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(54) Title: AN IMPROVED PROCESS FOR ERLOTINIB HYDROCHLORIDE

(57) Abstract: The present invention provides an improved and commercially viable process for preparation of erlotinib substantially free of N-methoxyethyl impurity, namely N-[(3-ethynylphenyl)-(2-methoxyethyl)]-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and its pharmaceutically acceptable acid addition salts thereof in High purity and in high yield. According to the present invention, erlotinib or a pharmaceutically acceptable acid addition salt of erlotinib substantially free of N-methoxyethyl impurity is prepared by isolating erlotinib or a pharmaceutically acceptable salt of erlotinib from a solvent medium comprising dimethyl sulfoxide and an alcoholic solvent.



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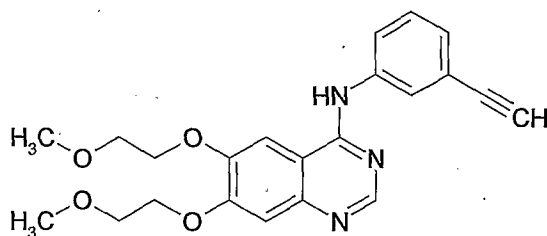
AN IMPROVED PROCESS FOR ERLOTINIB HYDROCHLORIDE

FIELD OF THE INVENTION

The present invention provides an improved and commercially viable process for preparation of erlotinib substantially free of N-methoxyethyl impurity, namely N-[(3-ethynylphenyl)-(2-methoxyethyl)]-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and its pharmaceutically acceptable acid addition salts thereof in high purity and in high yield.

BACKGROUND OF THE INVENTION

U.S. Patent No. 5,747,498 disclosed 4-(substituted phenylamino)quinazoline derivatives, processes for their preparation, pharmaceutical compositions in which they are present and method of use thereof. These compounds are Tyrosine Kinase Inhibitors and are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals. Among them, erlotinib hydrochloride, chemically N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride is a selective inhibitor of the erbB family of oncogenic and protooncogenic protein tyrosine kinases, such as epidermal growth factor receptor (EGFR), and is useful for the treatment of proliferative disorders, such as cancers, particularly non small cell lung cancer, pancreatic cancer, ovarian cancer, breast cancer, glioma, head cancer or neck cancer. Erlotinib is represented by the following structure:



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Various processes for the preparation of erlotinib and related compounds were disclosed in U.S. Patent No. 5,747,498, European Patent Application No. 1044969 A2, PCT Patent Publication No. WO 01/34574 A1 and PCT Patent Publication No. WO 2007/060691 A2.

As per the process described in the U.S. Patent No. 5,747,498 (herein after referred to as '498 patent), erlotinib hydrochloride can be prepared by the reaction of 4-chloro-6,7-bis-(2-methoxyethoxy)-quinazoline, obtained by reaction of 6,7-bis(2-methoxyethoxy)-quinazolinone with oxalylchloride in a solvent system

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containing chloroform and dimethylformamide, with 3-ethynylaniline or its hydrochloride salt in a solvent such as a (C₁-C₆)-alcohol, dimethylformamide, N-methylpyrrolidin-2-one, chloroform, acetonitrile, tetrahydrofuran, 1,4-dioxane, pyridine or other aprotic solvent, preferably isopropyl alcohol; in the presence or
5 absence of a base, preferably an alkali or alkaline earth metal carbonate or hydroxide or a tertiary amine base, such as pyridine, 2,6-lutidine, collidine, N-methyl-morpholine, triethylamine, 4-dimethylamino-pyridine or N,N-dimethylaniline; at a temperature from about ambient to about the reflux temperature of the solvent, preferably from about 35°C to about reflux; under an
10 inert atmosphere such as dry nitrogen. The crude erlotinib hydrochloride (residue) obtained is then basified with saturated aqueous NaHCO₃ in the presence of methanol and chloroform followed by flash chromatography on silica using 30% acetone in hexane to afford erlotinib free base, which is further treated with hydrochloric acid in the presence of diethyl ether and chloroform to
15 give erlotinib hydrochloride.

