

(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF PIRFENIDONE

![Figure 1](image_url)

(57) Abstract: The present invention is relates to an improved process for the preparation of pure pirfenidone. The present invention also relates to a crystalline form of pirfenidone and its pharmaceutical composition thereof.
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“AN IMPROVED PROCESS FOR THE PREPARATION OF PIRFENIDONE”

PRIORITY

This application claims the benefit under Indian Provisional Application No. 201641001390, filed on January 14, 2016 entitled “An improved process for the preparation of pirfenidone”, the content of each of which are incorporated by reference herein.

FIELD OF THE INVENTION:

The present invention relates to an improved process for the preparation of pure pirfenidone. The present invention also relates to a crystalline form of pirfenidone and is pharmaceutical composition thereof.

BACKGROUND OF THE INVENTION:

Pirfenidone is an anti-fibrotic drug for the treatment of idiopathic pulmonary fibrosis (IPF). It works by reducing lung fibrosis through down regulation of the production of growth factors and procollagens I and II. Pirfenidone was approved by USFDA for the treatment of idiopathic pulmonary fibrosis on Oct 15, 2014. Pirfenidone is chemically known as 5-methyl-l-phenyl-2-l(H)-pyridone and represented by the following structural formula (I)

\[
\text{Formula (I)}
\]

Idiopathic pulmonary fibrosis (IPF) is a rare disease of unknown etiology that is characterized by progressive fibrosis of the interstitium of the lung, leading to decreasing lung volume and progressive pulmonary insufficiency.

The process for the preparation of pirfenidone was first disclosed in US3839346. The disclosed process involves reaction of 5-methyl-2-(IH)-pyridone with iodobenzene in presence of anhydrous potassium carbonate and zinc precipitated copper powder to get pirfenidone.
PCT publication WO 2002/085858 disclosed the purification process for pirfenidone, which involves dissolution of pirfenidone in 5% aqueous acetic acid at 90°C and adding 25% aqueous sodium hydroxide followed by isolating pure pirfenidone.

PCT publication WO 2003/014087 disclosed an improved process of pirfenidone, which involves the reaction of 5-methyl-2(H)-pyridinone with bromobenzene in the presence of cuprous oxide and potassium carbonate at 156°C followed by isolation and purification of pirfenidone by acid-base treatment.

US patent No. US8519140 ("the 140 patent") disclosed an improved process for the preparation of pure pirfenidone, which involves the reaction of 5-methyl-2(H)-pyridinone with bromobenzene having less than 0.15% by weight dibromobenzene in presence of a cuprous oxide, potassium carbonate in dimethylsulfoxide followed by crystallization of obtained pirfenidone by acid-base treatment. According to this patent, purity of dibromobenzene is important, as amount of dibromobenzene impurity in the bromobenzene can lead to dimer type byproducts, which complicate the purification of pirfenidone and difficult to remove from final pirfenidone. Further states that bromobenzene with less that 0.15% of dibromobenzene is not readily available and moreover expensive when compared with the regular bromobenzene.

PCT publication WO20 16/122420 disclosed an improved process for the preparation of pirfenidone, which involves the reaction of 5-methyl-2-pyridone with low quantity of bromobenzene in a low quantity of solvent, in presence of copper catalyst such as Cu(I) or Cu(II) salts and a base. This publication Further disclosed the purification of pirfenidone by formation of pirfenidone acid adducts with strong acids followed by recovery of pirfenidone from the adduct.

Further number of patents/publications such as CN100396669 C, WO2008/147170 , CN101891676 A and CN102558040 disclosed the improved process for the preparation of pirfenidone, which involves similar chemistry i.e., reaction of 5-methyl-2-(H)-pyridinone with iodo or bromobenzene in presence of copper catalyst and a base in a suitable solvent.
Hence there is a need in the art to develop an improved process for the preparation of pure pirfenidone with high product yield and purity with commercially available bromobenzene having dibromobenzene content about 0.2% or more, in a convenient and cost efficient manner and on a commercial scale.

