IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SHILPA PHARMA, INC., Plaintiff, v. NOVARTIS PHARMACEUTICALS CORPORATION, Defendant.	C.A. No. 21-558-MN JURY TRIAL DEMANDED

JOINT CLAIM CONSTRUCTION BRIEF APPENDIX
VOLUME I OF III: EXHIBITS 1-6

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JA-1

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Shrawat et al.

(10) **Patent No.: US 9,266,816 B2**
(45) **Date of Patent: Feb. 23, 2016**

(54) **FINGOLIMOD POLYMORPHS AND THEIR PROCESSES**

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C07C 215/28 (2006.01)

(52) **U.S. Cl.**
CPC ***C07C 213/10*** (2013.01); ***C07C 215/28*** (2013.01); *C07B 2200/13* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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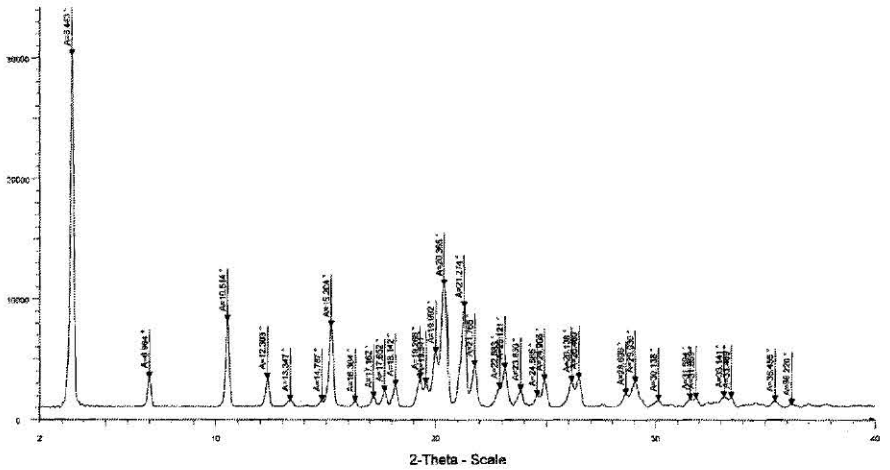
Primary Examiner — Clinton Brooks

(57) **ABSTRACT**

The present invention provides crystalline polymorphic forms of Fingolimod HCl (I) and processes for preparation thereof.

The application provides processes for preparation of crystalline polymorphic forms-α, β and μ substantially free from process related impurities. The crystalline polymorphic forms of Fingolimod HCl (I) obtained by the processes according to the present invention having an XRDP pattern as per FIGS. **1**, **3** and **5**, which are useful as active pharmaceutical ingredient in pharmaceutical compositions for the treatment or prevention of autoimmune related disorder including multiple sclerosis.

6 Claims, 5 Drawing Sheets



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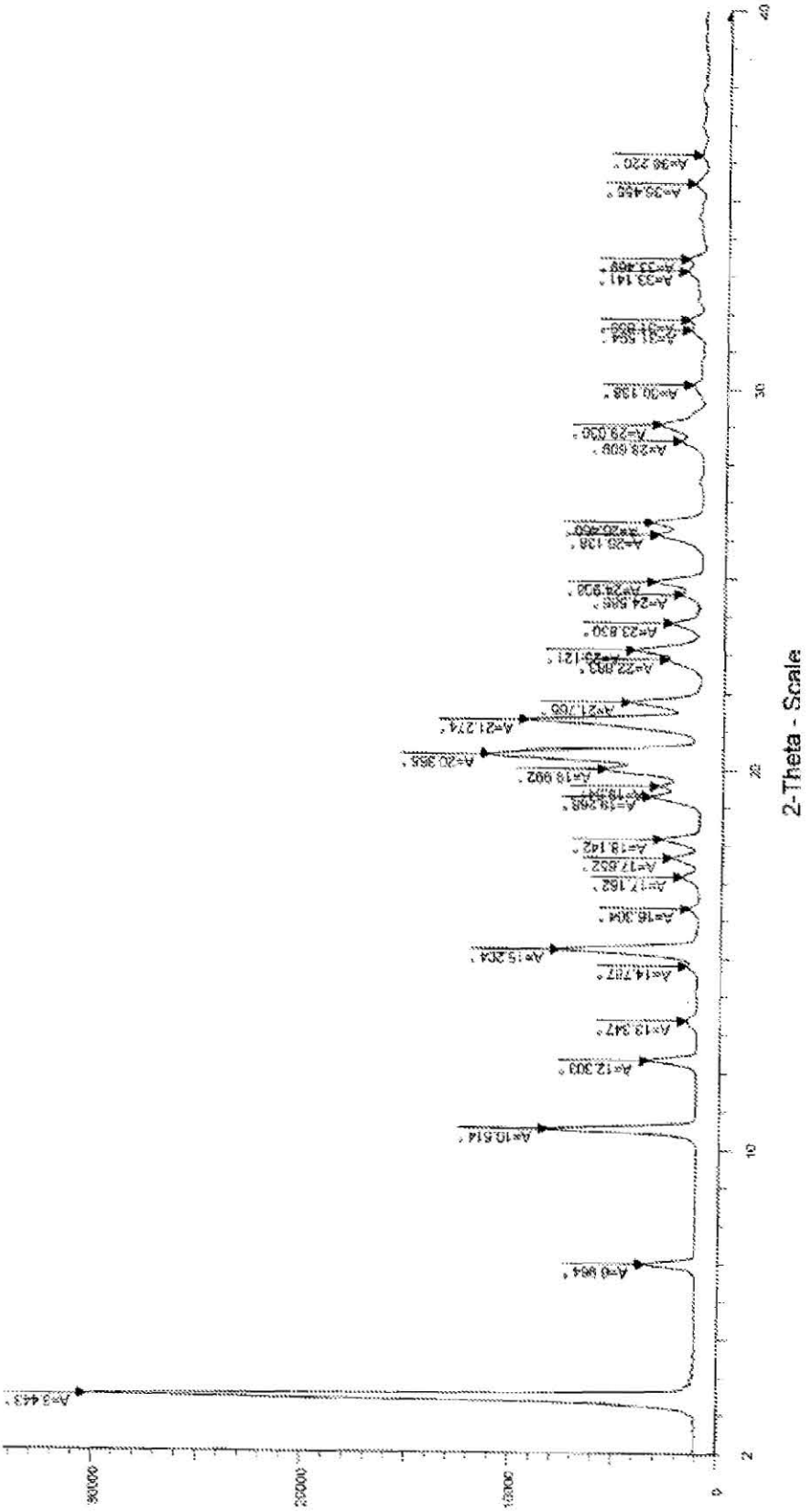
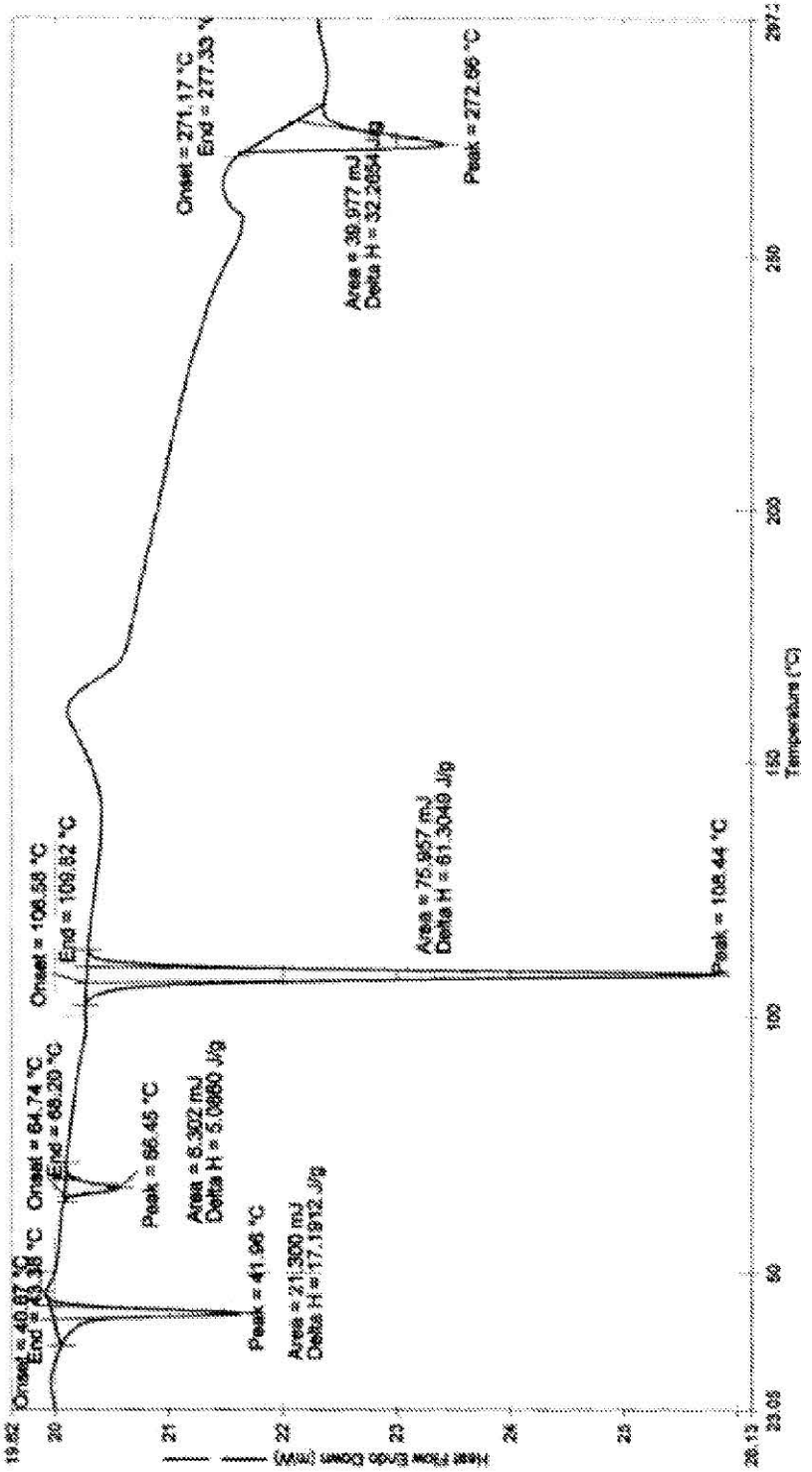


