(51) International Patent Classification:

C07D 213/81 (2006.01) A61P 35/00 (2006.01)

A61K 31/44 (2006.01)

(21) International Application Number:

PCT/IB2015/057037

(22) International Filing Date:

14 September 2015 (14.09.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

4473/CHE/2014 12 September 2014 (12.09.2014) IN

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Declarations under Rule 4.17:

— as to applicant’s entitlement to apply for and be granted a patent (Rule 4.1.7(I))

— as to the applicant’s entitlement to claim the priority of the earlier application (Rule 4.1.7(ii))

Published:

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

(54) Title: PROCESS FOR THE PREPARATION OF CRystalline FORM I OF REGORAFENIB

(57) Abstract: The present disclosure relates to a process for the preparation of a crystalline form-I of regorafenib that is viable on an industrial scale. The disclosed process permits the high yield production of high-purity crystalline form-I of regorafenib.
PROCESS FOR THE PREPARATION OF CRYSTALLINE FORM I OF
REGORAFENIB

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of earlier Indian provisional patent application number 4473/CHE/2014 filed on September 12, 2014, which is incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to the field of pharmaceutical sciences and more specifically to a process for the preparation of crystalline form-I of regorafenib.

BACKGROUND OF THE INVENTION

Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. Regorafenib is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if the cancer is KRAS wild type, an anti-EGFR therapy. Regorafenib is also indicated for treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