**SUMMARY OF THE INVENTION:**

Accordingly the present invention provides an improved process for the preparation of pure pirfenidone. More specifically, provides an improved process for pirfenidone which comprise of reacting the 5-methyl-1H-pyridin-2-one of formula-II with bromobenznene, wherein the bromobenzene contain about 0.2% or more by weight dibromobenzene.

In one embodiment, the present invention provides an improved process for the preparation of pirfenidone of formula (I),

![Formula (I)](image)

which comprises the reaction of 5-methyl-1H-pyridin-2-one of formula (II)

![Formula (II)](image)

with bromobenzene of formula (III)

![Formula (III)](image)

in the presence of a suitable copper catalyst and a base in a suitable organic solvent under sufficient conditions to provide pirfenidone, wherein the bromobenzene contain about 0.2% or more by weight dibromobenzene.

In another embodiment, the present invention provides an improved process for the preparation of pirfenidone, which comprises the reaction of 5-methyl-1H-pyridin-2-one with bromobenzene in presence of copper chloride and potassium carbonate in
dimethylformamide under sufficient conditions to provide pirfenidone, wherein the bromobenzene contain about 0.2% or more by weight dibromobenzene.

In another embodiment the present invention provides crystalline pirfenidone characterized by its Powder X-ray diffractogram having one or more peaks at about 8.76, 14.22, 14.90, 18.36, 18.72, 19.86, 20.90, 21.92, 22.52, 22.86, 24.22, 26.96, 27.20, 28.16, 28.80, 29.50, 30.20, 31.42, 32.32, 37.02, 39.40 and 43.38 ± 0.2° 2Θ or by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 1.

In another embodiment, the present invention provides crystalline pirfenidone characterized by a differential scanning calorimetry (DSC) substantially in accordance with Figure 2.

In another embodiment, the present invention provides a process for the purification of pirfenidone, comprising:

a) treating pirfenidone with alkaline base; and

b) isolating pure pirfenidone.

In another embodiment, the present invention provides a process for preparing pirfenidone having less than 0.1% by HPLC of dimer impurity of Formula IV comprising: dissolving pirfenidone in an ester solvent or aromatic hydrocarbon solvent and isolating the pirfenidone.

In another embodiment, the present invention provides a process for preparing pirfenidone having a particle size with D90 from 50 microns to 500 microns, comprising:

a) dissolving pirfenidone in an organic solvent;

b) adding an anti-solvent to the above reaction mass; and

c) isolating the pirfenidone.

In another embodiment, the present invention provides a pharmaceutical composition comprising pirfenidone prepared by the process of the invention and at least one pharmaceutically acceptable excipient.

**BRIEF DESCRIPTION OF THE DRAWINGS:**

The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

Figure 1: illustrates the characteristic powder X-ray diffraction (XRD) pattern of crystalline pirfenidone.
Figure 2: illustrates the characteristic differential scanning calorimetric (DSC) thermogram of crystalline pirfenidone.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention provides an improved process for the preparation of pure pirfenidone using the commercially available bromobenzene having about 0.2% or more by weight dibromobenzene.

According to US patent publication US8519140, the purity of the bromobenzene is more important for the preparation of pirfenidone, as amount of dibromobenzene impurity in the bromobenzene leads to produce dimer-type byproducts, which are difficult to remove from final pirfenidone using regular purification techniques. In order to control the dimer impurity, the ’140 patent utilizes bromobenzene having less than 0.15% by weight dibromobenzene. The present invention provides an improved process for preparation of pure pirfenidone utilizing commercially available bromobenzene having about 0.2% or more by weight dibromobenzene. Thereby avoiding the sourcing difficulties and cost associated with sourcing of bromobenzene with particular purity level.

