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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 January 2016 (07.01.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/001844 A1

(51) International Patent Classification:
A61K 31/43 (2006.01)

(21) International Application Number:
PCT/IB2015/054919

(22) International Filing Date:
30 June 2015 (30.06.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1738/DEL/2014 30 June 2014 (30.06.2014) IN

(71) Applicant: **SUN PHARMACEUTICAL INDUSTRIES LIMITED** [IN/IN]; Sun House, Plot No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai, Maharashtra 400 063 (IN).

(72) Inventors: **VERMA, Shyam Sunder**; Krishna Nagar (Darekhoo), Jagatpur, Varanasi, Uttar Pradesh 221302 (IN). **SINGH, Shravan Kumar**; House No. 34, Post - Pachewara, Village - Vishunapura, Tehsil - Chunar, Mirzapur, Uttar Pradesh 231305 (IN). **SINGH, Kaptan**; Flat No. B-02, Saket Enclave, Rajendra Nagar, Sahibabad, Ghaziabad, Uttar Pradesh 201005 (IN). **PRASAD, Mohan**; H. No. P-3/3, Phase-II, DLF Qutab Enclave, Gurgaon, Haryana 122001 (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, BN, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, 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, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, 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, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2016/001844 A1

(54) **Title**: AMORPHOUS FORM OF AFATINIB DIMALEATE

(57) **Abstract**: The present invention provides an amorphous form of afatinib dimaleate, processes for its preparation, a pharmaceutical composition comprising it, and its use for the treatment of metastatic non-small cell lung cancer. The present invention provides an amorphous form of afatinib dimaleate, processes for its preparation, a pharmaceutical composition comprising it, and its use for the treatment of metastatic non-small cell lung cancer. The amorphous form of afatinib dimaleate Is a highly pure, easy to filter, free-flowing solid, and is stable towards polymorphic conversion.

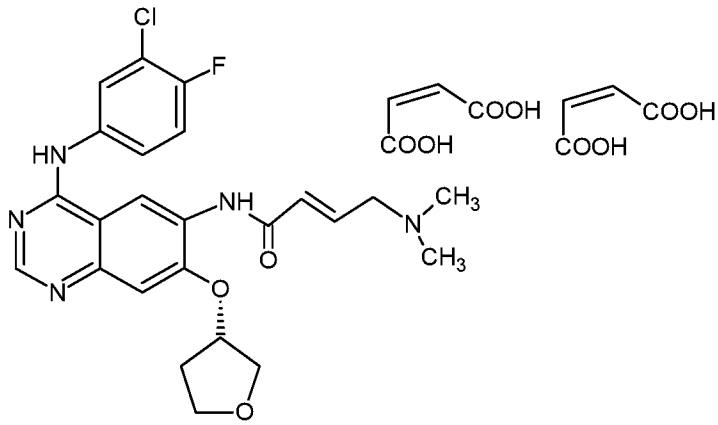
AMORPHOUS FORM OF AFATINIB DIMALEATE

Field of the Invention

The present invention provides an amorphous form of afatinib dimaleate, processes for its preparation, a pharmaceutical composition comprising it, and its use for the treatment of metastatic non-small cell lung cancer.

Background of the Invention

Afatinib dimaleate is a tyrosine kinase inhibitor, chemically designated as 2-butenamide, *N*-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3*S*)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-,(2*E*)-, (2*Z*)-2-butenedioate (1:2) having the structure depicted by Formula I.



Formula I

U.S. Patent Nos. RE43,431 and 6,251,912 provide processes for the preparation of afatinib dimaleate.

U.S. Patent No. 8,426,586 and PCT Publication Nos. WO 2012/121764 and WO 2013/052157 provide processes for the preparation of crystalline forms of afatinib and their salts.

Summary of the Invention

The present invention provides an amorphous form of afatinib dimaleate, processes for its preparation, a pharmaceutical composition comprising it, and its use for the treatment of metastatic non-small cell lung cancer. The amorphous form of afatinib

dimaleate is a highly pure, easy to filter, free-flowing solid, and is stable towards polymorphic conversion.