Regorafenib is chemically known as 4-[4-({[4-chloro-3-(trifluoromethyl) phenyl] carbamoyl} amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide and has the chemical structural as shown below in formula-I.

```
  Cl     CF3
      O     O
      N     N
    H     H
  F     N

Formula-I
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A process for preparing regorafenib is disclosed in U.S. Patent No. 8,637,553, which is hereby incorporated by reference in its entirety. PCT Publication No. WO2005/009961, which is hereby incorporated by reference in its entirety, also discloses a
method for preparing regorafenib and the afforded material corresponds to the crystalline form-I polymorph. The crystalline form-I polymorph is further characterized in U.S. Patent Publication No. 2014/0315958, which is hereby incorporated by reference in its entirety.

U.S. Patent Publication No. 2010/0173953, which is hereby incorporated by reference in its entirety, discloses crystalline regorafenib monohydrate and provides a process for the preparation of crystalline regorafenib monohydrate.

U.S. Patent Publication No. 2010/0113533, which is hereby incorporated by reference in its entirety, discloses crystalline regorafenib form-II and a process for the preparation of crystalline regorafenib form-II.

U.S. Patent Publication No. 2010/0063112, which is hereby incorporated by reference in its entirety, discloses crystalline regorafenib form-III as well as a process for the preparation of crystalline regorafenib form-III.

The present invention provides a novel process for the preparation of crystalline form-I of regorafenib that may be implemented efficiently on an industrial scale.

**SUMMARY OF THE INVENTION**

One aspect of the present invention provides a process for the preparation of crystalline form-I of regorafenib which may include the following steps:

a) dissolving regorafenib in a mixture of a nitrile solvent and an organic solvent to create a solution;

b) cooling the solution; and

c) isolating crystalline form-I of regorafenib.

The dissolving step may be undertaken at a temperature of about 65 °C to about 75 °C. Further, a portion of the solvent may be removed from the solution prior to cooling the solution. In the cooling step, the temperature of the solution may be reduced to about 0 °C to about 5 °C. Optionally, solvent may be removed before the cooling step, using practices well known in the art. In some embodiments of the present invention, an additional cooling step may be undertaken prior to the removal of solvent, where the solution is cooled to
about 25 °C to about 30 °C. Finally, the isolated crystalline form-I of regorafenib may be dried at about 50 °C.

The nitrile solvent may be acetonitrile. The organic solvent may, for example, be an ester solvent, an alcohol solvent, a ketone solvent, or mixtures thereof. The ester solvent may, for example, be methyl acetate, ethyl acetate, and mixtures thereof. The alcoholic solvent may, for example, be methanol, ethanol, n-propanol, isopropyl alcohol, or mixtures thereof. The ketone solvent may, for example, be acetone, methyl ethyl ketone, or mixtures thereof.

The processes of the present invention permit high yields for crystalline form-I of regorafenib of about 50% to about 70%. These high yields of recovery are achieved without the use of hazardous or toxic chemicals (e.g., diethyl ether) and are simple to implement efficiently on an industrial scale.

DETAILED DESCRIPTION OF THE INVENTION

It is to be understood that the descriptions of the present invention have been simplified to illustrate elements that are relevant for a clear understanding of the invention, while eliminating, for purposes of clarity, other elements that may be well known.

The present disclosure provides a process for the preparation of crystalline form-I of regorafenib.

One aspect of the present invention provides a process for the preparation of crystalline form-I of regorafenib which may include the following steps:

a. obtaining a regorafenib solution, wherein the solution comprises a nitrile solvent;

b. optionally adding an organic solvent to the regorafenib solution;

c. cooling the solution; and

d. isolating a polymorph of regorafenib.
In some embodiments, the addition of an organic solvent to the solution of regorafenib and nitrile solvent is not optional.

Another aspect of the present invention provides a process for the preparation of crystalline form-I of regorafenib which may include the following steps:

b) dissolving regorafenib in a mixture of nitrile solvent and organic solvent to form a solution;

c) cooling the solution; and

d) isolating a polymorph of regorafenib.

In some embodiments, the isolated polymorph of regorafenib is crystalline. In some embodiments, the isolated polymorph of regorafenib is crystalline form-I.

In some embodiments, the solution of regorafenib in nitrile solvent or nitrile and organic solvent is heated. In some embodiments, dissolving regorafenib in a nitrile solvent requires heating. In some embodiments, the heating refers to heating at solvent reflux temperature to obtain a substantially clear or clear solution. In some embodiments, the heating is to about 30° C, 35° C, 40° C, 45° C, 50° C, 55° C, 60° C, 65° C, 70° C, 75° C, 80° C, 85° C, or 90° C, or greater than any of the aforementioned degrees, or between about any of the aforementioned degrees and room temperature, or heated between a range bounded by any of the aforementioned degrees or about any of the aforementioned degrees. In some embodiments, heating is to about 65 °C to about 75 °C.

Within the context of the present invention, the nitrile solvent may be, for example, acetonitrile. In some embodiments, the nitrile solvent is a C₂-C₅ carbon containing nitrile (e.g. acetonitrile, propionitrile, butyronitrile, or pentanitrile) or mixtures thereof. The organic solvent may be an ester solvent, an alcohol solvent, a ketone solvent, or mixtures thereof. Suitable ester solvents include, as examples, methyl acetate, ethyl acetate, C₂-C₅ carbon-containing esters, or mixtures thereof. Examples of suitable alcohol solvents include methanol, ethanol, n-propanol, isopropyl alcohol, C₁-C₅ carbon-containing alcohols, or mixtures thereof. Ketone solvents may be, for example, acetone, methyl ethyl ketone, C₃-C₅ carbon-containing ketones, or mixtures thereof.
