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WO 2010/040212 A1

(54) **Title**: PROCESSES FOR THE PREPARATION OF ERLOTINIB HYDROCHLORIDE

(57) **Abstract**: There is provided processes to prepare erlotinib hydrochloride. The processes may comprise exposing solid erlotinib free base containing residual solvent to hydrogen chloride gas. The processes may comprise spraying hydrogen chloride gas in an organic solvent onto solid erlotinib free base. Erlotinib hydrochloride prepared by such methods is also provided.

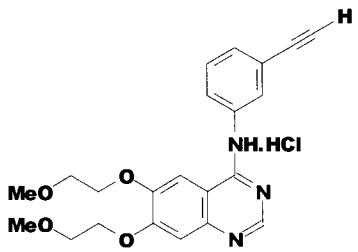
PROCESSES FOR THE PREPARATION OF ERLOTINIB HYDROCHLORIDE.

TECHNICAL FIELD

This invention relates to processes for the preparation of erlotinib hydrochloride.

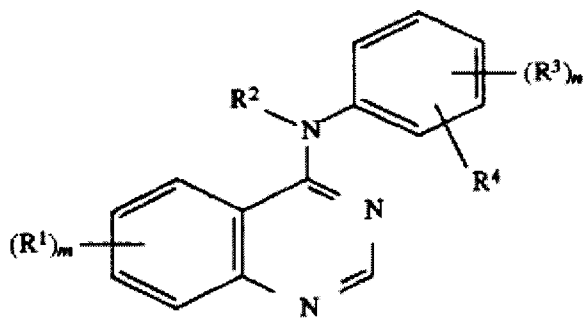
BACKGROUND

Erlotinib hydrochloride (**1**) is an inhibitor of epidermal growth factor receptor (Her1/EGFR/ErbB-1) tyrosine kinase. Erlotinib hydrochloride is marketed as Tarceva® (formally OSI-774) and is used for the treatment of proliferative disorders like non-small cell lung cancer (NSCLC) and pancreatic cancer. The chemical name of erlotinib hydrochloride is *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride and it belongs to the functionalized quinazolinamine group of cancer drugs such as Gefinitib®.

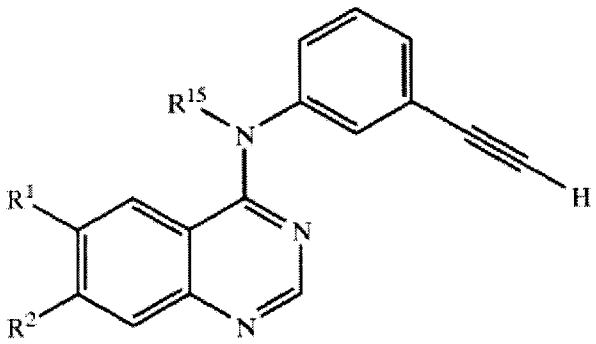


1, Erlotinib Hydrochloride (Tarceva®)

U.S. 5,747,498 discloses processes for making compounds of the following formula:



U.S. 6,476,040 relates to a process for preparing compounds of the formula:



U.S. 2004/0102463 relates to the anhydrous and hydrate forms of *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine mesylate. US 2004/0102463 also relates to pharmaceutical compositions containing N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine mesylate and to methods of treating hyperproliferative disorders, such as cancer, by administering N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazoleinamine mesylate.

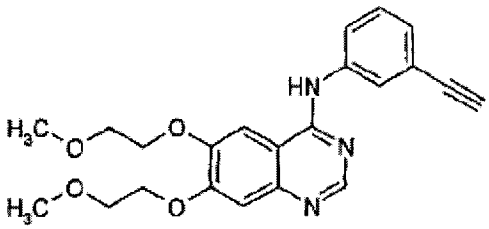
U.S. 6,900,221 relates to a stable crystalline form of *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride designated the B polymorph, its production in essentially pure form, and its use. U.S. 6,900,221 also relates to the pharmaceutical compositions containing the stable polymorph B form of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine as hydrochloride, as well as other forms of the compound, and to methods of treating hyperproliferative disorders such as cancer, by administering the compound.

WO 2004/072049 is concerned with a polymorph of [6,7-bis(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl)amine hydrochloride.