A first aspect of the present invention provides an amorphous form of afatinib dimaleate.

A second aspect of the present invention provides a process for the preparation of an amorphous form of afatinib dimaleate comprising:

i) adding afatinib to maleic acid in the presence of one or more solvents and heating at a temperature of about 40°C to about 80°C to form a reaction mixture;
ii) stirring the reaction mixture;
iii) cooling the reaction mixture; and
iv) isolating the amorphous form of afatinib dimaleate.

A third aspect of the present invention provides a process for the preparation of an amorphous form of afatinib dimaleate comprising:

i) adding afatinib to maleic acid in the presence of one or more solvents and heating at a temperature of about 40°C to about 80°C to form a reaction mixture;
ii) stirring the reaction mixture;
iii) cooling the reaction mixture;
iv) scratching the reaction mixture; and
v) isolating the amorphous form of afatinib dimaleate.

A fourth aspect of the present invention provides a process for the preparation of an amorphous form of afatinib dimaleate comprising subjecting a solution of afatinib dimaleate to spray drying, agitated thin film drying, lyophilization, or concentrating a reaction mixture containing afatinib dimaleate in a solvent under reduced pressure.

A fifth aspect of the present invention provides a pharmaceutical composition comprising an amorphous afatinib dimaleate and one or more pharmaceutically acceptable carriers, diluents, or excipients.

A sixth aspect of the present invention provides the use of an amorphous form of afatinib dimaleate for the first-line treatment of patients with metastatic non-small cell

lung cancer (NSCLC) whose tumors have an epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

Other objects, features, advantages, and aspects of the present invention will become apparent to those skilled in the art from the description provided herein.

Brief Description of the Drawing

Figure 1: X-ray powder diffraction (XRPD) pattern of an amorphous form of afatinib dimaleate.

Detailed Description of the Invention

Various embodiments and variants of the present invention are described hereinafter.

The term "about," as used herein, refers to any value which lies within the range defined by a number up to ±10% of the value.

The term "ambient temperature," as used herein, refers to a temperature in the range of about 20°C to about 35°C.

The term "scratching," as used herein, refers to the act of getting solid material (for example, seed crystals) out of a reaction mixture by rubbing or crushing the reaction vessel by any means, for example, through glass rod, spatula, etc.

Afatinib can be obtained by following the processes disclosed in U.S. Patent No. RE43,431.

In an embodiment of the present invention, the preparation of the amorphous form of afatinib dimaleate is carried out by reacting afatinib with maleic acid in the presence of one or more solvents and heating the reaction mixture at about 40°C to about 80°C for about 2 hours followed by cooling the reaction mixture to ambient temperature, then scratching the material obtained with a spatula.

The solvent may be selected from the group comprising alcohols, ketones, alkyl acetates, and mixtures thereof. Examples of alcohols include methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol, and 2-methyl-1-pentanol. Examples of ketones include acetone, methyl ethyl ketone, and *t*-butyl ketone. Examples of alkyl acetates include ethyl acetate, propyl acetate, and *t*-butyl acetate.

Isolation of the amorphous form of afatinib dimaleate from its reaction mixture is carried out by concentration, precipitation, cooling, filtration, centrifugation, or a combination thereof, followed by drying. Drying can be carried out using any suitable method, such as drying under reduced pressure, air drying, vacuum tray drying or heating.

In an embodiment of the present invention, the isolation of the amorphous form of afatinib dimaleate is carried out by filtration, followed by drying at a temperature of about 40°C to about 55°C.

In another embodiment of the present invention, the amorphous form of afatinib dimaleate can be prepared by subjecting a solution of afatinib dimaleate to spray drying, agitated thin film drying, lyophilization, or concentrating a reaction mixture containing afatinib dimaleate in a solvent under reduced pressure

The amorphous form of afatinib dimaleate of the present invention exhibits an X-ray powder diffraction (XRPD) pattern substantially as depicted in Figure 1.