Erlotinib hydrochloride obtained by the process described in the '498 patent is not satisfactory from purity point of view. The yield of erlotinib hydrochloride obtained according to the process described in the '498 patent is very poor and the process involves column chromatographic purifications. Methods involving
20 column chromatographic purifications cannot be used for large-scale operations, thereby making the process commercially not viable.

According to the European Patent No. 1044969, erlotinib hydrochloride is prepared, either by (i) reacting 6,7-bis(2-methoxyethoxy)-N-[3-
[(trimethylsilyl)ethynyl]phenyl]-4-quinazolinamine monohydrochloride, obtained
25 by the reaction of 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline with a solution of 3-[(trimethylsilyl)ethynyl]aniline in 2-propanol at reflux, with tetra-n-butylammonium fluoride in an aprotic solvent such as tetrahydrofuran, diethyl ether, dimethoxyethane, toluene, dichloromethane and chloroform, and then treating the reaction mass with concentrated hydrochloric acid in 2-propanol; or
30 (ii) reacting 4-[3-[[6,7-bis(2-methoxyethoxy)-4-quinazolinyl]amino]phenyl]-2-methyl-3-butyne-2-ol or its monohydrochloride salt, obtained by the reaction of 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline with 4-(3-aminophenyl)-2-methyl-3-butyne-2-ol in acetonitrile at reflux, with an alkali-metal or alkaline-metal hydroxide such as sodium hydroxide, lithium hydroxide, cesium hydroxide,

calcium hydroxide, magnesium hydroxide and potassium hydroxide, in an alcoholic solvent such as 1-butanol, 2-butanol and 2-propanol, and then treating the reaction mass with concentrated hydrochloric acid in an alcoholic solvent.

The synthetic routes of erlotinib hydrochloride as described in the European Patent No. 1044969 involve lengthy processes and expensive raw materials, and the yields obtained in these routes are not satisfactory, thereby making the processes commercially not viable.

PCT Patent Publication No. WO 99/55683 disclosed erlotinib mesylate anhydrate and hydrate polymorphic forms, their method of preparation and pharmaceutical compositions containing thereof.

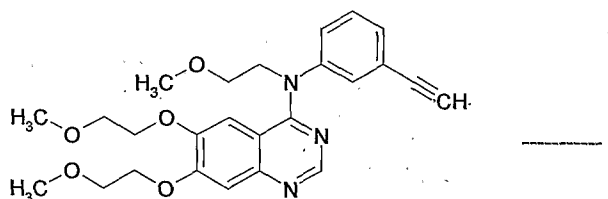
The PCT Patent Publication No. WO 01/34574 A1 described a process for the preparation of erlotinib hydrochloride in crystalline polymorphic form B, which comprises: a) reacting 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline, obtained by reaction of 4-hydroxy-6,7-bis(2-methoxyethoxy)quinazoline with thionyl chloride in a solvent mixture of methylene chloride and dimethylformamide, with 3-ethynylaniline, prepared by reaction of 4-(3-aminophenyl)-2-methyl-3-butyn-2-ol with a suspension of sodium hydroxide (or potassium hydroxide, or a combination) in toluene with heating, to give N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride; b) recrystallizing the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, in a solvent comprising alcohol and water, into the polymorphic form B.