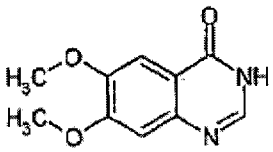
U.S. 2006/0154941 relates to an amorphous form of [6,7-Bis(2-methoxy-ethoxy)-quinazolin-4-yl]-(3-ethynyl-phenyl) (erlotinib hydrochloride), to solid amorphous dispersion of erlotinib hydrochloride and a carrier such as PVP or solid PEG, to processes for their preparations, to pharmaceutical compositions containing them and to method of treatment using the same. The amorphous form or solid amorphous dispersion of

erlotinib hydrochloride obtained is useful in preparing pharmaceutical dosage forms.

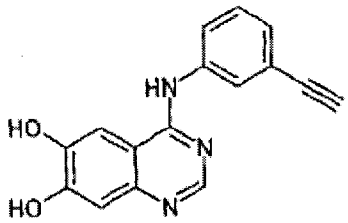
WO 2007/060691 discloses a process for the preparation of erlotinib (N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine) of formula



(1): (1), which comprises: (I demethylation of commercially available 6,7-dimethoxy-4(3H)-quinazolinone of formula



; acetylation using acetic anhydride; (iii) introduction of a leaving group at C-4 position in quinazolinone; (iv) condensation with 3-ethynylaniline to compound of formula (12); (v) deacetylation to get



dihydroxy compound of formula ; and (vi) O-alkylation with 2-iodoethylmethyl ether to get the erlotinib base of formula (1). Erlotinib base is purified by recrystallization from ethyl acetate to get a HPLC purity of >99.5%. Salt formation of this base with hydrogen chloride gave pharmaceutically acceptable erlotinib hydrochloride with a HPLC purity of >99.8%.

EP 1856108 describes a process for the preparation of an acid addition salt of an organic base comprising exposing the organic base in solid form to a gaseous acid, with the proviso that ziprasidone, its acid addition salts and intermediates thereof are excluded.

SUMMARY

In illustrative embodiments of the present invention, there is provided methods for the preparation of erlotinib hydrochloride. Methods of the present invention may be efficient, scalable and environmentally friendly and suitable for the preparation of erlotinib hydrochloride having high pharmaceutical purity (>99.5%) and in substantially pure Form A.

In illustrative embodiments of the present invention, there is provided a process to prepare erlotinib hydrochloride comprising:

i) exposing solid erlotinib free base containing residual solvent to hydrogen chloride gas;

ii) optional isolation; and

iii) drying.

In illustrative embodiments of the present invention, there is provided a process to prepare erlotinib hydrochloride comprising spraying hydrogen chloride in an organic solvent onto solid erlotinib free base.

Erlotinib hydrochloride made by these processes retains essentially the same pharmaceutical purity as the starting erlotinib free base. It often has a purity level of generally >99.5%. The starting erlotinib free base can be prepared by any procedure, for example the one taught in US 5,747,498.

Illustrative embodiments of the present invention provide processes that are scalable, robust and/or provide substantially polymorphically pure Form A. The isolated Form A may be polymorphically and chemically stable.

Illustrative processes of the present invention may avoid the use of solvents to dissolve the erlotinib free base. This provides for environmentally and industrially friendly processes that may also be cost-effective. Illustrative processes of the present invention may deliver an essentially quantitative yield of erlotinib hydrochloride which may be suitable for use as a pharmaceutically active ingredient.

Illustrative embodiments of the present invention provide a process to prepare erlotinib hydrochloride comprising exposing solid erlotinib free base containing residual solvent to hydrogen chloride gas.

Illustrative embodiments of the present invention provide a process described herein further comprising isolation.

Illustrative embodiments of the present invention provide a process described herein wherein the isolation comprises filtration.

Illustrative embodiments of the present invention provide a process described herein wherein the isolation comprises centrifugation.

Illustrative embodiments of the present invention provide a process described herein further comprising drying.

Illustrative embodiments of the present invention provide a process described herein wherein the residual solvent is selected from the group consisting of: C_1-C_4 alcohols; toluene, benzyl alcohol, PEG and mixtures thereof.

Illustrative embodiments of the present invention provide a process described herein wherein the residual solvent is a C_1-C_4 alcohol selected from the group consisting of: methanol, ethanol, isopropanol, 2-butanol and mixtures thereof.

Illustrative embodiments of the present invention provide a process described herein wherein the solid erlotinib free base comprises between about 1% to about 50% (w/w) of residual solvent.

Illustrative embodiments of the present invention provide a process described herein wherein the hydrogen chloride gas is added to the erlotinib hydrochloride at a temperature of about -20°C to about 40°C.