FIG.1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End = 277.33 °C
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Area = 39.977 mJ
Delta H = 32.2654 J/g
Onset = 106.58 °C
End = 109.82 °C
Peak = 108.44 °C
Area = 75.857 mJ
Delta H = 61.3049 J/g
Onset = 64.74 °C
End = 68.20 °C
Peak = 66.46 °C
Area = 6.902 mJ
Delta H = 5.0880 J/g
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Area = 21.300 mJ
Delta H = 17.1912 J/g
Temperature (°C)
Heat Flow Endo Down (mW)

FIG.2

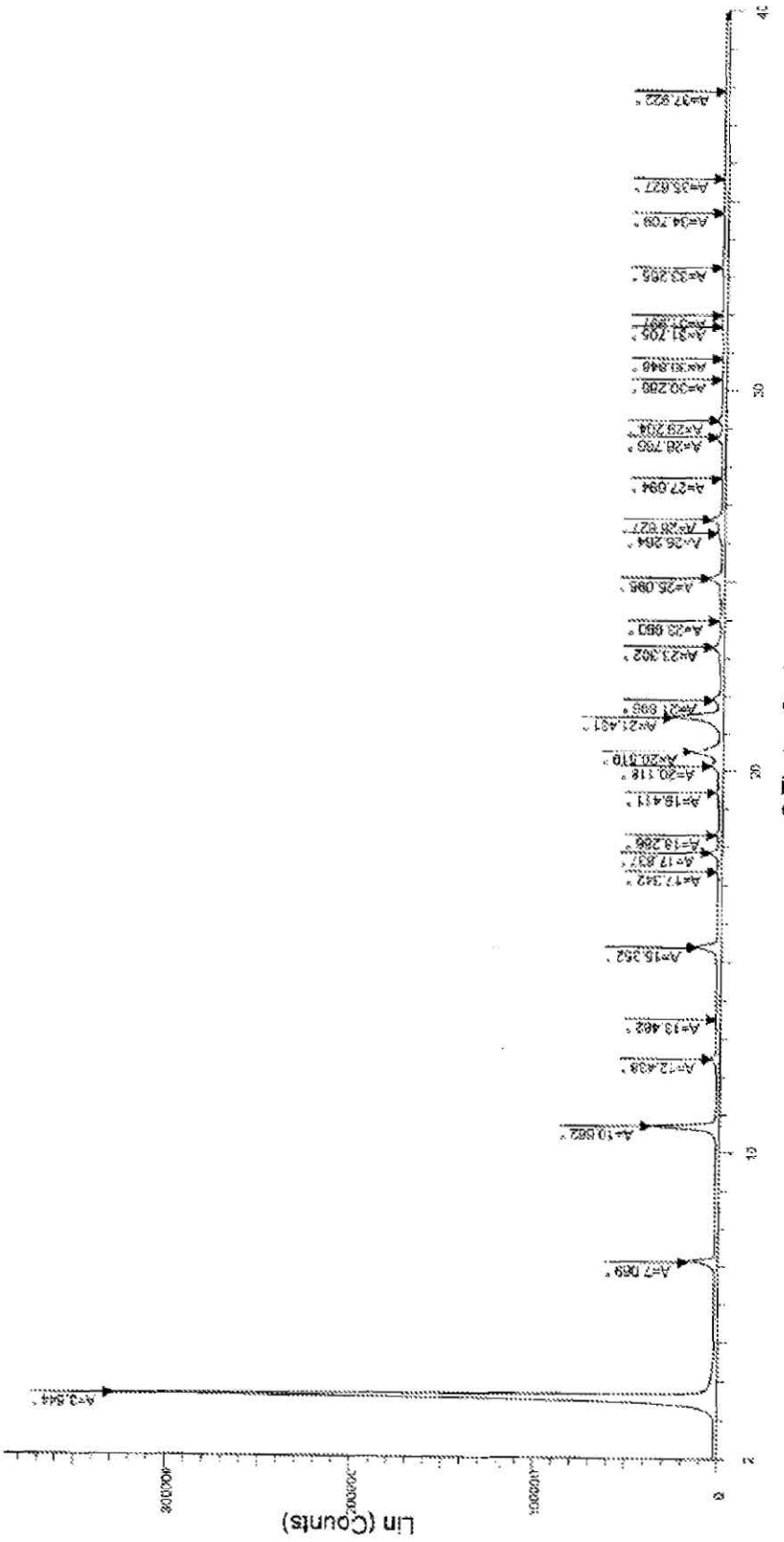
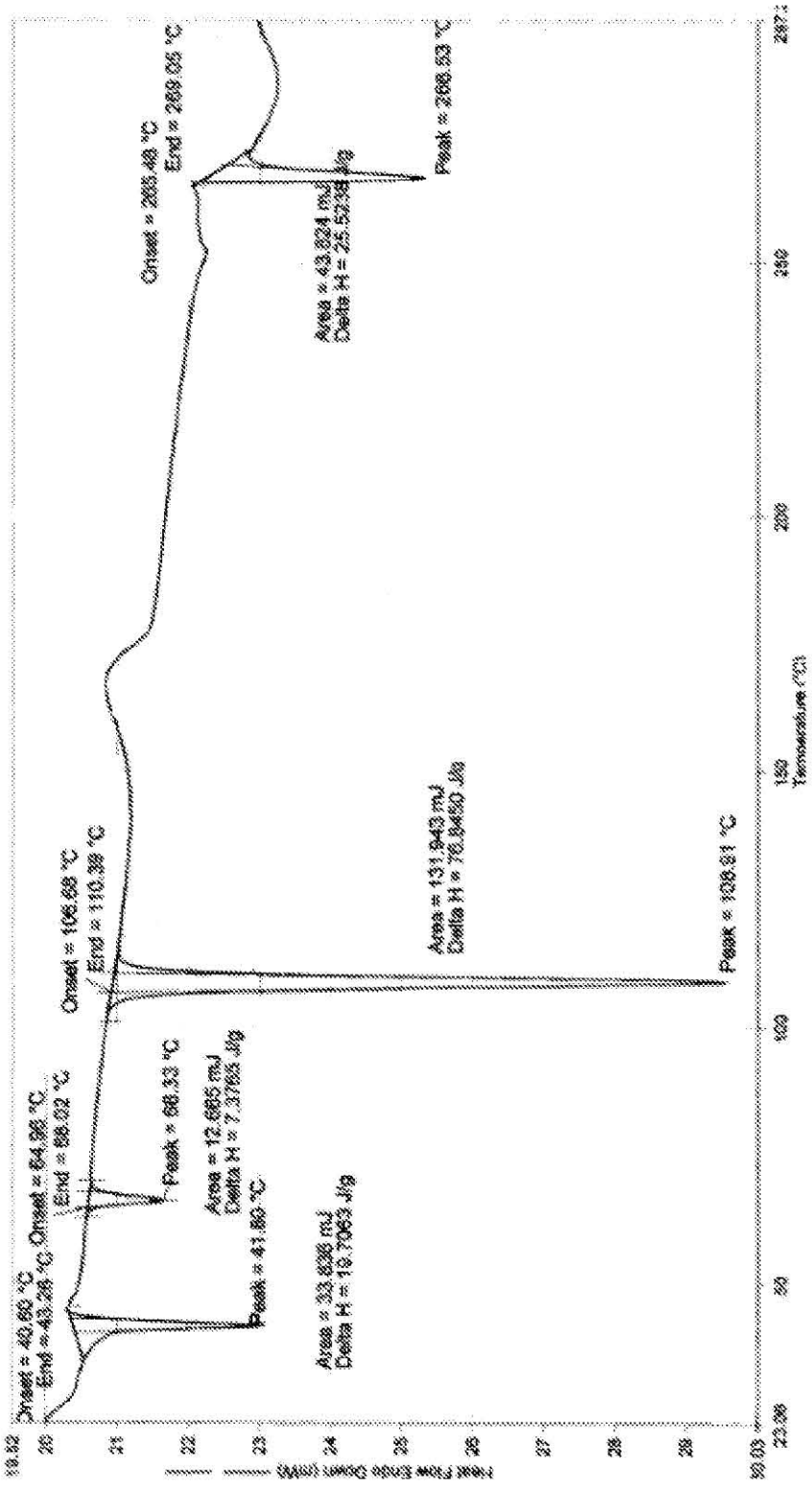