The PCT Patent Publication No. WO 2007/060691 A2 described an improved process for the preparation of erlotinib hydrochloride, which comprises: i) reacting 6,7-dimethoxy-4-(3H)-quinazolinone with aqueous hydrobromic acid or pyridine hydrochloride at elevated temperature to get a hydrobromide or hydrochloride salt of 6,7-dihydroxy-4-(3H)-quinazolinone which on neutralization with a base to give 6,7-dihydroxy-4-(3H)-quinazolinone; ii) acylating the dihydroxy compound using an acylating agent at a temperature in the range of 20 – 150°C and in the presence of a catalyst to give 6,7-diacetoxy-4-(3H)-quinazolinone; iii) reacting the diacetoxy compound with oxalyl chloride at a temperature of 10 – 100°C to give 4-chloro-6,7-diacetoxy-quinazoline; iv) condensing the reaction mass containing the chloro compound with 3-ethynylaniline in an organic solvent selected from chloroform, methylene

chloride, acetonitrile; isopropyl alcohol, toluene, tetrahydrofuran, dioxane, cyclohexane and dimethylformamide, at a temperature of 10 – 100°C to give N-(3-ethynylphenyl)-6,7-diacetoxy-4-quinazolinamine hydrochloride which on further treatment with a base such as aqueous sodium or potassium hydroxide, or aqueous ammonia solution in alcohols at a temperature of 20 – 60°C to give N-(3-ethynylphenyl)-6,7-hydroxy-4-quinazolinamine; v) reacting the N-(3-ethynylphenyl)-6,7-hydroxy-4-quinazolinamine with 2-halo-ethylmethyl ether in the presence of a base at a temperature of 25 – 100°C to give crude erlotinib base; vi) recrystallizing the crude erlotinib base from different solvents like ethyl acetate, acetonitrile, isopropyl alcohol, methanol, ethanol, acetone, methyl ethyl ketone, water or a mixture thereof to give pure erlotinib base; vii) reacting pure erlotinib base by dissolving or suspending in an organic solvent or water or a mixture thereof with aqueous hydrochloric acid or hydrogen chloride gas dissolved in an organic solvent selected from chloroform, toluene, ethanol, methanol, isopropyl alcohol, acetone, methyl ethyl ketone, acetonitrile, ethyl acetate, dimethylformamide, dimethyl ether, diethyl ether and tetrahydrofuran to give erlotinib hydrochloride.

The synthetic route of erlotinib hydrochloride described in the PCT Patent Publication No. WO 2007/060691 A2 involves lengthy process, and the yields obtained in this route are very low.

Erlotinib obtained by the processes described in the art is not satisfactory from purity point of view. We have repeated the erlotinib synthetic procedures as described in the prior art mentioned above and found that relatively large amounts of impurities were obtained along with erlotinib. Among these impurities, the N-methoxyethyl impurity, namely N-[(3-ethynylphenyl)-(2-methoxyethyl)]-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, of formula I:



was identified and isolated. In a specific run, we have found that erlotinib prepared by the above procedures contained about above 0.15% of the N-methoxyethyl impurity at about 1.1 Relative Retention Time (RRT) measured by

High Performance Liquid Chromatography (HPLC), which could not be eliminated by re-crystallization, hence the only way to purify erlotinib was by column chromatography.

However, a need still remains for an improved and commercially viable process of preparing pure erlotinib hydrochloride that should solve the aforesaid problems associated with processes described in the prior art, which will be suitable for large-scale preparation, in terms of simplicity, chemical yield and purity of the product.

Extensive experimentation is carried out by the present inventors to find the way to eliminate this N-methoxyethyl impurity. As a result, it has been found that the N-methoxyethyl impurity formed in the preparation of the erlotinib hydrochloride can be reduced or avoided by isolating erlotinib hydrochloride from a solvent medium comprising dimethyl sulfoxide and an alcoholic solvent in high purity and in high yield.

The object of the present invention is to provide an improved and commercially viable process for preparation of erlotinib substantially free of N-methoxyethyl impurity, namely N-[(3-ethynylphenyl)-(2-methoxyethyl)]-6,7-bis(2-methoxy ethoxy)-4-quinazolinamine, and its pharmaceutically acceptable acid addition salts thereof in high purity and in high yield.

Another object of the present invention is to provide erlotinib substantially free of N-methoxyethyl impurity, namely N-[(3-ethynylphenyl)-(2-methoxyethyl)]-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and its pharmaceutically acceptable acid addition salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

According to one aspect of the present invention, there is provided erlotinib substantially free of N-methoxyethyl impurity, namely N-[(3-ethynylphenyl)-(2-methoxyethyl)]-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and its pharmaceutically acceptable acid addition salts thereof.