Illustrative embodiments of the present invention provide a process described herein wherein the hydrogen chloride gas is added to the erlotinib hydrochloride at a temperature of about -10°C to about 10°C.

Illustrative embodiments of the present invention provide a process described herein wherein the hydrogen chloride gas is added to the erlotinib hydrochloride at a temperature of about 0°C.

Illustrative embodiments of the present invention provide a process described herein wherein the temperature is maintained at a temperature of from about -10°C to about 10°C.

Illustrative embodiments of the present invention provide a process described herein wherein the temperature is maintained at a temperature of about 0°C.

Illustrative embodiments of the present invention provide a process described herein wherein the erlotinib free base is exposed to the hydrogen chloride gas until substantially complete conversion to the hydrochloride salt is obtained.

Illustrative embodiments of the present invention provide a process to prepare erlotinib hydrochloride comprising: spraying hydrogen chloride gas in an organic solvent onto solid erlotinib free base.

Illustrative embodiments of the present invention provide a process described herein wherein the spraying is done at a temperature of about -20°C to about 40°C.

Illustrative embodiments of the present invention provide a process described herein wherein the spraying is done at a temperature of about -10°C to about 10°C.

Illustrative embodiments of the present invention provide a process described herein wherein the spraying is done at a temperature of about 0°C.

Illustrative embodiments of the present invention provide a process described herein wherein the temperature is maintained at about -10°C to about 10°C.

Illustrative embodiments of the present invention provide a process described herein wherein the temperature is maintained at about 0°C.

Illustrative embodiments of the present invention provide a process described herein wherein the molar ratio of hydrogen chloride relative to erlotinib free base is from about 1.0 mole to about 5.0 moles.

Illustrative embodiments of the present invention provide a process described herein wherein the hydrogen chloride is in the organic solvent at a concentration of about 5% to about 30%.

Illustrative embodiments of the present invention provide a process described herein wherein the organic solvent is isopropanol.

Illustrative embodiments of the present invention provide a process described herein further comprising mixing the solid erlotinib free base with the hydrogen chloride gas.

Illustrative embodiments of the present invention provide a process described herein wherein the erlotinib hydrochloride is substantially pure Form A.

Illustrative embodiments of the present invention provide Erlotinib hydrochloride prepared by a process described herein wherein the erlotinib hydrochloride contains trace levels of C_1-C_4 alcohols; toluene, benzyl alcohol, PEG or mixtures thereof.

Illustrative embodiments of the present invention provide Erlotinib hydrochloride prepared by a process described herein wherein the erlotinib hydrochloride contains trace levels of isopropanol.

Illustrative embodiments of the present invention provide Erlotinib hydrochloride prepared by a process described herein wherein the erlotinib hydrochloride has a purity of greater than 99.5%.

These and other features, aspects, and advantages of the present invention will become better understood with regard to the following description and assembled claims.

DETAILED DESCRIPTION

Erlotinib hydrochloride may be obtained by exposing solid erlotinib free base containing residual solvent to hydrogen chloride gas. Often such exposing occurs while mixing and often at a temperature of about -20°C to about 40°C. Often the temperature is from about -10°C to about 10°C. Often the temperature is about 0 °C. This may be done for a suitable length of time to effect complete hydrochloride salt formation. The length of time is often from about 30 minutes to about 24 hours. Optionally, the erlotinib hydrochloride may then be isolated. Isolation of the erlotinib hydrochloride may be achieved by filtration or centrifugation. Drying the erlotinib hydrochloride or the isolated erlotinib hydrochloride may also be carried out. Drying is often done in a vacuum oven at a temperature of about 15°C to about 45°C and often at room temperature. The degree of residual solvent is from often from about 1% w/w to about 50% w/w. The residual solvent may be selected from the group consisting of C_1-C_4 alcohols; toluene; benzyl alcohol; PEG or mixtures thereof. Often, the solvents are methanol, ethanol, isopropanol and 1- propanol.