In one embodiment, the present invention provides an improved process for the preparation of pirfenidone of formula (I)

\[
\begin{align*}
\text{Formula (I)}
\end{align*}
\]

which comprise the reaction of 5-methyl-1H-pyridin-2-one of formula (II)

\[
\begin{align*}
\text{Formula (II)}
\end{align*}
\]

with bromobenzene of formula (III)

\[
\begin{align*}
\text{Formula (III)}
\end{align*}
\]
in the presence of a suitable copper catalyst and a base in a suitable organic solvent under sufficient conditions to provide pirfenidone, wherein the bromobenzene contain about 0.2% or more by weight dibromobenzene.

5 The starting material 5-methyl-1H-pyridin-2-one of formula (II) can be prepared by the methods known in the art or by the method exemplified herein the present invention.

The another starting material bromobenzene of formula (III) is commercially available and having dibromobenzene isomer content such as 1,4-dibromobenzene, 1,3-dibromobenzene and 1,2-dibromobenzene, is in the range of about 0.2% to about 1% w/w.

10 The suitable copper catalyst used herein for the reaction of formula (II) with formula (III) is selected from copper(I)chloride, copper(I) bromide, copper(I)iodide and the like. Preferably copper(I)chloride.

The suitable base used herein is selected from alkali metal carbonates such as potassium carbonate, potassium bicarbonate, sodium carbonate, sodium bicarbonate and the like; alkali metal hydroxide such as potassium hydroxide, sodium hydroxide, lithium hydroxide and the like, or mixtures thereof; organic base such as triethylamine, diisopropylethylamine and the like. Preferably the suitable base is potassium carbonate.

15 The suitable organic solvent used herein is selected from hydrocarbon solvents such as benzene, chlorobenzene, toluene, xylene, heptane, hexane, cyclohexane, methyl cyclohexane, cyclopentane and the like; amide solvents such as dimethylacetamide, dimethylformamide, N-methylformamidone, dimethylimidazolidinone, N-methyl pyrrolidinone and the like; dimethylsulfoxide; and mixtures thereof. Preferably, the suitable solvent is dimethylformamide.

20 The reaction of formula (II) with formula (III) can be suitably carried out at a temperature of about 30°C to about 180°C, preferably at about 100°C to about 160°C for sufficient period of time to complete the reaction, preferably for 1 to 24 hrs, more preferably for 8-12 hrs. The product formed can be isolated by the techniques known in the art; preferably by filtration.

25 In another embodiment, the present invention provides a process for the purification of pirfenidone, comprising:

a) treating pirfenidone with alkaline base; and
b) isolating pure pirfenidone.
The starting pirfenidone and alkaline base is taken in a flask at about 25°C to about 35°C and raising the reaction mass temperature at about 70 to about 90°C to completely dissolving the reactants. Then, isolating the pure pirfenidone by methods known in the art, for example, cooling the reaction mass to below about 20°C followed by filtration and drying at suitable temperature. The suitable alkaline base is selected from sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate and the like, and mixtures thereof; preferably aqueous sodium hydroxide solution.

In another embodiment the present invention provides crystalline pirfenidone characterized by its Powder X-ray diffractogram having one or more peaks at about 8.76, 14.22, 14.90, 18.36, 18.72, 19.86, 20.90, 21.92, 22.52, 22.86, 24.22, 26.96, 27.20, 28.16, 28.80, 29.50, 30.20, 31.42, 32.32, 37.02, 39.40 and 43.38 ± 0.2 °2Θ or by a powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 1.

In another embodiment, the present invention provides crystalline pirfenidone characterized by a differential scanning calorimetry (DSC) substantially in accordance with Figure 2.

In another embodiment, the present invention provides a process for preparation of pirfenidone having less than 0.1% by HPLC of dimer impurity of Formula IV, comprising: dissolving pirfenidone in an ester solvent or aromatic hydrocarbon solvent and isolating the pirfenidone.