FIG.3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End = 110.38 °C
Area = 131.843 mJ
Delta H = 76.8450 J/g
Peak = 108.81 °C
Onset = 265.48 °C
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Delta H = 25.5239 J/g
Peak = 268.53 °C
Temperature (°C)

FIG.4

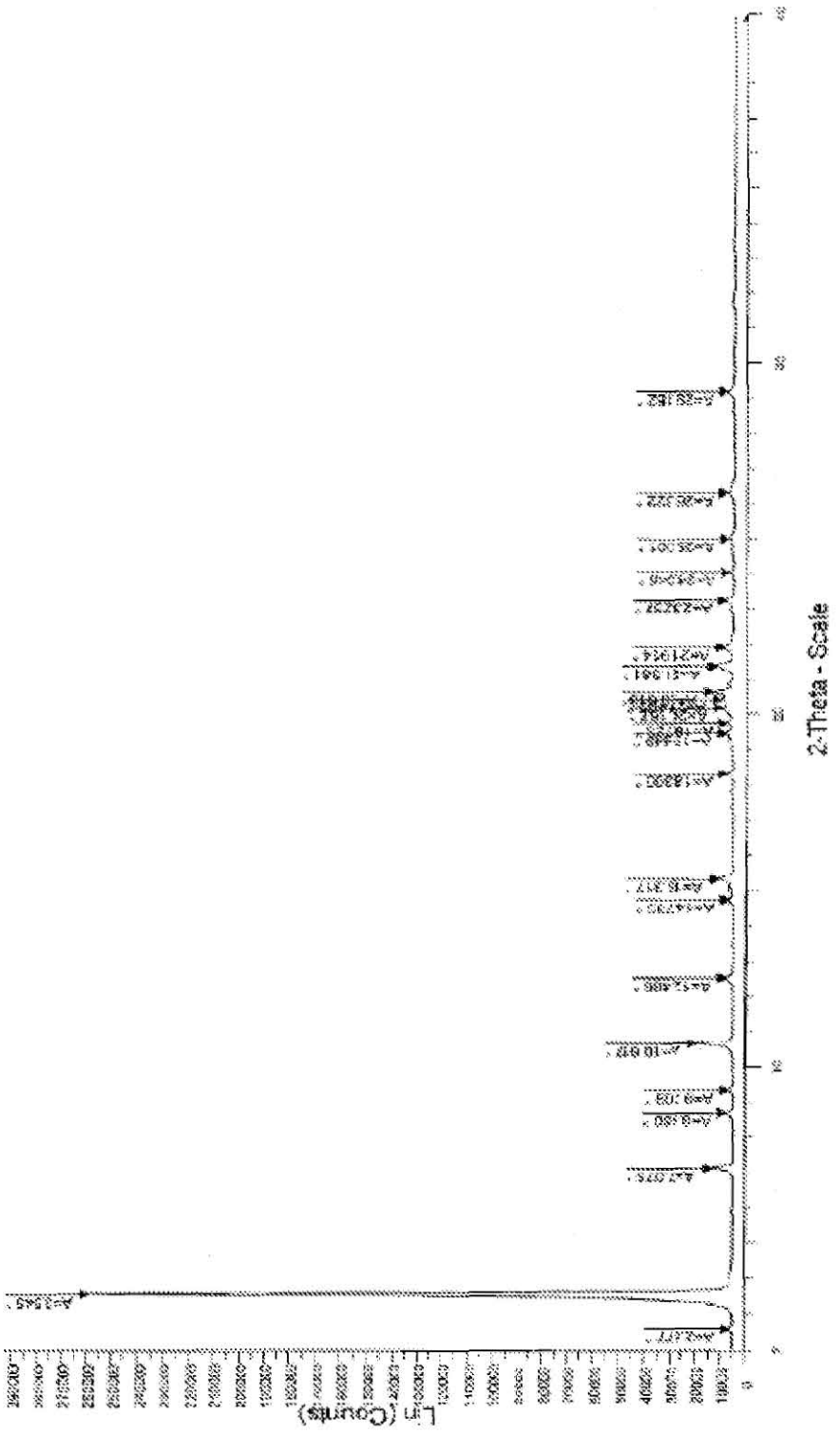


FIG.5

FINGOLIMOD POLYMORPHS AND THEIR PROCESSES

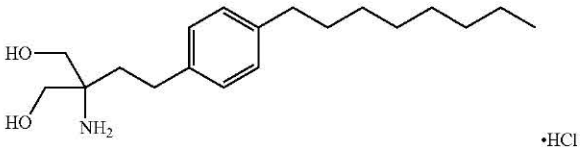
FIELD OF THE INVENTION

Particular aspects of the present application relates to the crystalline polymorphic forms α, β and μ of Fingolimod HCl (I) and processes for preparation thereof.

BACKGROUND OF THE INVENTION

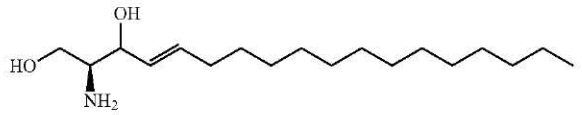
Fingolimod hydrochloride has the IUPAC name as 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride and have the following structure—

(I)



It is a structural analogue of sphingosine (II) which gets phosphorylated by sphingosine kinases

(II)



in the cell (specifically sphingosine kinase 2).

Fingolimod being a sphingosine 1-phosphate receptor (S1P-R) modulator, it binds to the S1P receptor on circulating lymphocytes, sequestering them in lymph nodes away from the CNS. It appears to be the first oral S1P-R modulator to be developed, which appears to reduce the number of inflammatory T cells in the circulation and CNS and in doing so, it reduces their potential to damage nerve cells.

U.S. Pat. No. 5,604,229 is the first disclosure of the Fingolimod and other related compounds. It has been found to be useful in the treatment or prevention of various autoimmune conditions, including multiple sclerosis.

Mutz et al in WO2010055028A2 reported various polymorphic forms of Fingolimod hydrochloride designated as Form-I (at room temperature), Form-II (however at a transition temperature of approximately 40° C.) and Form-III (however at a transition temperature of approximately 66° C.). Further, the patent application also mentions that approximately 107° C., Fingolimod hydrochloride forms a phase with lower crystalline order. However, other than thermal transition based forms, no exact crystalline form have been reported in the literature.

In view of the existence of few known thermal transition based polymorphic forms of Fingolimod hydrochloride, there stills appears to be a need of novel crystalline forms, which are not only stable as well as convenient to scale up but also their processes provides improved yields & quality.

SUMMARY OF THE INVENTION

Particular aspects of the present application relates to the crystalline polymorphic forms α, β and μ of Fingolimod HCl (I) and processes for preparation thereof.

The application relates to processes for preparation of crystalline polymorphic forms-α, β and μ substantially free from process related impurities. The crystalline polymorphic forms of Fingolimod HCl (I) obtained by the processes according to the present invention are useful as active pharmaceutical ingredient in pharmaceutical compositions for the treatment or prevention of autoimmune related disorder including multiple sclerosis.

Different aspects of the present application are summarized herein below individually.

In one aspect of the present application, the present invention provides Fingolimod hydrochloride crystalline Form-α characterized by X-ray powder diffraction pattern comprising at least 5 characteristic 2θ° peaks selected from the XRPD peak set of 10.51, 15.20, 19.27, 21.77, 23.12, 24.91, 26.14, 26.46, 29.03, 33.47 and 35.46±0.1 2θ°. The said crystalline Form-α is further characterized by DSC isotherm comprising at least three endothermic peaks ranging between—

a. Peak-1—Between 40 to 43° C.
b. Peak-2—Between 65 to 68° C.
c. Peak-3—Between 105 to 110° C.
d. Peak-4—Between 270 to 280° C.

In another aspect of the present application, the present invention provides process for preparing Fingolimod hydrochloride crystalline Form-α comprising the steps of—

a. Combining the Fingolimod hydrochloride with an organic acid
b. Optionally heating up to about 40-50° C.
c. cooling the solution up to about 0-5° C.
d. isolating the crystalline Form-α

In yet another aspect of the present application, the present invention provides Fingolimod hydrochloride crystalline Form-β characterized by X-ray powder diffraction pattern comprising
at least 4 characteristic 2θ° peaks selected from the XRPD peak set of 3.54, 7.07, 10.66, 15.35, 20.52, 21.43 and 25.10±0.1 2θ°. The said crystalline Form-β is further characterized by DSC
isotherm comprising at least three endothermic peaks ranging between—

a. Peak-1—Between 40 to 45° C.
b. Peak-2—Between 65 to 70° C.
c. Peak-3—Between 107 to 115° C.
d. Peak-4—Between 265 to 270° C.