Erlotinib hydrochloride may be obtained by spraying hydrogen chloride in organic solvent onto solid erlotinib free base. The solid erlotinib may or

may not contain residual solvent. Often, the temperature is from about -20°C to about 40°C. Often the temperature is from about -10°C to about 10°C and is often about 0 °C. Often, the reaction is done while mixing the solid erlotinib and hydrogen chloride for a suitable length of time to effect complete conversion to the hydrochloride salt. Often the mixing is carried out from about 30 minutes to about 24 hours. The equivalents of hydrogen chloride relative to the erlotinib free base is often from about 1.0 to about 5.0. Optionally, the erlotinib hydrochloride may then be isolated. Isolation of the erlotinib hydrochloride may be achieved by filtration or centrifugation. Drying the erlotinib hydrochloride or the isolated erlotinib hydrochloride may also be carried out. The drying may be done in a vacuum oven at a temperature of about 15°C to about 45°C. The hydrogen chloride may be in an organic solvent at a concentration of about 5% to about 30% and the organic solvent may be isopropanol.

The erlotinib hydrochloride may be substantially pure Form A and may have a purity of >99.5%. The erlotinib hydrochloride used may be chosen so that it is suitable for use as an active pharmaceutical ingredient. In some cases, it may retain some residual solvent within acceptable limits. Often the residual solvent retained is about <0.5% w/w relative to the erlotinib hydrochloride.

The following non-limiting examples further illustrate the manner of carrying out the inventive process described herein.

Example 1:

Erlotinib free base (180 g) containing 15% w/w isopropyl alcohol (IPA) was charged into a three necked flask under nitrogen and cooled to 0°C. The solid was exposed to hydrogen chloride gas for about 1 hour to form the hydrochloride salt with stirring. The erlotinib hydrochloride was then dried at 20°C to 25°C in a vacuum oven. The yield was quantitative. ^{1}H NMR (DMSO-d_6): δ 3.36 (s, 6H), 3.79 (m, 4H), 4.28 (s, 1H), 4.31 (t, J = 4.6 Hz, 2H), 4.41 (t, J = 4.8 Hz, 2H), 7.39-7.43 (m, 2H), 7.48 (t, J = 7.9 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 8.51 (s, 1H), 8.83 (s, 1H), 11.68 (s, 1H).

Example 2:

Erlotinib free base (20 g) containing 15% w/w of isopropanol was charged into a three necked flask under nitrogen and cooled to 0°C whereupon HCl in isopropyl alcohol (IPA) (16% w/w, 1.5 eq) was sprayed into the flask with mixing for 10 min to form erlotinib hydrochloride. The erlotinib hydrochloride was then dried at ambient temperature in a vacuum oven. The yield was quantitative.

Example 3

Form A erlotinib hydrochloride prepared by a processes described in Example 1 or Example 2 was set aside in a closed container in a chamber set at 40°C and a relative humidity of 75% for a period of at least 4 months. The Form A set aside in this manner was found to be polymorphically and chemically stable at the end of the period.

Example 4

Form A erlotinib hydrochloride prepared by a processes described in Example 1 or Example 2 was set aside for 1 month in an open container that was exposed to the ambient atmosphere. The Form A set aside in this manner was found to be polymorphically and chemically stable at the end of the period.

Although various embodiments of the invention are disclosed herein, many adaptations and modifications may be made within the scope of the invention in accordance with the common general knowledge of those skilled in this art. Such modifications include the substitution of known equivalents for any aspect of the invention in order to achieve the same result in substantially the same way. Numeric ranges are inclusive of the numbers defining the range. Furthermore, numeric ranges include each individual number within the range as well as each numeric range within the range as if each individual number and each range were explicitly set out individually. The word "comprising" is used herein as an open-ended term, substantially equivalent to the phrase "including, but not limited to", and the word "comprises" has a corresponding meaning. As used herein, the singular forms "a", "an" and "the"

include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a thing" includes more than one such thing. Citation of references herein is not an admission that such references are prior art to the present invention. Any priority document(s) are incorporated herein by reference as if each individual priority document were specifically and individually indicated to be incorporated by reference herein and as though fully set forth herein. The invention includes all embodiments and variations substantially as hereinbefore described and with reference to the examples and drawings.