Preferable pharmaceutically acceptable acid addition salts of erlotinib, but not limited to, are obtained from hydrochloric acid, hydrobromic acid, hydroiodic acid, methanesulfonic acid and benzenesulfonic acid, and more preferable salt being erlotinib hydrochloride.

According to another aspect of the present invention, there is provided a process for preparation of erlotinib substantially free of N-methoxyethyl impurity,

namely N-[(3-ethynylphenyl)-(2-methoxy ethyl)]-6,7-bis(2-methoxyethoxy)-4-quinazolinamine or a pharmaceutically acceptable salt thereof, which comprises isolating erlotinib or a pharmaceutically acceptable salt of erlotinib from a solvent medium comprising dimethyl sulfoxide and an alcoholic solvent.

5 Preferable alcoholic solvent is methanol, ethanol, isopropanol, tert-butanol, amyl alcohol, isoamyl alcohol, tert-amyl alcohol, or a mixture thereof, more preferable alcoholic solvent is methanol or ethanol, and most preferable alcoholic solvent is methanol.

10 The process of the invention may be carried out by a) reacting 4-chloro-6,7-bis-(2-methoxyethoxy)-quinazoline with 3-ethynylaniline or its hydrochloride salt in a solvent medium comprising dimethylsulfoxide and an alcoholic solvent in the presence or absence of a base; and b) isolating erlotinib as free base or a pharmaceutical acceptable acid addition salt substantially free of N-methoxyethyl impurity.

15 The reaction in step (a) may be carried out between 60°C and reflux temperature of the solvent medium used, preferably carried out between 65°C and reflux temperature of the solvent medium used, and more preferably carried out between 70°C and reflux temperature of the solvent medium used.

20 As used herein, "reflux temperature" means the temperature at which the solvent or solvent system refluxes or boils at atmospheric pressure.

Erlotinib free base substantially free of N-methoxyethyl impurity obtained as a product when the reaction is carried out in the presence of a base in step (a) followed by isolation of the compound obtained in step (b).

25 Preferably the base used in step (a) is an alkali or alkaline earth metal carbonate or hydroxide or a tertiary amine base, such as pyridine, 2,6-lutidine, collidine, N-methyl-morpholine, triethylamine, 4-dimethylamino-pyridine or N,N-dimethylaniline.

30 Preferably the reaction in step (a) is carried out in the absence of a base. Erlotinib hydrochloride substantially free of N-methoxyethyl impurity is obtained as a product when the reaction is carried out in the absence of a base in step (a) followed by isolation of the compound obtained in step (b).

If required, erlotinib free base or hydrochloride salt obtained in step (a) may be converted into pharmaceutically acceptable acid addition salts by conventional methods.

Isolation of erlotinib free base or a pharmaceutically acceptable acid addition salt of erlotinib substantially free of N-methoxyethyl impurity in step (b) may be carried out by methods usually known in the art such as cooling, partial removal of the solvent from the solution, addition of precipitating solvent or a combination thereof.

Pharmaceutically acceptable acid addition salts of erlotinib are formed with appropriate organic or inorganic acids by methods known in the art.

Preferable pharmaceutically acceptable acid addition salts of erlotinib, but not limited to, are obtained from hydrochloric acid, hydrobromic acid, hydroiodic acid, methanesulfonic acid and benzenesulfonic acid, and more preferable salt being erlotinib hydrochloride.

4-Chloro-6,7-bis-(2-methoxyethoxy)-quinazoline and 3-ethynylaniline used as starting materials may be obtained by processes described in the art, for example by the processes described in the U.S. Patent No. 5,747,498.