In further another aspect of the present application, the present invention provides process for
preparing Fingolimod hydrochloride crystalline Form-β comprising the steps of—

a. Combining the Fingolimod hydrochloride with organic solvent selected from dimethylformamide, dimethylacetamide, tetrahydrofuran, 2-methoxyethanol
b. Optionally heating up to about 40-50° C. followed by cooling
c. isolating the crystalline Form-β using another co-solvent by recrystallization

In yet another aspect of the present application, the present invention provides Fingolimod Hydrochloride crystalline Form-μ characterized by X-ray powder diffraction pattern comprising at least 4 characteristic 2θ° peaks selected from the XRPD peak set of 3.54, 8.65, 10.64, 12.49, 19.45, 21.38 and 24.05±0.1 2θ°.

In yet further another aspect of the present application, the present invention provides process
for preparing Fingolimod hydrochloride crystalline Form-μ comprising the steps of—

a. Raising the Fingolimod hydrochloride temperature up to at least melting point but less than 130° C.
b. Cooling the melt liquid
c. isolating the crystalline Form-μ

In further aspect, the Crystalline Forms-α, β and μ of Fingolimod HCl obtained by the processes of the present application may be formulated as solid compositions for oral administration in the form of capsules, tablets, pills, powders or granules useful in the treatment or prevention of autoimmune related disorder including multiple sclerosis.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an Illustration of an X-ray powder diffraction (XRPD) pattern of Fingolimod hydrochloride-Form α, prepared according to Example-1

FIG. **2** is an Illustration of a differential scanning calorimetric ("DSC") curve of Fingolimod hydrochloride, prepared according to Example-1

FIG. **3** is an Illustration of an X-ray powder diffraction (XRPD) pattern of Fingolimod hydrochloride-Form β, prepared according to Example-2 Process-A

FIG. **4** is an Illustration of a differential scanning calorimetric ("DSC") curve of Fingolimod hydrochloride, prepared according to Example-2 Process-A

FIG. **5** is an Illustration of an X-ray powder diffraction (XRPD) pattern of Fingolimod hydrochloride-Form μ, prepared according to Example-3

DETAILED DESCRIPTION

As set forth herein, aspects of the present invention provides crystalline polymorphic forms α, β and μ of Fingolimod HCl (I) and processes for preparation thereof.

Individual embodiments of the present invention are detailed herein below separately.

In one embodiment of the present application, it provides Fingolimod hydrochloride crystalline Form-α characterized by X-ray powder diffraction pattern comprising at least 5 characteristic 2θ° peaks selected from the XRPD peak set of 10.51, 15.20, 19.27, 21.77, 23.12, 24.91, 26.14, 26.46, 29.03, 33.47 and 35.46±0.1 2θ°. The said crystalline Form-α may be further characterized by DSC isotherm comprising at least three endothermic peaks ranging between—

a. Peak-1—Between 40 to 43° C.
b. Peak-2—Between 65 to 68° C.
c. Peak-3—Between 105 to 110° C.
d. Peak-4—Between 270 to 280° C.

Fingolimod hydrochloride crystalline Form-α characterized by X-ray powder diffraction pattern comprising at least 5 characteristic 2θ° peaks selected from the XRPD peak set of 10.51, 15.20, 19.27, 21.77, 23.12, 24.91, 26.14, 26.46, 29.03, 33.47 and 35.46±0.1 2θ° is having X-ray powder diffraction pattern substantially according to FIG. **1** and DSC isotherm comprising the endothermic peaks ranging between 40 to 43° C. (Peak-1), 65 to 68° C. (Peak-2), 105 to 110° C. (Peak-3) and/or 270 to 280° C. (Peak-4) is having DSC isothermal pattern substantially according to FIG. **2**.

The characteristic peaks and their d spacing values of the new crystalline Form-α are tabulated in the Table-1.

TABLE 1

Characteristic XRPD Peaks of Crystalline Form-α

S. No.	Angle (2θ°)	d Spacing Value (A°)
1.	10.51	8.407
2.	15.20	5.823
3.	19.27	4.602
4.	21.77	4.080
5.	23.12	3.844

TABLE 1-continued

Characteristic XRPD Peaks of Crystalline Form-α

S. No.	Angle (2θ°)	d Spacing Value (A°)
6.	24.91	3.572
7.	26.14	3.407
8.	26.46	3.366
9.	29.03	3.073
10.	33.47	2.675
11.	35.46	2.530

In another embodiment of the present invention, it provides process for preparing Fingolimod hydrochloride crystalline Form-α characterized by X-ray powder diffraction pattern comprising at least 5 characteristic 2θ° peaks selected from the XRPD peak set of 10.51, 15.20, 19.27, 21.77, 23.12, 24.91, 26.14, 26.46, 29.03, 33.47 and 35.46±0.1 2θ° and DSC isotherm comprising the endothermic peaks ranging between 40 to 43° C. (Peak-1), 65 to 68° C. (Peak-2), 105 to 110° C. (Peak-3) and/or 270 to 280° C. (Peak-4) comprising the steps of—

a. Combining the Fingolimod hydrochloride with an organic acid
b. Optionally heating up to about 40-50° C.
c. cooling the solution up to about 0-5° C.
d. isolating the crystalline Form-α

Combining the Fingolimod hydrochloride with as Organic acid comprise either mixing or suspending or making solution with organic acids, selected from C1 to C4 carboxylic acid. In one of the particular embodiment, acetic acid is used as an organic acid for making Form-α. The combining of an organic acid may be carried out at ambient temperature; however temperature may be raised to any temperature up to below 50° C., if desired.

Any form of Crude or Pure Fingolimod Hydrochloride obtained by known processes can be used for preparing Form-α.

The combined mixture may be maintained for about 1-2 hrs, however, this time may be more, but, depending upon achieving the clear solution and equilibration to impurity profile compliance.

The process related impurities, including unreacted intermediates, side products, degradation products and other medium dependent impurities, that appears in the impurity profile of the Fingolimod hydrochloride can substantially removed by the process of the present invention resulting in the formation crystalline form-α. A substantially pure product having purities more than 99% (by HPLC) can be obtained by the process of the present invention. In view of maintaining the equilibrium to the impurity profile compliance, the process requires quality checks, while raising the temperature, wherever required up to 50° C.

Reaction mass can be cooled up to 25-30° C. and subjected to stir for about 1-2 hrs. Further cooling the reaction mass ranging between 0-10° C. followed by stirring for about 1-2 hours may also carried out. The product may be isolated from the reaction mass by conventional processes including filtering and optional drying, which may be carried out at room temperature for the suitable durations to retain the crystalline polymorphic form characteristics.

In yet another embodiment of the present application, it provides Fingolimod hydrochloride crystalline Form-β characterized by X-ray powder diffraction pattern comprising at least 4 characteristic 2θ° peaks selected from the XRPD peak set of 3.54, 7.07, 10.66, 15.35, 20.52, 21.43 and 25.10±0.1

2θ°. The said crystalline Form-β may be further characterized by DSC isotherm comprising at least three endothermic peaks ranging between—

a. Peak-1—Between 40 to 45° C.
b. Peak-2—Between 65 to 70° C.
c. Peak-3—Between 107 to 115° C.
d. Peak-4—Between 265 to 270° C.

Fingolimod hydrochloride crystalline Form-β characterized by X-ray powder diffraction pattern comprising at least 4 characteristic 2θ° peaks selected from the XRPD peak set of 3.54, 7.07, 10.66, 15.35, 20.52, 21.43 and 25.10±0.1 2θ° is having X-ray powder diffraction pattern substantially according to FIG. **3** and DSC isotherm comprising the endothermic peaks ranging between 40 to 45° C. (Peak-1), 65 to 70° C. (Peak-2), 107 to 115° C. (Peak-3) and/or 265 to 270° C. (Peak-4) is having DSC isothermal pattern substantially according to FIG. **4**.

The characteristic peaks and their d spacing values of the new crystalline Form-β are tabulated in the Table-2.

TABLE 2

Characteristic XRPD Peaks of Crystalline Form-β

S. No.	Angle (2θ°)	d Spacing Value (A°)
1.	3.54	24.908
2.	7.07	12.494
3.	10.66	8.290
4.	15.35	5.767
5.	20.52	4.325
6.	21.43	4.143
7.	25.10	3.546

In another embodiment of the present invention, it provides process for preparing Fingolimod hydrochloride crystalline Form-β characterized by X-ray powder diffraction pattern comprising at least 4 characteristic 2θ° peaks selected from the XRPD peak set of 3.54, 7.07, 10.66, 15.35, 20.52, 21.43 and 25.10±0.1 2θ° and DSC isotherm comprising the endothermic peaks ranging between 40 to 45° C. (Peak-1), 65 to 70° C. (Peak-2), 107 to 115° C. (Peak-3) and/or 265 to 270° C. (Peak-4) comprising the steps of—

a. Combining the Fingolimod hydrochloride with organic solvent selected from dimethylformamide, dimethylacetamide, tetrahydrofuran, 2-methoxyethanol
b. Optionally heating up to about 40-50° C. followed by cooling
c. isolating the crystalline Form-β using another co-solvent by recrystallization

Combining the Fingolimod hydrochloride with as Organic solvents for preparing Form-β comprise either mixing or suspending or making solution with organic solvent selected from dimethylformamide, dimethylacetamide, tetrahydrofuran, 2-methoxyethanol. In one of the particular embodiment, dimethylformamade is used as an organic solvent for making Form-β. The combining of an organic solvent may be carried out at ambient temperature; however temperature may be raised to any temperature up to below 50° C., whenever desired.