In some embodiments, portions of the one or more solvent(s) may be removed from the regorafenib solution prior to isolating the regorafenib polymorph. Removal of the one or more solvent(s) may be achieved by methods well known in the art, such as distillation or evaporation.

In some embodiments, solutions comprising regorafenib and one or more solvent(s) may be treated with activated carbon and filtered prior to isolating the regorafenib polymorph.

In certain embodiments of the present invention, the regorafenib solution was cooled to about -15°C, -10°C, -5°C, 0°C, 5°C, 10°C, 15°C, 20°C, 25°C, 30°C, or 35°C, or less than any of the aforementioned degrees, or between a range bounded by about any of the aforementioned degrees. In some embodiments, the cooling of the regorafenib solution occurred while stirring the solution. In some embodiments, portions of the solvent(s) were removed upon cooling. In some embodiments, the regorafenib solution was filtered after an initial cooling and the filtrate was subjected to additional cooling at a lower temperature or temperature range than the initial cooling temperature. In some embodiments, the initial cooling temperature is about 25°C to about 30°C. In some embodiments, the subsequent or additional cooling of the filtrate occurs at about 0°C to about 5°C.

In some embodiments, the heating or cooling of the regorafenib solution occurs for a certain period of time at a certain temperature or range of temperatures. In some embodiments, such times are about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, 60 minutes, 1.5 hours, or 2 hours, or greater than about any of the aforementioned times, or between a range bounded by any of the aforementioned times or about any of the aforementioned times.

Crystalline regorafenib form-I may then be isolated from that solution. Isolation of crystalline regorafenib form-I may be carried out according to methods well known in the art, for example, by filtering and drying. In some embodiments, the drying occurs at about 30°C, 35°C, 40°C, 45°C, 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, or 90°C, or greater than about any of the aforementioned degrees, or between about any of the aforementioned degrees and room temperature, or heated between a range bounded by any
of the aforementioned degrees or about any of the aforementioned degrees. In some embodiments, a temperature of about 50 °C is utilized.

The methods of the present invention provide several benefits over the prior art. The methods disclosed here achieve a high yield of crystalline form-I of regorafenib of between about 50% and 70% weight/weight. Further, the purity of the recovered crystalline form-I of regorafenib is very high. In some embodiments, the purity is about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 100%, greater than about any of the aforementioned percentages, or between about any of the aforementioned percentages.

Additionally, the methods of the present invention achieve high-quality products, while avoiding the use of hazardous and toxic chemicals (e.g., diethyl ether) that the art teaches a skilled artisan to use to prepare crystalline form-I of regorafenib. Thus, the methods of the present invention are more safely and easily implemented on an industrial scale than prior art methods.

The resulting crystalline regorafenib may be characterized by powder X-ray diffraction ("PXRD") or other methods known in the art for characterizing polymorph form-I.

The regorafenib disclosed herein may be incorporated into oral dosage forms, for example, a tablet. Within the context of the present invention, regorafenib may be incorporated into dosage forms with a variety of excipients well known in the art. Suitable excipients include, for example, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, and colloidal silicon dioxide. Coatings of formulations in tablet form may contain ferric oxide red, ferric oxide yellow, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. Within the context of the present invention, dosage forms may have about 40 milligrams of regorafenib.

One of skill in the art will be familiar with a variety of excipients and formulations that may be used to prepare desirable dosage forms with desired release characteristics and pharmacokinetic properties without undue experimentation.

When administered to human and non-human patients, formulations of regorafenib may be adjusted to compensate for the age, weight, and physical condition of the patient.
Regorafenib may be administered over a wide dosage range from about 40 to 160 milligrams per day.

When administered to patients, the regorafenib of the present invention may be useful for treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. Regorafenib may also be useful for treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

All patents and patent applications cited herein by reference should be considered in their entirety. Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the disclosure in any manner. Variants of these examples would be evident to person ordinarily skilled in the art.

EXAMPLES

Example 1: Preparation of crystalline form-I of regorafenib

Regorafenib (1 g, 2.07 mmol) was taken in acetonitrile (40 ml) and heated to 65-70 °C. To this, ethyl acetate (15 ml) was added, the mixture was heated to 65-70 °C to get a clear solution and the mixture was maintained for 30 min at 65-70 °C. The mixture was slowly cooled to 25-30°C, stirred for 30 min at 25-30 °C, and further cooled to 0-5 °C where it was maintained for 45 minutes. The resulting solid was filtered and washed with acetonitrile (5 ml) and dried under vacuum (10 mbar) at temperature 50 °C to get crystalline form-I of regorafenib (Yield: 0.5 or 50% w/w).

Example 2: Preparation of crystalline form-I of regorafenib