The amorphous form of afatinib dimaleate is a highly pure, easy to filter, free-flowing solid, and is stable towards polymorphic conversion.

In the foregoing section, embodiments are described by way of an example to illustrate the process of the present invention. However, this is not intended in any way to limit the scope of the present invention. Several variants of the example would be evident to persons ordinarily skilled in the art which are within the scope of the present invention.

Method

X-ray diffraction patterns were recorded using a PANalytical® X'pert PRO with X'celerator® as the detector, 0.02 as step size, and 3-40° 2θ as range, using CuKα radiation.

Example: Preparation of an amorphous form of afatinib dimaleate

In a round bottom flask, a mixture of afatinib (3 g) and ethyl acetate (30 mL) was heated to about 65°C to obtain a turbid solution. In another round bottom flask, a mixture of maleic acid (1.6 g) and ethyl acetate (30 mL) was heated to about 50°C to obtain a clear solution. The maleic acid solution was added to the afatinib solution, and then the reaction mixture was heated at about 75°C to about 80°C. The reaction mixture was stirred at about 75°C to about 80°C for about 1 hour. The reaction mixture was cooled to about

20°C to obtain a sticky material. The sticky material was scratched with a spatula, and then the reaction mixture was further stirred at about 20°C to about 25°C for about 1 hour. The material obtained was filtered, and then washed with ethyl acetate (20 mL). The solid obtained was dried under vacuum at about 45°C to about 50°C for about 15 hours to obtain the amorphous form of afatinib dimaleate.

Yield: 2.5 g (56%)

We Claim:

1. An amorphous form of afatinib dimaleate.

2. The amorphous form of afatinib dimaleate according to claim 1, characterized by an X-ray powder diffraction pattern substantially as depicted in Figure 1.

3. A process for the preparation of the amorphous form of afatinib dimaleate of claim 1, comprising:

i) adding afatinib to maleic acid in the presence of one or more solvents and heating at a temperature of about 40°C to about 80°C to form a reaction mixture;

ii) stirring the reaction mixture;

iii) cooling the reaction mixture; and

iv) isolating the amorphous form of afatinib dimaleate.

4. A process for the preparation of the amorphous form of afatinib dimalaete according to claim 1 comprising:

i) adding afatinib to maleic acid in the presence of one or more solvents and heating at a temperature of about 40°C to about 80°C to form a reaction mixture;

ii) stirring the reaction mixture;

iii) cooling the reaction mixture;