As mentioned earlier, any form of Crude or Pure Fingolimod Hydrochloride obtained by known processes can be used for preparing Form-β.

The combined mixture may be maintained for about 1-2 hrs, however, this time may be more, but, depending upon achieving the clear solution and equilibration to impurity profile compliance.

The process related impurities, including unreacted intermediates, side products, degradation products and other medium dependent impurities, that appears in the impurity profile of the Fingolimod hydrochloride can substantially removed by the process of the present invention resulting in the formation crystalline form-β. In view of maintaining the equilibrium to the impurity profile compliance, the process requires quality checks, while raising the temperature, whenever required up to 50° C.

Reaction mass can be cooled up to 0-30° C. and subjected to stir for about 1-2 hrs. The product may be isolated from the reaction mass by combining with co-solvent selected from ketone (C3 to C8) or nitrile (C2 to C4) or alcohol (C1 to C4), followed by conventional processes including filtering and optional drying, which may be carried out at room temperature for the suitable durations to retain the crystalline polymorphic form characteristics.

In yet another embodiment of the present application, it provides Fingolimod hydrochloride crystalline Form-μ characterized by X-ray powder diffraction pattern comprising at least 4 characteristic 2θ° peaks selected from the XRPD peak set of 3.54, 8.65, 10.64, 12.49, 19.45, 21.38 and 24.05±0.1 2θ°.

Fingolimod hydrochloride crystalline Form-μ characterized by X-ray powder diffraction pattern comprising at least 4 characteristic 2θ° peaks selected from the XRPD peak set of 3.54, 8.65, 10.64, 12.49, 19.45, 21.38 and 24.05±0.1 2θ° is having X-ray powder diffraction pattern substantially according to FIG. **5**.

The characteristic peaks and their d spacing values of the new crystalline Form-μ are tabulated in the Table-3.

TABLE 3

Characteristic XRPD Peaks of Crystalline Form-μ

S. No.	Angle (2θ°)	d Spacing Value (A°)
1.	3.54	24.905
2.	8.65	10.214
3.	10.64	8.310
4.	12.49	7.084
5.	19.45	4.560
6.	21.38	4.152
7.	24.05	3.698

In another embodiment of the present invention, it provides process for preparing Fingolimod hydrochloride crystalline Form-μ characterized by X-ray powder diffraction pattern comprising at least 4 characteristic 2θ° peaks selected from the XRPD peak set of 3.54, 8.65, 10.64, 12.49, 19.45, 21.38 and 24.05±0.1 2θ° comprising the steps of—

a. Raising the Fingolimod hydrochloride temperature up to at least melting point but less than 130° C.
b. Cooling the melt liquid
c. isolating the crystalline Form-μ.

Any form of Crude or Pure Fingolimod Hydrochloride obtained by known processes can be used for preparing Form-μ. The rise in temperature for the preparing melt of the Fingolimod Hydrochloride can be slow in order to provide consistency and uniformity of the melt liquid phase. In a particular embodiment, melt temperature attained was 120-125° C.

Simultaneously, it is essentially required to cool the melt in the successive lower rate of cooling in order to retain the characteristics of Form-μ.

Crystalline Form-μ can be isolated by conventional processes, which are not limited to scrapping, breaking, triturating and if required conventional drying.

In further aspect, the Crystalline Forms-α, β and μ of Fingolimod HCl obtained by the processes of the present

application may be formulated as solid compositions for oral administration in the form of capsules, tablets, pills, powders or granules useful in the treatment or prevention of autoimmune related disorder including multiple sclerosis.

Different crystalline forms of the present invention may have one or more advantageous and desirable properties compared to the known Fingolimod Base, which are not limited to better stability, solubility and quality parameter leading to improved storage and distribution.

The Crystalline Forms-α, β and μ of Fingolimod HCl described herein may be characterized by X-ray powder diffraction pattern (XRPD) and Thermal techniques such as differential scanning calorimetric (DSC) Analysis. The samples of Fingolimod HCl Crystalline Forms-α, β and μ were analyzed by XRPD on a Bruker AXS D8 Advance Diffractometer using X-ray source-Cu Kα radiation using the wavelength 1.5418 Å, however, DSC analysis were carried out on a Perkin Elmer Pyris 7.0 instrument. Illustrative examples of analytical data for the crystalline solids 'Form-α, β and μ' obtained in the Examples are set forth in the FIGS. **1-5**.

In another embodiment, the Crystalline Forms-α, β and μ of Fingolimod HCl obtained by the processes of the present application may be formulated as solid compositions for oral administration in the form of capsules, tablets, pills, powders or granules. In these compositions, the active product is mixed with one or more pharmaceutically acceptable excipients. The drug substance can be formulated as liquid compositions for oral administration including solutions, suspensions, syrups, elixirs and emulsions, containing solvents or vehicles such as water, sorbitol, glycerine, propylene glycol or liquid paraffin.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilization may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilizing agents in the composition, by irradiation or by heating. They may be prepared in the form of sterile compositions, which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

Pharmaceutically acceptable excipients used in the compositions comprising Crystalline Forms-α, β and μ of Fingolimod HCl of the present application include, but are but not limited to diluents such as starch, pregelatinized starch, lactose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar and the like; binders such as acacia, guar gum, tragacanth, gelatin, pre-gelatinized starch and the like; disintegrants such as starch, sodium starch glycolate, pregelatinized starch, Croscarmellose sodium, colloidal silicon dioxide and the like; lubricants such as stearic acid, magnesium stearate, zinc stearate and the like; glidants such as colloidal silicon dioxide and the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants, waxes and the like. Other pharmaceutically acceptable excipients that are of use include but not limited to film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants and the like.

Pharmaceutically acceptable excipients used in the compositions derived from Crystalline Forms-α, β and μ of Fingolimod HCl of the present application may also comprise to include the pharmaceutically acceptable carrier used for the preparation of solid dispersion, wherever utilized in the desired dosage form preparation.

Certain specific aspects and embodiments of the present application will be explained in more detail with reference to the following examples, which are provided by way of illustration only and should not be construed as limiting the scope of the invention in any manner.

EXAMPLE 1

Preparation of Crystalline Fingolimod Hydrochloride (Form-α)

Charge 10 ml acetic acid at ambient temperature followed by slow addition of 1.0 gm of Crude or Pure Fingolimod Hydrochloride obtained from any source in round bottom flask under continued stirred. Raise the temperature up to about 40-50° C. and maintained for about 1-2 hrs. (This time may be more, however, depending upon achieving the clear solution and equilibration to impurity profile compliance). Cool the reaction mass up to 25-30° C. and stir for about 1-2 hrs at 25-30° C. Further, cool the reaction mass up to 0-5° C. and stir for about 2 hrs. Filter the reaction mass and isolating the crystalline product after 12 hours of drying at room temperature.

Yield 0.36 gm

XRPD as per FIG. **1**; and DSC as per FIG. **2**

EXAMPLE 2

Preparation of Crystalline Fingolimod Hydrochloride (Form-β)

Process-A:

Charge 3 ml DMF at ambient temperature followed by slow addition of 2.0 gm of Crude or Pure Fingolimod Hydrochloride obtained from any source in round bottom flask under continued stirred. Stirr and maintain the solution for 15-30 minutes to ensure clear solution. Slowly add 30.0 ml acetone at ambient temperature in about 1 hour time. Cool the reaction mass up to 0-5° C. and stir for about 2 hrs. Filter the reaction mass and isolating the crystalline product after 12 hours of under vacuum drying at room temperature.

Yield 1.37 gm

XRPD as per FIG. **3**; and DSC as per FIG. **4**

Process-B:

Charge 3 ml THF at ambient temperature followed by slow addition of 2.0 gm of Crude or Pure Fingolimod Hydrochloride obtained from any source in round bottom flask under continued stirred. Stir and maintain the solution for 10-20 minutes to ensure clear solution. Slowly add 60.0 ml acetone at ambient temperature in about 1 hour time. Cool the reaction mass up to 0-5° C. and stir for about 2 hrs. Filter the reaction mass and isolating the crystalline product after 12 hours of under vacuum drying at about 45° C.

Yield 1.51 gm

Process-C:

Charge 5 ml 2-Methoxy ethanol at ambient temperature followed by slow addition of 2.0 gm of Crude or Pure Fingolimod Hydrochloride obtained from any source in round bottom flask under continued stirred. Stir and maintain the solution for 10-15 minutes to ensure clear solution. Slowly add 60.0 ml Acetonitrile at room temperature in about 1 hour time. Stir for about 2 hours at room temperature. Cool the reaction mass up to 0-5° C. and maintained the stirring for

about 2 hrs. Filter the reaction mass and isolating the crystalline product after 12 hours of under vacuum drying at about 20-25° C.