Regorafenib (1 g, 2.07 mmol) was taken in a mixture of ethyl acetate (20 ml) and acetonitrile (20 ml). The mixture was then heated to 70-75 °C to get a clear solution and maintained for 30 minutes. The mixture was slowly cooled to 25-30 °C, stirred for 60 min at 25-30 °C, and further cooled to 0-5 °C where it was maintained for 60 minutes. The
resulting solid was filtered, washed with acetonitrile (5 ml), and dried under vacuum (10 mbar) at temperature 50 °C to get crystalline form-I of regorafenib (Yield: 60% w/w).

Example 3: Preparation of crystalline form-I of regorafenib

Regorafenib (1 g, 2.07 mmol) was taken in a mixture of ethyl acetate (10 ml) and acetonitrile (30 ml). The mixture was heated to 70-75 °C to get a clear solution and maintained for 30 minutes. The mixture was slowly cooled to 25-30 °C, stirred for 60 min at 25-30 °C, and further cooled to 0-5 °C and maintained for 60 minutes. The resulting solid was filtered and washed with acetonitrile (5 ml) and dried under vacuum (10 mbar) at temperature 50 °C to get crystalline form-I of regorafenib (Yield: 60% w/w).

Example 4: Preparation of crystalline form-I of regorafenib

Regorafenib (1 g, 2.07 mmol) was taken in a mixture of acetone (20 ml) and acetonitrile (40 ml). The mixture was heated to 70-75 °C to get a clear solution and maintained for 30 minutes. The mixture was slowly cooled to 25-30 °C, stirred for 60 min at 25-30 °C and distilled out solvent under vacuum at 50 °C to retained 10 volume in mass. The mass was cooled to 0-5 °C and maintained for 60 minutes. The resulted solid was filtered and washed with acetonitrile (5 ml) and dried under vacuum (10 mbar) at temperature 50 °C to get crystalline form-I of regorafenib (Yield: 60% w/w).

Example 5: Preparation of crystalline form-I of regorafenib

Regorafenib (1 g, 2.07 mmol) was taken in a mixture of isopropyl alcohol (20 ml) and acetonitrile (40 ml). The mixture was heated to 70-75 °C to get a clear solution and maintained for 30 minutes. The mixture was slowly cooled to 25-30 °C, stirred for 60 minutes at 25-30 °C, and distilled out solvent under vacuum at 50 °C to retained 10 volume in reaction mass. The mass was cooled to 0-5 °C and maintained for 60 minutes. The resulting solid was filtered and washed with acetonitrile (5 ml) and dried under vacuum (10 mbar) at temperature 50 °C to get regorafenib form-I (Yield: 70% w/w).

Example 6: Preparation of crystalline form-I of regorafenib

Regorafenib (1 g, 2.07 mmol) was taken in mixture of methanol (20 ml) and acetonitrile (40 ml). The mixture was heated to 70-75 °C to get a clear solution and maintained for 30 minutes. The mixture was slowly cooled to 25-30 °C, stirred for 60 min at 25-30 °C and distilled out solvent under vacuum at 50 °C to retained 10 volume in mass.
The mass was cooled to 0-5 °C and maintained for 60 minutes. The resulting solid was filtered and washed with acetonitrile (5 ml) and dried under vacuum (10 mbar) at temperature 50 °C to get crystalline form-I of regorafenib (Yield: 60% w/w)
We claim:

1. A process for the preparation of crystalline form-I of regorafenib comprising the steps of:
   a. obtaining a regorafenib solution, wherein the solution comprises a nitrile solvent;
   b. optionally adding an organic solvent to the regorafenib solution;
   c. cooling the solution; and
   d. isolating a polymorph of regorafenib.

2. The process of Claim 1, wherein the organic solvent is added to the regorafenib solution and the resulting solution is heated.

3. The process of any one of Claims 1-2, wherein the nitrile solvent is a C2-C5 carbon containing nitrile or mixtures thereof.

4. The process of any one of Claims 1-3, wherein the nitrile solvent is acetonitrile.

5. The process of any one of Claims 1-4, wherein the organic solvent is selected from the group consisting of ester solvents, alcohol solvents, ketone solvents, and mixtures thereof.

6. The process of Claim 5, wherein the ester solvent is selected from the group consisting of methyl acetate, ethyl acetate, and mixtures thereof.

7. The process of Claim 5, wherein the alcoholic solvent is selected from the group consisting of methanol, ethanol, n-propanol, isopropyl alcohol, and mixtures thereof.
8. The process of Claim 5, wherein the ketone solvent is selected from the group consisting of acetone, methyl ethyl ketone, and mixtures thereof.

9. The process of any one of Claims 1-8, wherein the regorafenib solution is obtained by heating at a temperature of about 65° C to about 75° C.

10. The process of any one of Claims 1-9, wherein the temperature for the cooling of the solution between about 0° C to about 5° C.

11. The process of any one of Claims 1-10, further comprising a step of removing solvent after the obtaining step and before the cooling step.

12. The process of Claim 11, further comprising a step of cooling the solution to about 25° C to about 30° C after the obtaining step and before the removing step.

13. The process of any one of Claims 1-12, further comprising a step of drying the regorafenib polymorph at about 50° C after the isolating step.

14. The process of any one of Claims 1-13, wherein the polymorph of regorafenib is isolated in a yield of about 40% to about 80%.

15. A process for preparing a pharmaceutical composition of regorafenib, comprising:

   a. obtaining a regorafenib polymorph according to the process of any one of Claims 1-14; and

   b. combining the regorafenib polymorph with a pharmaceutically acceptable excipient to obtain the pharmaceutical composition.

16. The process of Claim 15, wherein the pharmaceutical composition is a tablet.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D213/81 A61K31/44 A61P35/00

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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 practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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* Special categories of cited documents:

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

Date of the actual completion of the international search 17 November 2015

Date of mailing of the international search report 25/11/2015

Authorized officer Elliot, Adrian
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