The process of the invention may also be carried out by dissolving crude erlotinib free base in a solvent medium comprising dimethylsulfoxide and an alcoholic solvent to form a clear solution, adding an acid to the solution, and collecting the precipitated solid to obtain erlotinib pharmaceutically acceptable acid addition salt substantially free of N-methoxyethyl impurity.

Crude erlotinib free base used as starting material may be obtained by processes described in the art, for example by the processes described in the U.S. Patent No. 5,747,498.

The precipitated erlotinib pharmaceutically acceptable acid addition salt substantially free of N-methoxyethyl impurity is collected by filtration or centrifugation.

The acid used in the above reaction is an organic or inorganic acid. Preferable acids are hydrochloric acid, hydrobromic acid, hydroiodic acid, methanesulfonic acid and benzenesulfonic acid, and more preferable acid is hydrochloric acid. Hydrochloric acid used may be in the form of aqueous hydrochloric acid or in the form of hydrogen chloride gas or hydrogen chloride dissolved in an organic solvent. The organic solvent used for dissolving hydrogen chloride gas or hydrogen chloride is selected from the group consisting of ethanol, methanol, isopropyl alcohol, ethyl acetate, diethyl ether, dimethyl ether and acetone.

The process of the invention may also be carried out by dissolving or suspending crude erlotinib pharmaceutically acceptable acid addition salt in a solvent medium comprising dimethylsulfoxide and an alcoholic solvent, and isolating erlotinib pharmaceutically acceptable acid addition salt substantially free of N-methoxyethyl impurity.

Crude erlotinib pharmaceutically acceptable acid addition salt used as starting material may be obtained by processes described in the art, for example by the processes described in the U.S. Patent No. 5,747,498.

Isolation of erlotinib pharmaceutically acceptable acid addition salt substantially free of N-methoxyethyl impurity may be carried out by methods usually known in the art such as cooling, partial removal of the solvent from the solution, addition of precipitating solvent or a combination thereof.

Preferable alcoholic solvent is methanol, ethanol, isopropanol, tert-butanol, amyl alcohol, isoamyl alcohol, tert-amyl alcohol, or a mixture thereof, more preferable alcoholic solvent is methanol or ethanol, and most preferable alcoholic solvent is methanol.

Preferable pharmaceutically acceptable acid addition salts of erlotinib are obtained from hydrochloric acid, hydrobromic acid, hydroiodic acid, methanesulfonic acid and benzenesulfonic acid, and more preferable salt being erlotinib hydrochloride.

The purity (measured by HPLC) of the product obtained according to the present invention is preferably about above 99.5%, more preferably about above 99.7% and still more preferably about above 99.9%.

The term "erlotinib or pharmaceutically acceptable acid addition salts of erlotinib substantially free of N-methoxyethyl impurity" refers to the erlotinib or pharmaceutically acceptable acid addition salts of erlotinib having the content of N-methoxyethyl impurity in less than about 0.1% by weight, preferably less than about 0.05% by weight and still more preferably having no traces of the N-methoxyethyl impurity.

The terms "crude erlotinib" or "crude erlotinib hydrochloride" in the specification refers to erlotinib or erlotinib hydrochloride having the content of N-methoxyethyl impurity in more than about 0.1% by weight.

HPLC Method used in the specification is provided below:

Column: HYPERSIL BDS-C18, 150x4.6mm 5µm

Flow rate: 1.0 ml/min
Temperature: Ambient
Detector: 247 nm
Mobile Phase: Sol-A: - BUFFER
5 Sol-B: - WATER: CH₃CN (5:95)
Buffer: Dissolve 0.77 g of Ammonium acetate in 1000mL of
distilled water and adjust pH = 4.0 with acetic acid.
Sample Preparation: Sol-A: Sol-B (1:1)
Final Concentration: 0.5 mg/mL
10 Run Time: 45min
Injection volume: 20 µL

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitation on the scope or spirit of the invention.