The dimer impurity of pirfenidone represented by the following structural formula (IV)

![Image of structural formula (IV)]

The process of dissolving pirfenidone in an ester solvent or aromatic hydrocarbon solvent is carried out at a temperature of about 25°C to about reflux, preferably at reflux temperature. The esters include, but are not limited to ethyl acetate, methyl acetate, isopropyl acetate and the like; aromatic hydrocarbons such as toluene, xylene and the like; preferably ethyl acetate or toluene. In order to form a solution, the contents may be stirred for sufficient period of time, preferably for about 10 min to about 30 min for complete dissolution. Then, the solution may be optionally concentrated to partially reduce the solvent volume and cooled to
a temperature from about 25°C or less such that the pirfenidone can be isolated by conventional techniques, for example by filtration.

In another embodiment, the present invention provides a process for preparing pirfenidone having a particle size with D90 from 50 microns to 500 microns, comprising:

a) dissolving pirfenidone in an organic solvent;

b) adding an anti-solvent to the above reaction mass; and

c) isolating the pirfenidone.

Step a) of the forgoing process involves the dissolution of pirfenidone in an organic solvent, wherein the organic solvent includes but are not limited to aromatic hydrocarbons such as toluene, xylene and the like; esters such as isopropyl acetate, methyl acetate, ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; alcohols such as methanol, ethanol, isopropanol, n-propanol, n-butanol, isobutanol and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; ethers such as methyl tertiary butyl ether, tetrahydrofuran, dimethyl ether, diisopropyl ether, 1,4-dioxane or mixtures thereof.

Optionally the reaction mixture may be heated to complete dissolution of the contents in the solvent. The suitable temperature may be selected from 35°C to about reflux temperature of the solvent used; preferably at about 50°C to about 65°C.

Adding the solution obtained in step a) to the anti-solvent, or adding an anti-solvent to the solution obtained in step iv) to effect the crystallization of the product; preferably the antisolvent is added to step a) reaction solution.

The anti-solvent used for step b) includes but are not limited to water, hydrocarbon solvents such as n-pentane, n-hexane, n-heptane, cyclohexane, methyl cyclohexane, cycloheptane or mixture thereof.

The addition of antisolvent at different temperatures leads to formation of pirfenidone particles with different sizes; for instance: anti solvent addition at 0 to -10°C, preferably at -5±2°C temperature forms small particles (D90: 50-100 µ), at 0 to 10°C, preferably at 7±3°C temperature forms particles of D90 at 100-150µ and at below 45°C forms particles of D90 at 250-500 µ.

In step c) of the foregoing process involves the isolation of pirfenidone. The isolation can be carried out by conventional techniques known in the art, for example filtration.

The step c) of the isolation of the pirfenidone is particularly carried out by stirring the step b) reaction solution at less than about 30°C, preferably at about 0-5°C, at about 5-10°C and at about room temperature for about 10 minutes to about 4 hours and the precipitated
crystals can be isolated by methods known in the art, filtration, followed by drying the resultant crystals at temperature below 65°C under vacuum.

The pirfenidone prepared according to the present invention is having purity of at least about 98% as measured by HPLC, preferably at least about 99% as measured by HPLC; more preferably at least about 99.5% as measured by HPLC.

In another embodiment, the present invention provides a pharmaceutical composition comprising pirfenidone prepared by the process of the invention and at least one pharmaceutically acceptable excipient.

**EXAMPLES:**

The following examples are provided by way of illustration only, and are not intended to be limiting of the present invention. Further, the present invention covers all the possible combinations of particular and preferred embodiments indicated herein.

**Example-1: Preparation of 5-methyl-lH-pyridin-2-one**

DM water (800 ml) was added to concentrated sulfuric acid (227 g) at 0-5°C and stirred for 15 mins. To this, 2-amino-5-methyl pyridine (100 g) followed by aqueous sodium nitrite (83 g of sodium nitrite dissolved in 200 ml of water) was added at below 10°C. The reaction mass was stirred for an hour at 0-5°C. After the reaction completion, reaction mass temperature was raised to 25-35°C and stirred for 4 hrs. Aqueous sulphamic acid (26.9 g of sulphamic acid dissolved in 100 ml of water) was added to the reaction mass and stirred for 60 mins at 25-35°C. The reaction mass was cooled to 10-15°C and pH was adjusted to 7 with aqueous sodium hydroxide solution. The reaction mass was heated to 55-65°C and extracted with ethyl acetate (6 X 500 ml). The solvent from the extract was distilled off completely under mild vacuum at below 60°C. Ethyl acetate (200 ml) was added to the obtained residue and the reaction mixture was cooled to 25-35°C then stirred for an hour. The precipitated solid was filtered, washed with ethyl acetate and dried at 45-55°C.