iv) scratching the reaction mixture; and

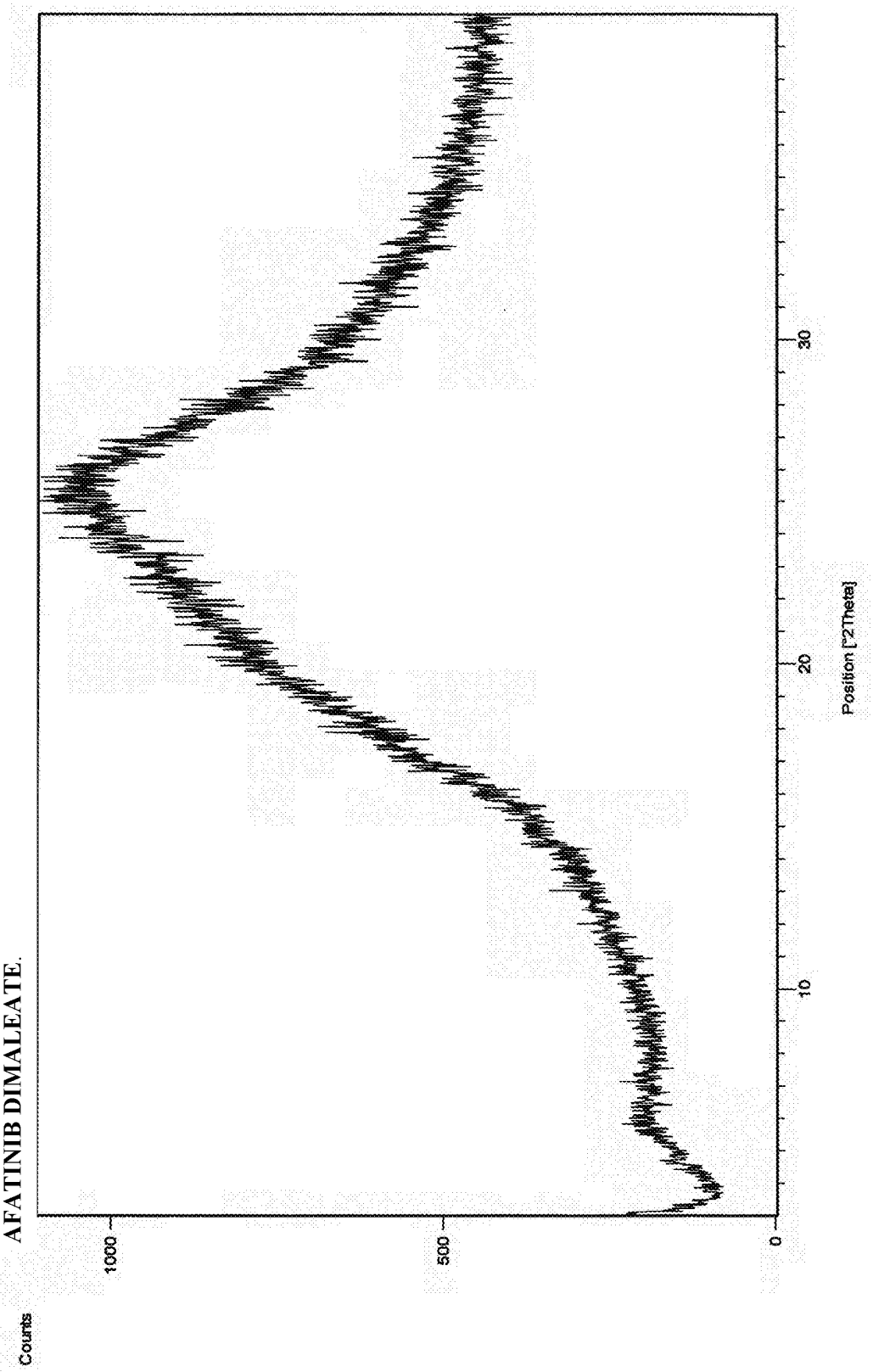
v) isolating the amorphous form of afatinib dimaleate.

5. The process according to claim 3 or claim 4, wherein the solvent is selected from the group comprising alcohols, ketones, alkyl acetates, and mixtures thereof.

6. The process according to claim 3 or claim 4, wherein the solvent is ethyl acetate.

7. A process for the preparation of the amorphous form of afatinib dimaleate according to claim 1 comprising subjecting a solution of afatinib dimaleate to spray drying, agitated thin film drying, lyophilization, or concentrating a reaction mixture containing afatinib dimaleate in a solvent under reduced pressure.

FIGURE 1: X-RAY POWDER DIFFRACTION (XRPD) PATTERN OF AN AMORPHOUS FORM OF AFATINIB DIMALEATE.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/054919

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/43 (2015.01)
CPC - A61K 31/43 (2015.09)
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(8) - A61K 9/00, 31/424, 31/429, 31/43 (2015.01)
CPC - A61K 31/43; C07D 471/04, 499/00 (2015.09)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/192, 200, 249; IPC(8) - A61K 9/00, 31/424, 31/429, 31/43; CPC - A61K 31/43; C07D 471/04, 499/00 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar
Search terms used: crystallization afatinib dimaleate amorphous

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2012/121764 A1 (RATIOPHARM GMBH et al) 13 September 2012 (13.09.2012) entire document	1, 2, 7 --- 3-6
Y	US 2007/0027170 A1 (SOYKA et al) 01 February 2007 (01.02.2007) entire document	3-6
Y	US 2004/0242661 A1 (RUKHMAN et al) 02 December 2004 (02.12.2004) entire document	4

☐ 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
29 September 2015	03 NOV 2015
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774