15

REFERENCE EXAMPLES

Reference example 1

6,7-Bis(2-methoxy-ethoxy)-quinazalone (68 gm), chloroform (1360 ml) and dimethylformamide (7.5 ml) are taken in a reaction flask at 25 – 30°C and start stirring. To the contents added oxalyl chloride (120 ml) at 25 – 30°C slowly
20 for 30 minutes, heated to reflux for 1 hour 30 minutes. Distilled the solvent at 55 – 60°C under vacuum, diisopropyl ether (560 ml) is added, cooled to 25 – 30°C and then stirred for 30 minutes. Filtered the compound and washed with diisopropyl ether (100 ml). The compound is added to chloroform (1000 ml), washed the chloroform two times with 8% NaHCO₃ solution (each time 680 ml) and the
25 resulting organic layer is washed with water (500 ml), dried the organic layer over sodium sulfate and distilled the solvent under vacuum at 55 – 60°C. To the residue added n-heptane and stirred for 1 hour at 25 – 30°C. Filtered the material, washed with n-heptane (100 ml) and then dried the material at 50°C under vacuum to get 65 gm of 4-Chloro-6,7-bis-(2-methoxyethoxy)-quinazoline.

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Reference example 2

Step-I:

4-Chloro-6,7-bis-(2-methoxyethoxy)-quinazoline (63 gm) and isopropyl alcohol (990 ml) are added to 3-ethynylaniline (23.6 gm) at 25 – 30°C under stirring, the contents are heated to reflux and then refluxed for 1 hour 30 minutes

to 2 hours. The reaction mass is cooled to 25 – 30°C and stirred for 30 minutes. Filtered the material, washed with chilled isopropyl alcohol (400 ml) followed by n-hexane (300 ml) and then dried the material at 50 – 60°C under vacuum for 6 hours to give 75 gm of crude erlotinib hydrochloride [HPLC purity: 97%; Content of N-methoxyethyl impurity: 0.24% (at 1.14 RRT)].

Step-II:

Crude erlotinib hydrochloride (37 gm, obtained in step-I), water (370 ml) and chloroform (370 ml) are taken into a reaction flask at 25 – 30°C and start stirring. The contents are heated to 50 – 55°C, sodium hydroxide solution is added at 50 – 55°C and then stirred for 15 minutes at 50°C (clear solution not observed). To the reaction mass added chloroform (200 ml) and methanol (60 ml) and stirred for 15 minutes at 50°C (clear solution observed). Separated the layers at 50°C, the organic layer is washed with water (200 ml) at 50°C and then combined the organic layers. To the organic layer added methanol (60 ml) dried over sodium sulfate and distilled the total solvent under vacuum at 50 – 55°C. To the residue added n-heptane (300 ml) and stirred for 30 minutes at 25 – 30°C. Filtered the material, washed with n-heptane (70 ml) and then dried the material at 60 – 65°C under vacuum for 3 hours 30 minutes to give 34 gm of erlotinib free base [HPLC purity: 98.2%; Content of N-methoxyethyl impurity: 0.24% (at 1.14 RRT)].

Step-III:

Erlotinib free base (5 gm, obtained in step-II) is dissolved in chloroform (200 ml) at 25 – 30°C to form a clear solution and then added diethyl ether (50 ml). To the resulting solution slowly added 15% diethyl ether HCl (5 ml) at 25 – 30°C and stirred for 30 minutes at 25 – 30°C. Filtered the material, washed with a mixture of diethyl ether (10 ml) and chloroform (10 ml), and then dried at 60 – 65°C under vacuum to give 4.9 gm of erlotinib hydrochloride [HPLC purity: 99.7%; Content of N-methoxyethyl impurity: 0.24% (at 1.14 RRT)].