Yield: 80 g

**Example-2: Preparation of pirfenidone:**

A mixture of 5-methyl-lH-pyridin-2-one (100 g), bromo benzene (259 g, comprising greater than 0.2% by weight dibromobenzene isomers) and dimethylformamide (200 ml) were added in to a round bottom flask and stirred up to complete dissolution. Potassium carbonate (254 g) and copper (I) chloride (18.2 g) was added to the above reaction mass and then heated to 130-140°C. The reaction mass was stirred at 130-140°C for 10 hrs. After the reaction completion, the reaction mass was cooled to 25-35°C. Toluene (500 ml), aqueous
sodium chloride (75 g of sodium chloride in 500 ml of water) was added to the reaction mass and stirred for 15-30 mins at 25-35°C. The reaction mass was filtered and the filtrate was allowed to settle. Organic and aqueous layers were separated and the aqueous layer was extracted with toluene. Organic layers combined and was washed with aqueous sodium chloride, treated with carbon and filtered through hyflo. The solvent from the filtrate was distilled off completely under vacuum at below 60°C. Toluene (300 ml) was added to the obtained residue and stirred for 30 mins. The reaction mass was heated to 77-83°C and stirred for 45 mins. The reaction mass was cooled to 25-35°C over 60 mins. The reaction mass was further cooled to 0-6°C. The solid obtained was filtered, washed with toluene and dried under vacuum. DM water (500 ml) was added to the above obtained wet compound followed by 50% aqueous sodium hydroxide solution (10 g of sodium hydroxide in 20 ml of water) at 25-35°C. The reaction mass was heated to 75-85°C and stirred for 30-60 mins. The reaction mass was then gradually cooled to 25-35°C and stirred for 60 mins. The reaction mass was further cooled to 0-5°C and stirred for 3 hrs. The obtained solid was filtered, washed with water and dried to provide the title compound.

Yield: 120 g;
Purity by HPLC: 99%;
The XRPD is set forth in Figure 1;
The DSC is set forth in Figure 2.

**Example-3: Purification of pirfenidone (from ethyl acetate).**

A suspension of crude Pirfenidone (50g), contaminated with the dimer impurity (-0.14% by HPLC) in ethyl acetate (100 mL) was maintained at 65-75°C till the material completely dissolved. The reaction mass was treated with activated carbon (5g) and filtered through a short bed of Hyflo. The flask was rinsed with hot ethyl acetate (50 mL) and the combined filtrate was partially concentrated, under reduced pressure (till -2.0 volumes remaining in the flask), while maintain temperature below 60°C. The mixture was gradually cooled to 30±5°C and then stirred for another 30-60 min. The suspension was cooled to 0-5°C and maintained for another 2-3h, at the same temperature. The precipitated material was filtered and then dried at 60±5°C, for 6-8h, to afford Pirfenidone as white colored powder. Yield: 45 g, HPLC purity 99.9%; dimer content 0.03%.

**Example-4: Purification of pirfenidone (from toluene).**

A suspension of crude Pirfenidone (59g), contaminated with the dimer impurity (-0.14% by HPLC) in toluene (150 mL) was maintained at 75-85°C till the material completely dissolved. The reaction mass was treated with activated carbon (5g) and filtered through a short bed of Hyflo. The flask was rinsed with hot toluene (50 mL) and the combined filtrate was again heated to 75-85°C and then gradually cooled to 30±5°C and then stirred for another 30-60 min. The suspension was cooled to 0-5°C and maintained for another 2-3h, at
the same temperature. The precipitated material was filtered and then dried at 60±5°C, for 6-8h, to afford Pirfenidone as white colored powder. Yield: 41g, HPLC purity 99.9%; dimer content 0.07%.