CLAIMS

1. A process to prepare erlotinib hydrochloride comprising exposing solid erlotinib free base containing residual solvent to hydrogen chloride gas.
2. The process of claim 1 further comprising isolation.
3. The process of claim 2 wherein the isolation comprises filtration.
4. The process of claim 2 wherein the isolation comprises centrifugation.
5. The process of any one of claims 1 to 4 further comprising drying.
6. The process of any one of claims 1 to 5 wherein the residual solvent is selected from the group consisting of: C_1-C_4 alcohols; toluene, benzyl alcohol, PEG and mixtures thereof.
7. The process of any one of claims 1 to 6, wherein the residual solvent is a C_1-C_4 alcohol selected from the group consisting of: methanol, ethanol, isopropanol, 2-butanol and mixtures thereof.
8. The process of any one of claims 1 to 7 wherein the solid erlotinib free base comprises between about 1% to about 50% (w/w) of residual solvent.
9. The process of any one of claims 1 to 8 wherein the hydrogen chloride gas is added to the erlotinib hydrochloride at a temperature of about -20°C to about 40°C.
10. The process of any one of claims 1 to 9 wherein the hydrogen chloride gas is added to the erlotinib hydrochloride at a temperature of about -10°C to about 10°C.
11. The process of any one of claims 1 to 10 wherein the hydrogen chloride gas is added to the erlotinib hydrochloride at a temperature of about 0°C.
12. The process of any one of claims 1 to 11 wherein the temperature is maintained at a temperature of from about -10°C to about 10°C.
13. The process of any one of claims 1 to 12 wherein the temperature is maintained at a temperature of about 0°C.
14. The process of any one of claims 1 to 13 wherein the erlotinib free base is exposed to the hydrogen chloride gas until substantially complete conversion to the hydrochloride salt is obtained.

15. A process to prepare erlotinib hydrochloride comprising: spraying hydrogen chloride gas in an organic solvent onto solid erlotinib free base.
16. The process of claim 15 wherein the spraying is done at a temperature of about -20°C to about 40°C.
17. The process of claim 15 or 16 wherein the spraying is done at a temperature of about -10°C to about 10°C.
18. The process of any one of claims 15 to 17 wherein the spraying is done at a temperature of about 0°C.
19. The process of any one of claims claim 15 to 18 wherein the temperature is maintained at about -10°C to about 10°C.
20. The process of any one of claims claim 15 to 19 wherein the temperature is maintained at about 0°C.
21. The process of any one of claims 15 to 20 wherein the molar ratio of hydrogen chloride relative to erlotinib free base is from about 1.0 mole to about 5.0 moles.
22. The process of any one of claims 15 to 21 wherein the hydrogen chloride is in the organic solvent at a concentration of about 5% to about 30%.
23. The process of any one of claims 15 to 22 wherein the organic solvent is isopropanol.
24. The process of any one of claims 1 to 23 further comprising mixing the solid erlotinib free base with the hydrogen chloride gas.
25. The process of any one of claims 1 to 24 wherein the erlotinib hydrochloride is substantially pure Form A.
26. Erlotinib hydrochloride prepared by the process of any of claims 1 to 25 wherein the erlotinib hydrochloride contains trace levels of C_1-C_4 alcohols; toluene, benzyl alcohol, PEG or mixtures thereof.
27. Erlotinib hydrochloride prepared by the process of any of claims 1 to 25 wherein the erlotinib hydrochloride contains trace levels of isopropanol.
28. Erlotinib hydrochloride prepared by the process of any of claims 1 to 25 wherein the erlotinib hydrochloride has a purity of greater than 99.5%.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2009/001416

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07D 239/94*** (2006.01) , *A61P 35/00* (2006.01) , *A61K 31/517* (2006.01)
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)
C07D 239/94 (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN, Delphion, Canadian Patent Database (erlotinib, hydrogen chloride gas)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	CA 2682013 A1 (RAO, D.R. et al.) 16 October 2008 (16-10-2008) *examples*	26-27
X	WO 2006/094395 A1 (REY, A. W. et al) 14 September 2006 (14-09-2006) *whole document*	1-14 and 24
X	US 5747498 B1 (SCHNUR, R.C. et al.) 05 May 1998 (05-05-1998) *example 20*	26
X	US 6476040 B1 (NORRIS, T. et al.) 05 November 2002 (05-11-2002) *example s*	26-27
X	WO 2004/072049 A1 (BUBENDORF, A. G. et al.) 26 August 2004 (26-08-2004) *examples*	26
X	WO 2007/138612 A2 (CHANDREGOWDA, V. et al.) 06 December 2007 (06-12-2007) *examples*	26

[X] Further documents are listed in the continuation of Box C. [X] 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)
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"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
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 February 2010 (03-02-2010)	25 February 2010 (25-02-2010)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Karla Randell (819) 956-6118

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/060691 A2 (JYOTHI PRASAD, R. et al.) 31 May 2007 (31-05-2007) *page 10 and the examples*	15-28
X	WO 2008/102369 A1 (JYOTHI PRASAD, R. et al.) 28 August 2008 (28-08-2008) *page 4 and the examples*	15-28

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