EXAMPLES

Example 1

4-Chloro-6,7-bis-(2-methoxyethoxy)-quinazoline (50 gm) and dimethyl sulfoxide (250 ml) are added to methanol (500 ml) under stirring at 25 – 30°C, 3-ethynylaniline (20.5 gm) is added to the reaction mixture at 25 – 30°C and then

the contents are heated to 85°C. The reaction mass is stirred for 2 hours at 80 – 85°C, cooled the mass to 25 – 30°C and then stirred for 1 hour. Filtered the material, washed with a mixture of dimethyl sulfoxide (50 ml) and methanol (100 ml), and then dried at 60°C under vacuum for 4 hours to give 60 gm of erlotinib hydrochloride [HPLC purity: 99.65%; Content of N-methoxyethyl impurity: 0.09% (at 1.14 RRT)].

Example 2

Crude erlotinib free base (10 gm, HPLC purity: 98.2%; Content of N-methoxyethyl impurity: 0.24%) is dissolved in dimethylsulfoxide (50 ml) at 25 – 30°C, to the solution added 15% methanolic HCl (100 ml) at 25 – 30°C while pH of the mass adjusted to 2 and then stirred for 30 – 40 minutes at 25 – 30°C. Filtered the material, washed with a mixture of dimethyl sulfoxide (10 ml) and methanol (20 ml), and then dried the material at 60 – 65°C under vacuum for 5 hours to give 8.9 gm of pure erlotinib hydrochloride [HPLC purity: 99.92%; Content of N-methoxyethyl impurity: 0.02% (at 1.14 RRT)].

Example 3

Crude erlotinib hydrochloride (20 gm, HPLC purity: 99.7%; Content of N-methoxyethyl impurity: 0.24%) is suspended in dimethylsulfoxide (225 ml) at 25 – 30°C and heated to 65 – 70°C (clear solution not observed). To the suspension added methanol (475 ml) at 65 – 70°C, stirred for 30 minutes at 70°C to form a clear solution, the solution is gradually cooled to 20°C and then stirred for 1 hour at 20 – 25°C. Filtered the material, washed with a mixture of dimethyl sulfoxide (10 ml) and methanol (20 ml), and then dried the material at 60 – 65°C under vacuum for 5 hours to give 16.8 gm of pure erlotinib hydrochloride (HPLC purity: 99.95%; Content of N-methoxyethyl impurity: Not detected).

We claim:

1. A process for preparation of erlotinib substantially free of N-methoxyethyl impurity, namely N-[(3-ethynylphenyl)-(2-methoxyethyl)]-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or a pharmaceutically acceptable salt thereof, which comprises isolating erlotinib or a pharmaceutically acceptable salt of erlotinib from a solvent medium comprising dimethyl sulfoxide and an alcoholic solvent.
2. The process as claimed in claim 1, wherein the alcoholic solvent is methanol, ethanol, isopropanol, tert-butanol, amyl alcohol, isoamyl alcohol, tert-amyl alcohol, or a mixture thereof.
3. The process as claimed in claim 2, wherein the alcoholic solvent is methanol or ethanol.
4. The process as claimed in claim 3, wherein the alcoholic solvent is methanol.
5. The process as claimed in claim 1, wherein the pharmaceutically acceptable acid addition salts of erlotinib are obtained from hydrochloric acid, hydrobromic acid, hydroiodic acid, methanesulfonic acid and benzenesulfonic acid.
6. The process as claimed in claim 5, wherein the pharmaceutically acceptable acid addition salt of erlotinib is erlotinib hydrochloride.
7. The process as claimed in claim 1, wherein the process of the invention is carried out by a) reacting 4-chloro-6,7-bis-(2-methoxyethoxy)-quinazoline with 3-ethynylaniline or its hydrochloride salt in a solvent medium comprising dimethylsulfoxide and an alcoholic solvent in the presence or absence of a base; and b) isolating erlotinib as free base or a pharmaceutically acceptable acid addition salt substantially free of N-methoxyethyl impurity.
8. The process as claimed in claim 7, wherein the reaction in step (a) is carried out between 60°C and reflux temperature of the solvent medium used.
9. The process as claimed in claim 8, wherein the reaction is carried out between 65°C and reflux temperature of the solvent medium used.
10. The process as claimed in claim 9, wherein the reaction is carried out between 70°C and reflux temperature of the solvent medium used.
11. The process as claimed in claim 7, wherein the reaction in step (a) is carried out in the absence of a base.