5 Purification of pirfenidone (from ethyl acetate + n-heptane):

Example 5:

Pirfenidone (83g) was dissolved in ethyl acetate (425 mL), at 55-65°C, and then added to pre-cooled (-5±2°C) n-Heptane (425 mL), over a period of 15-20 min, while maintaining temperature below 20°C. The suspension was stirred, at 0-5°C, for 1-2h; filtered the product washed with chilled ethyl acetate (50 mL). The wet material was dried, at 60°C, under vacuum, for 6-8h, to afford Pirfenidone as white colored powder. Yield: 65 g, HPLC purity 99.9%, PSD: (D90) 50-100µ.

Example 6:

Pirfenidone (81g) was dissolved in ethyl acetate (425 mL), at 55-65°C, and then added to pre-cooled (7±3°C) n-Heptane (425 mL), over a period of 15-20 min, while maintaining temperature below 20°C. The suspension was stirred, at 0-5°C, for 1-2h; filtered the product washed with chilled ethyl acetate (50 mL). The wet material was dried, at 60°C, under vacuum, for 6-8h, to afford Pirfenidone as white colored powder Yield: 61 g, HPLC purity 99.9%, PSD: (D90) 100-150µ.

Example 7:

Pirfenidone (81g) was dissolved in ethyl acetate (500 mL), at 50-55°C, and then added to pre-cooled (8±3°C) n-Heptane (500 mL), over a period of 15-20 min, while maintaining temperature below 25°C. The suspension was stirred, at 5-10°C, for 1-2h; filtered the product washed with chilled ethyl acetate (50 mL). The wet material was dried, at 60°C, under vacuum, for 6-8h, to afford Pirfenidone as white colored powder Yield: 57 g, HPLC purity 99.9%, PSD: (D90) 150-250µ.

Example 8:

Pirfenidone (80g) was dissolved in ethyl acetate (400 mL), at 55-65°C, and then added to n-Heptane (400 mL), over a period of 5-10 min, while maintaining temperature below 45°C. The suspension was stirred, at 25-30°C, for 1-2h; filtered the product washed with chilled ethyl acetate (50 mL). The wet material was dried, at 60°C, under vacuum, for 6-8h, to afford Pirfenidone as white colored powder, Yield: 55 g, HPLC purity 99.9%, PSD: (D90) 250-500µ.
WE CLAIM

Claim 1: An improved process for preparation of pirfenidone of formula (I), comprising:

\[
\text{Formula (I)}
\]

a) reacting 5-methyl-lH-pyridin-2-one of formula (II)

\[
\text{Formula (II)}
\]

with bromobenzene of formula (III)

\[
\text{Formula (III)}
\]

in presence of a suitable copper catalyst and a base in a suitable organic solvent under sufficient conditions to provide pirfenidone, wherein the bromobenzene contain about 0.2% or more by weight dibromobenzene; and

b) isolating the pirfenidone.

Claim 2: The process of claim 1, wherein the suitable copper catalyst is selected from the group consisting of copper(I)chloride, copper (I) bromide and copper(I)iodide.

Claim 3: The process of claim 1, wherein the base is selected from the group consisting of potassium carbonate, potassium bicarbonate, sodium carbonate, sodium bicarbonate, potassium hydroxide, sodium hydroxide, lithium hydroxide, triethylamine and diisopropylethylamine.

Claim 4: The process of claim 1, wherein the suitable organic solvent used herein is selected from the group comprising hydrocarbon solvents selected from benzene,
chlorobenzene, toluene, xylene, heptane, hexane, cyclohexane, methyl cyclohexane, or cyclopentane; amide solvents selected from dimethylacetamide, dimethylformamide, N-methylformamide, dimethylimidazolidinone, or N-methyl pyrrolidinone; dimethylsulfoxide; and mixtures thereof.

