.11.2007
		DE 102007021043 A1	22.11.2007
		DE 102007021043 B4	08.04.2010
WO 2005095379 A2	13.10.2005	EP 1742933 A2	17.01.2007
		US 2007197545 A1	23.08.2007
		US 7732601 B2	08.06.2010
		PL 374074 A	02.10.2006
		PL 366885 A	03.10.2005
WO 2009151899 A2	17.12.2009	WO 2009151899 A3	25.02.2010
		EP 2291366 A	09.03.2011

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2010/001888

Continuation of "**CLASSIFICATION OF SUBJECT MATTER**"

C07D401/14 (2006.01) i
C07D401/00 (2006.01) i
C07D403/14 (2006.01) i