12. The process as claimed in claim 7, wherein the pharmaceutically acceptable acid addition salts of erlotinib are obtained from hydrochloric acid, hydrobromic acid, hydroiodic acid, methanesulfonic acid and benzenesulfonic acid.
- 5 13. The process as claimed in claim 12, wherein the pharmaceutically acceptable acid addition salt of erlotinib is erlotinib hydrochloride.
14. The process as claimed in claim 1, wherein the process of the invention is carried out by dissolving crude erlotinib free base in a solvent medium comprising dimethylsulfoxide and an alcoholic solvent to form a clear
10 solution, adding an acid to the solution, and collecting the precipitated solid to obtain erlotinib pharmaceutically acceptable acid addition salt substantially free of N-methoxyethyl impurity.
15. The process as claimed in claim 14, wherein the acid used is an organic or inorganic acid.
- 15 16. The process as claimed in claim 15, wherein the acids are hydrochloric acid, hydrobromic acid, hydroiodic acid, methanesulfonic acid and benzenesulfonic acid.
17. The process as claimed in claim 16, wherein the acid is hydrochloric acid.
18. The process as claimed in claim 17, wherein the hydrochloric acid is used in
20 the form of aqueous hydrochloric acid or in the form of hydrogen chloride gas or hydrogen chloride dissolved in an organic solvent.
19. The process as claimed in claim 18, wherein the organic solvent used for dissolving hydrogen chloride gas or hydrogen chloride is selected from the group consisting of ethanol, methanol, isopropyl alcohol, ethyl acetate,
25 diethyl ether, dimethyl ether and acetone.
20. The process as claimed in claim 14, wherein the precipitated erlotinib pharmaceutically acceptable acid addition salt substantially free of N-methoxyethyl impurity is collected by filtration or centrifugation.
21. The process as claimed in claim 1, wherein the process of the invention is
30 carried out by dissolving or suspending crude erlotinib pharmaceutically acceptable acid addition salt in a solvent medium comprising dimethylsulfoxide and an alcoholic solvent, and isolating erlotinib pharmaceutically acceptable acid addition salt substantially free of N-methoxyethyl impurity.

22. The process as claimed in claim 21, wherein the Isolation of erlotinib pharmaceutically acceptable acid addition salt substantially free of N-methoxyethyl impurity is carried out by cooling, partial removal of the solvent from the solution, addition of precipitating solvent or a combination thereof.
- 5 23. The process as claimed in claim 1, wherein the erlotinib or a pharmaceutically acceptable salt of erlotinib obtained is having the content of N-methoxyethyl impurity in less than about 0.1% by weight.
24. The process as claimed in claim 23, wherein the erlotinib or a pharmaceutically acceptable salt of erlotinib is having the content of N-methoxyethyl impurity in less than about 0.05% by weight.
- 10 25. The process as claimed in claim 24, wherein the erlotinib or a pharmaceutically acceptable salt of erlotinib is having no traces of the N-methoxyethyl impurity.
26. Erlotinib substantially free of N-methoxyethyl impurity, namely N-[(3-ethynylphenyl)-(2-methoxyethyl)]-6,7-bis(2-methoxyethoxy)-4-
- 15 quinazolinamine, and its pharmaceutically acceptable acid addition salts thereof.
27. The compound as claimed in claim 26, wherein the erlotinib or a pharmaceutically acceptable salt of erlotinib is having the content of N-methoxyethyl impurity in less than about 0.1% by weight.
- 20 28. The compound as claimed in claim 27, wherein the erlotinib or a pharmaceutically acceptable salt of erlotinib is having the content of N-methoxyethyl impurity in less than about 0.05% by weight.
29. The compound as claimed in claim 28, wherein the erlotinib or a pharmaceutically acceptable salt erlotinib is having no traces of the N-methoxyethyl impurity.
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