Claim 5: The process of claim 1, wherein the suitable copper catalyst is copper (I) chloride, base is potassium carbonate, and organic solvent is dimethylformamide.

Claim 6: The process of claim 1, wherein the reaction is carried out at a temperature of about 100°C to about 160°C.

Claim 7: A process for the purification of pirfenidone, comprising:
   a) treating pirfenidone with alkaline base, and
   b) isolating pure pirfenidone; wherein the alkaline base is selected from sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate and mixtures thereof.

Claim 8: The process of claim 7, wherein the alkaline base is aqueous sodium hydroxide.

Claim 9: The process of claim 7, wherein the reaction is carried out at a temperature of about 70°C to about 90°C.

Claim 10: The process of claim 9, wherein isolating the pirfenidone of step b) comprises cooling of the reaction mass to below about 20°C and filtration.

Claim 11: A process for preparation of pirfenidone having less than 0.1% by HPLC of dimer impurity of Formula IV, comprising: dissolving pirfenidone in an ester solvent or aromatic hydrocarbon solvent and isolating the pirfenidone; wherein the ester solvent is selected from the group consisting of ethyl acetate, methyl acetate, isopropyl acetate and mixtures thereof; aromatic hydrocarbons selected from the group consisting of toluene, xylene and mixtures thereof.

Claim 12: The process of claim 11, wherein the ester solvent is ethyl acetate and the aromatic hydrocarbon solvent is toluene.

Claim 13: The process of claim 11, wherein the dissolution step is carried out at 25°C to reflux temperature.

Claim 14: The process of claim 11, wherein isolating the pure pirfenidone comprises cooling of the reaction mass to below about 25°C and filtration.
Claim 15: A process for preparing pirfenidone having a particle size with D90 from 50 microns to 500 microns, comprising:
   a) dissolving pirfenidone in an organic solvent;
   b) adding an anti-solvent to the above reaction mass; and
   c) isolating the pirfenidone; wherein the organic solvent is selected from toluene, isopropyl acetate, methyl acetate, ethyl acetate, methanol, ethanol, isopropanol, n-propanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tertiary butyl ether, tetrahydrofuran, dimethyl ether, diisopropyl ether, 1,4-dioxane or mixtures thereof and the anti-solvent is selected from water, hydrocarbon solvents such as n-pentane, n-hexane, n-heptane, cyclohexane, methyl cyclohexane, cycloheptane or mixture thereof.

Claim 16: The process of claim 15, wherein the solvent is ethyl acetate and the anti-solvent is n-heptane.

Claim 17: The process of claim 15, wherein the dissolution step is carried out at about 35°C to about reflux temperature.

Claim 18: The process of claim 15, wherein the anti-solvent is added at a temperature in between 0 to -10°C.

Claim 19: The process of claim 15, wherein the anti-solvent is added at a temperature in between 0 to 10°C.

Claim 20: The process of claim 15, wherein the anti-solvent is added at a temperature below 45°C.

Claim 21: The process of claim 15, wherein isolating the pirfenidone of step c) comprises optional cooling of the reaction mass to below about 30°C and filtration.

Claim 22: A pharmaceutical composition comprising pirfenidone prepared according to claims 1-21 and at least one pharmaceutically acceptable excipient.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/00 Version=2017.01
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)
A 61 K

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

Electronic database consulted during the international search (name of data base and, where practicable, search terms used)
Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO2010141600 A2 (INTERMUNE INC [US]) 09 December 2010 (09-12-2010) Abstract, claims 1-29 and Examples</td>
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Date of the actual completion of the international search: 30-03-2017
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Name and mailing address of the ISA/Indian Patent Office
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G Nagendra
Telephone No. +91-1125300200

Form PCT/ISA/210 (second sheet) (January 2015)
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