Yield −1.89 gm

EXAMPLE 3

Preparation of Crystalline Fingolimod Hydrochloride (Form-μ)

Charge 1.0 gm of Crude or Pure Fingolimod Hydrochloride obtained from any source in round bottom flask. Raise the temperature slowly till 120-125° C. Once the melt is formed and the clear melt becomes visible, cool the melted mass slowly up to 20-25° C. (RT) in about 2 hours time. Scrap the crystalline material as Form-μ.

Yield −0.89 gm

XRPD as per FIG. **5**

We claim:

1. Fingolimod hydrochloride crystalline Form-β characterized by X-ray powder diffraction pattern comprising characteristic 2θ° peaks selected from the XRPD peak set of 3.54, 7.07, 10.66, 15.35, 20.52, 21.43 and 25.10±0.1 2θ°.

2. Fingolimod hydrochloride crystalline Form-β according to claim **1**, which is further characterized by DSC isotherm comprising endothermic peaks ranging between—

a. Peak-1—Between 40 to 45° C.

b. Peak-2—Between 65 to 70° C.

c. Peak-3—Between 107 to 115° C.

d. Peak-4—Between 265 to 270° C.

3. Fingolimod hydrochloride crystalline Form-β characterized by X-ray powder diffraction pattern comprising characteristic 2θ° peaks selected from the XRPD peak set of 3.54, 7.07, 10.66, 15.35, 20.52, 21.43 and 25.10±0.1 2θ° and DSC isotherm comprising the endothermic peaks ranging between 40 to 45° C. (Peak-1), 65 to 70° C. (Peak-2), 107 to 115° C. (Peak-3) and/or 265 to 270° C. (Peak-4).

4. Fingolimod hydrochloride crystalline Form-β according to claim **3**, characterized by X-ray powder diffraction pattern as disclosed in FIG. **3** and DSC isothermal pattern as disclosed in FIG. **4**.

5. A process for preparing Fingolimod hydrochloride crystalline Form-β comprising the steps of—

a. combining the Fingolimod hydrochloride with organic solvent selected from dimethylformamide, dimethylacetamide, tetrahydrofuran and 2-methoxyethanol;

b. optionally heating upto about 40-50° C. followed by cooling; and

c. isolating the crystalline Form-β using another co-solvent selected from acetone or acetonitrile by recrystallization.

6. A process for preparing Fingolimod hydrochloride crystalline Form-β according to claim **5**, wherein organic solvent may be selected from dimethylformamide, dimethylacetamide, tetrahydrofuran, 2-methoxyethanol and co-solvent selected from acetone or acetonitrile.

* * * * *

JA-2

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SHILPA PHARMA, INC., Shilpa, v. NOVARTIS PHARMACEUTICALS CORPORATION, Defendant.	C.A. No. 21-558-MN

DECLARATION OF BART KAHR, PH.D.

1. I have been retained by Shilpa Pharma, Inc. ("Shilpa") as an expert consultant and witness in this litigation concerning Shilpa's claims of patent infringement of U.S. Pat. No. 9,266,816 ("the '816 Patent" or the "Patent-in-Suit"). I have been informed that Shilpa has asserted Claims 1-4 '816 patent against Novartis Pharmaceuticals Corporation ("Novartis).

2. I am being compensated at my regular consulting rate of $600/hr. My compensation is not dependent on the opinions expressed or the outcome of the litigation.

3. In have testified as an expert at trial or at deposition in the last five years in the following matters: *Mitsubishi Tanabe Pharma Corp. et al. v. Apotex, Inc. et al*., Civil Action No. 1:17-cv-00990-GMS (D. Del) (2017); *Pfizer Inc., et al., v. Micro Labs USA Inc., et al*., C.A. No. 17-158 (LPS) (2019*); H. Lundbeck A.S. et al. v. Apotex Inc*. et al. No. 18-88-LPS (D.Del.)(2020).

4. The materials that I have reviewed in forming my opinion are listed herein..

5. Below I provide comments about the knowledge of a person of ordinary skill in the art of pharmaceutical chemistry, the background of the technology underlying the '816 Patent, the characterization of crystalline forms through various solid-state analytical techniques, including but not limited to X-ray powder diffraction and DSC; crystals and their physical

properties and morphologies, including polymorphism and polyamorphism. I may also offer opinions and/or testify in rebuttal or response to reports submitted by Novartis, or testimony of experts delivered on behalf of Novartis.

6. I may use demonstrative exhibits or visual aids to support my views; I have not yet created any such exhibits or aids. I reserve the right to supplement or amend this report based on additional information obtained in the future.

BACKGROUND AND QUALIFICATIONS

7. I am currently a tenured Professor of Chemistry at New York University.

8. I was an Assistant Professor and then Associate Professor of Chemistry at Purdue University from 1990 to 1996, and an Associate Professor and then Professor of Chemistry at the University of Washington from 1997 to 2009. Within the past ten years, I also have held positions as Visiting Professor at the Université Louis Pasteur, Strasbourg and Queens University, Kingston, Ontario. I have held lectureships at the National Science Foundation, at Yale University, and at the Accademia delle Scienze di Torino in Italy.

9. I hold an A.B. from Middlebury College and a Ph.D. in Chemistry from Princeton University, which I received in 1988. From 1988–1990, I was a postdoctoral associate at Yale University. I studied the reactivity of single crystals and crystal optics in the laboratory of J. Michael McBride.

10. I have published 270 scientific articles, the large majority of which relate to the topic of crystalline structure of chemical compounds. I also hold two patents for applications of mixed crystals, a third for a new type of microscopy, and a fourth for the invention of a new class of optically responsive molecules. Additionally, I have two pending patent applications on the polymorphism of insecticides.

11. My current research interests are the areas of crystal growth and crystal optics. In particular, we are interested in polycrystalline pattern formation, and the measurement of the chiroptical properties of organized media. We have a special focus on crystals and their pathological physical properties and morphologies. I have been interested in polymorphism for almost 20 years. The following papers have focused on issues of polymorphism: as linked to my CV: Nos. 21, 37, 56, 124, 148, 149, 151, 202, 209, 219, 223, 227, 238, 242, 244, 251, 254, 257, 262, 268, 273. My CV is attached as JA-3.

12. I have given more than 250 invited lectures at universities throughout the world as well as at national and international conferences. About three quarters of these presentations have addressed the characterization of crystalline forms through various solid-state analytical techniques, including but not limited to X-ray powder diffraction and optical microscopy.

13. I have received a number of awards for my work in crystal growth and crystal optics, including a National Science Foundation Young Investigator Award, a Research and Development 100 Award for the invention of a new analytical instrument, as well as two Creativity Extensions in 2007 and 2012 for single investigator grants from the National Science Foundation.

14. A complete list of my professional and academic experiences, publications, and presentations can be found in my curriculum vitae, which is attached as JA-3

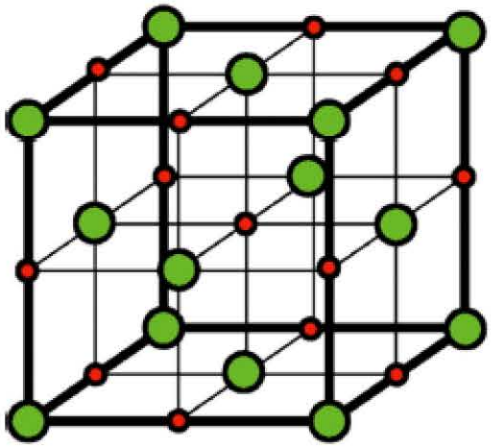
SCIENTIFIC AND TECHNOLOGICAL BACKGROUND

15. I have been asked to provide a brief background on the technology relevant to the '816 patent. This background is set forth below.

16. Crystalline solids contain atoms and molecules that are arranged in a long-range, repeating pattern in three-dimensional space. The internal structure (called the crystal structure)

of a compound is determined by the position of the atoms or molecules relative to each other and extending in three dimensions. Knowing the internal structure of a crystal allows one to construct a three-dimensional model with all atoms and molecules in the correct location relative to each other. A geometric lattice of points is a common and credible abstraction of real crystals.

17. The atoms and molecules within the crystal structure are held together by interactions between the atoms making up the substance. For example, the crystal structure of sodium chloride is illustrated below:



18. The red and green balls are schematic representations of the sodium and chloride ions, respectively. This ordered repeating pattern of alternating ions extends in three directions to provide the crystal lattice of the compound.

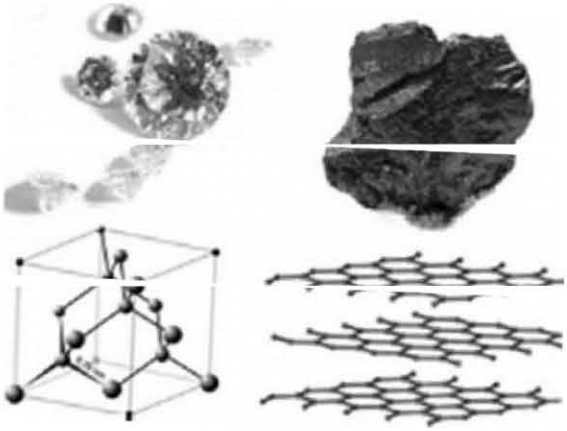
19. Solids that are not crystalline have no long-range order of the atoms and molecules that make up the solid. These materials are often referred to as amorphous solids. Glass is an example of an amorphous solid, in that the silicon dioxide molecules of glass lack that long-range three-dimensional order. An amorphous pharmaceutical solid is one in which the constituent molecules lack long range order. It is presumed that the constituents are arranged in a more or less random fashion on average. An amorphous pharmaceutical lacks long-range

intermolecular order although it may have local correlations between molecules. Amorphous solids are generally less stable than crystalline solids.

Polymorphism

20. For some solid substances, the atoms and molecules that make up the crystal structure can be arranged in more than one configuration in three-dimensional space. That is, the atoms or molecules can pack together in more than one way to produce different crystalline forms. The ability of atoms, molecules or ions to exist in more than one crystal form or structure is known as polymorphism, and the various different crystal forms of the same compound are known as polymorphs.

21. The different polymorphs of a compound can have very different properties despite the fact that they are made of the same molecule. A familiar related example involving the different arrangement of the same atom is carbon, which exists both as graphite and as diamond depending on the atoms' three-dimensional arrangement. The different forms of carbon are technically "allotropes," not polymorphs, but the example is no less applicable for this difference in nomenclature. In both cases, the elemental composition is identical but the components have distinct geometric arrangements.



comparison of diamond (left) and graphite (right)

22. It is quite common for crystals of organic compounds including salt forms to have different polymorphs. These different polymorphs will have different physical and chemical properties. For example, different polymorphs can exhibit different melting points, solubilities, chemical stabilities, hygroscopicities, X-ray crystal structures and XRPD patterns (discussed below), among many other properties.

23. Different polymorphs can also exhibit different relative stabilities under different environmental conditions. For example, one polymorph of a substance may be stable at room temperature, while another is stable only at elevated temperatures. Generally, it is common for organic compounds that exhibit polymorphism to have more than one form that is stable enough to be isolated and stored at room temperature.

24. That organic molecular crystals can have multiple polymorphs can be of great significance in the pharmaceutical industry. As stated, different polymorphs of different organic compounds must have different properties (e.g., solubility, hygroscopicity, dissolution rate, chemical and thermal stability) which in turn can affect the bioavailability, manufacturability,

and shelf life of a pharmaceutical product incorporating an active pharmaceutical ingredient ("API").

B. X-Ray Powder Diffraction to Identify Crystalline Forms

25. There are a number of analytical techniques that can be used to identify and characterize a crystal form of a compound. One of the most useful and reliable techniques is called X-ray powder diffraction (XRPD). This technique involves exposing the solid sample to a beam of X-ray radiation. The sample causes the X-rays to diffract in a pattern that is characteristic of the structure of the solid.

26. Because X-ray powder diffraction probes the nature of the packing of the molecules in three-dimensional space, the technique can be used to differentiate crystalline materials from amorphous materials, which have no long range order. Different crystalline forms of the same compound will exhibit differences in the XRPD patterns that arise from the different arrangements of the molecules within the crystal lattice. Therefore, comparison of the XRPD patterns obtained for different samples usually provides a method of distinguishing different solid forms of the same compound.

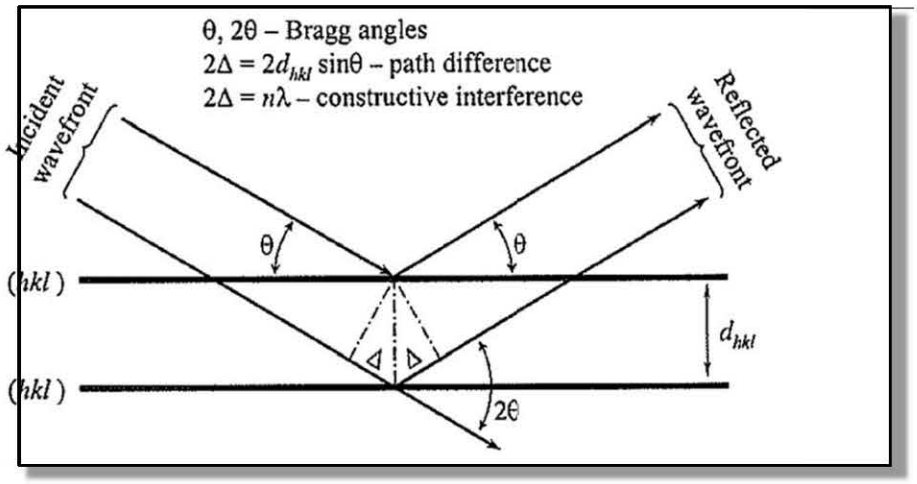
27. One common type of instrumental configuration used to analyze samples involves exposing the material to the X-rays in reflection. In this set-up the top of the sample is exposed to the X-ray radiation. In a typical XRPD experiment the angles of the source and detector are scanned as the intensity of the diffracted radiation is measured by the detector. The output of an XRPD analysis is a pattern that contains a series of peaks that are plotted on a chart with peak intensity as a function of diffraction angle (plotted in units of "degrees 2θ"). This chart is referred to as an "XRPD pattern" or "diffractogram."

28. When X-rays of particular wavelengths (0.5–2.5 Ångstroms) are directed at a sample, they are diffracted. These diffraction angles are measured. Because the distances between the atoms in a crystal are of a length similar to the X- ray wavelength, the presence of a crystal structure in the sample will produce an observable pattern.

29. The relationship between the wavelength of the X-rays and the spacing between atoms in a crystal is known as Bragg's law:

$$n\lambda = 2d \sin\theta$$

where n is an integer (normally 1), "λ" is the wavelength of the incident X-rays, "d" is the interplanar spacing in the crystal (referred to as "d-spacings"), and "θ" is the angle of incident X-rays on the crystal. The Figure below is a geometrical illustration of Bragg's law from the textbook Fundamentals of Powder Diffraction and Structural Characterization of Materials.



Interaction of an x-ray of wavelength λ with a set of parallel crystal planes (hkl) of interplanar spacing, d_{hkl}.
Vitalij K. Pecharsky, *Fundamentals of Diffraction*, *in*

FUNDAMENTALS OF POWDER DIFFRACTION AND STRUCTURAL CHARACTERIZATION OF MATERIALS 99, 148 (2005) (JA-4).

30. A device called a diffractometer measures the intensity of the diffracted X-rays at each of the angles of the incident X-rays, commonly referred to as Bragg angles, 2θ, "2-theta," or "two-theta" values. Figure 3 of the '816 patent provides an illustration of a diffractogram from XRPD testing:

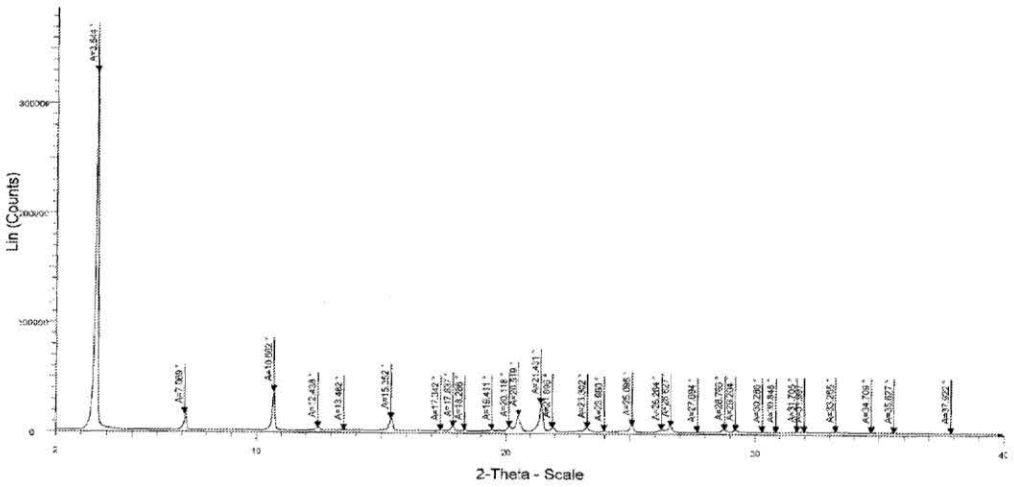


FIG.3

31. As can be seen in this figure, the XRPD diffractogram is an x-y plot. The horizontal (x) axis plots the 2-theta values in units of degrees. The vertical (y)-axis plots the intensity (detector response to X-rays detected at a particular 2-theta value). POSAs understand that intensity, which refers to the strength of the diffraction at a particular 2-theta value, is a parameter which is measured at all angles in a diffractogram. Relative intensity refers to the intensity of a peak at a particular 2-theta value as compared to the intensity of the strongest peak in the diffraction pattern.

32. The 2-theta values measured in XRPD can also be reported in the form of a peak list. In addition to Figure 3, the '816 patent also provide lists of the 2-theta values for the

characteristic peaks of crystalline Form-β of fingolimod hydrochloride (See section IV and e.g., '816 patent, 5:20-38 and Table 2).

33. The 2-theta values measured in XRPD vary depending on the wavelength of the X-rays used. Therefore, when X-ray data is reported in terms of 2-theta values, the wavelength of the monochromatic X-rays must be provided. The '816 patent explains that the XRPD measurements they report were collected using CuKα radiation at a wavelength of 1.5418 Å. Col. 7: ll. 10-22. This is a common wavelength for laboratory XRPD testing.

34. For a given X-ray wavelength, measured 2-theta values can also be used to calculate another parameter called the d-spacings. Unlike 2-theta values, the d-spacings for a crystalline form are independent of, and unaffected by, the wavelength of X-ray used in XRPD testing. As a result, data taken at different wavelengths can be compared by conversion to d-spacings. POSAs understand that d-spacings are related to 2-theta values by Bragg's law and must be calculated.

35. An XRPD diffractogram, in effect, provides a fingerprint for a crystalline form. One or more peaks form a characterizing XRPD pattern that can be used to identify a particular crystal form and distinguish that form from other known forms of a given compound. It is common to refer to peak positions, without referring to peak intensities, to uniquely identify a given crystalline form.

36. A POSA would understand how to review an X-ray diffractogram generated by a sample and compare it to a reference X-ray diffractogram of a particular crystalline form of a compound to determine whether that crystalline form is present in the sample. POSAs routinely perform such analyses.

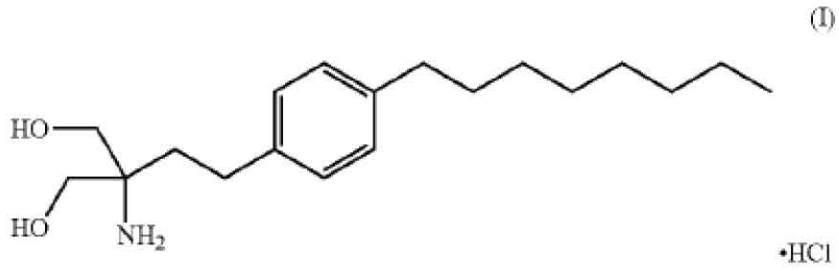
Differential Scanning Calorimetry

37. Another method used to analyze a particular polymorphic form of an API is differential scanning calorimetry ("DSC"). DSC is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a test sample and reference sample is measured as a function of temperature. The output yielded by DSC is a thermogram, which plots the heat flow (y-axis) against temperature (x-axis). If more heat is required to heat the sample compared to the reference an endotherm (negative peak) is observed, if less heat is required to heat the sample compared to the reference an exotherm (positive peak) is observed.

38. DSC may be used in combination with other analytical techniques to characterize polymorphic forms of a compound as different forms may exhibit different melting temperatures DSC can be used to measure a polymorph's melting point and relative stability. The melting point of solid is defined as the temperature at which the solid exists in equilibrium with its liquid phase under an external pressure of one atmosphere. When a crystal melts, a thermal curve representing the energy required to melt the crystal is observed. Melting point analysis via DSC can be visualized with a thermogram, shown in the '816 patent at Fig. 4.

IV. THE '816 PATENT

39. The '816 patent disclosure is generally directed to novel polymorphic forms of fingolimod, designated α-, β-, and μ- and processes for making the same. Fingolimod hydrochloride has the IUPAC name of 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride and has the following structure:



40. The '816 patent describes and claims polymorphic Form-β and processes for obtaining it by combining fingolimod hydrochloride with a specified solvent, heating to a specified temperature, cooling, and isolating the polymorphic form by recrystallization using a co-solvent. *See* JA-1 Column 2 lines 29-53; Column 5, lines 8-48; Column 8, lines 33-68. Polymorphic Form-β is characterized by reference to specific peaks 2θ in a XRPD spectrum and specific endothermic peaks in a DSC scan. The polymorphs are disclosed as highly pure (>99.5 by HPLC) according to the process of the invention and useful in pharmaceutical preparations when formulated with pharmaceutically acceptable excipients.

41. Characteristic XRPD Peaks for Polymorphic Forms α-, β-, and μ- of the '816 patent are summarized from Tables 1, 2 and 3 and are shown below:

S. No.	Angle ($2\theta^o$) Form-α	Angle ($2\theta^o$) Form-β	Angle ($2\theta^o$) Form-μ
1.	10.51	3.54	3.54
2.	15.20	7.07	8.65
3.	19.27	10.66	10.64
4.	21.77	15.35	12.49

5.	23.12	20.52	19.45
6.	24.91	21.43	21.38
7.	26.14	25.10	24.05
8.	26.46		
9.	29.03		
10.	33.47		
11.	35.46		

PERSON OF ORDINARY SKILL IN THE ART

42. I understand that a person of ordinary skill in the art ("POSA") is a hypothetical person considered to have normal skills and knowledge, and to be familiar with the published literature, in the field to which the patent relates at the time of filing of the earliest patent application, which I understand is November 25, 2010.

43. A POSA with respect to the claimed subject matter of the '816 patent would include a person who possesses an advanced degree (e.g. Master's degree or Ph.D., or foreign equivalents of either of the foregoing) in the fields of solid-state chemistry, chemical engineering, or a related discipline (i.e., organic chemistry) and several years of experience in crystallization technology. A POSA would also have experience performing and analyzing results from various analytical tests used to characterize solid state forms, such as XRPD and differential scanning calorimetry. A POSA could have a lower level of formal education, such as a Bachelor's degree, if such a person had a higher degree of experience.

44. I declare under penalty of perjury that the foregoing is true and correct.

Bart Kahr

March 25, 2022

Date

Bart Kahr, Ph.D.

JA-3

Curriculum Vitae

Bart Kahr
Department of Chemistry, New York University, 29 Washington Place, Silver Center, Room 1001, New York City, NY 10003
bart.kahr@nyu.edu

March 2022

1. PERSONAL DATA

Education

Middlebury College, Middlebury VT	AB (I.D. Reingold)	1983
Princeton U. Princeton NJ	MS	1985
Princeton U.	PhD (K. Mislow)	1988
Yale U. New Haven CT	Postdoctoral (J.M. McBride)	1988-90

Employment

Princeton U.	Crystallographer	1987
Purdue U. West Lafayette IN	Assistant Professor	1990–94
Purdue U.	Associate Professor	1995–96
U. of Washington, Seattle WA	Associate Professor	1997–99
U. of Washington	Professor	2000–09
New York U. New York NY	Professor	2009–
New York U. (Chemistry)	Director of Undergrad. Studies	2010–14

Distinctions

Phi Beta Kappa (Middlebury College)	1983
American Institute of Chemists' Prize (Middlebury College)	1983
Hugh Stott Taylor Prize (Princeton U.)	1984
National Science Foundation Young Investigator	1994–99
Troisième Cycle Lecturer, Western Swiss Universities	1996
President, Small Molecule Interest Group, American Crystal. Assn.	1998
H. H. King Lecturer, Kansas State U.	2001
Université Louis Pasteur, Strasbourg, Visiting Professor	2006
Honorary Symposium, *Accademia delle Scienze di Torino*	2007
National Science Foundation Creativity Extension	2007, 2013
Wiberg Lecturer, Yale U.	2009
Queens U. Kingston, Ontario, Visiting Professor	2011
Research and Development Magazine 100 Award	2013
NSF Distinguished Lectureship in Mathematics and Physical Science	2014
Visiting Professor, Waseda U. Tokyo	2015–19
Fellow, American Association for the Advancement of Science	2019

2. RESEARCH AND SCHOLARSHIP

Current Research Group

1.	Dr. Alexander Shtukenberg, research professor	2009–
2.	Ms. Anna Yusov, PhD candidate, yr. 4	2018–
3.	Ms. Marysol Finkenberg, MS candidate, yr. 4	2018–
4.	Mr. Bryan Erriah, PhD candidate, yr. 3	2019–
5.	Mr. Hengyou Zhou, PhD candidate, yr. 3	2019–
6.	Ms. Yongfan Yang, PhD candidate, yr. 3	2019–
7.	Ms. Leilani Smith, PhD candidate, yr. 2	2020–

8.	Mr. Akash Tiwari, PhD candidate, yr. 1	2021–
9.	Ms. Afton Gustafson, PhD candidate, yr. 1	2021–
10.	Ms. Sofia Sburlati, MS candidate	2021–
11.	Ms. Vivi Poschelle, senior	2020–
12.	Ms. Julia Sabino, junior	2020–
13.	Ms. Carolyn Zhang, junior	2020–

PhD Dissertations

Purdue University (5)

1997 Guy Crundwell: *Optical anomalies in solid solutions of simple isomorphous salts*

1998 Christine Mitchell: *Salting open-shell organic molecules*

1999 Anand Subramony: *Dyeing KDP*

2000 Scott Lovell: *Orientation of organic, inorganic, and biomolecular chromophores in aromatic carboxylic acid crystals*

2000 Richard Gurney: *Dyeing crystals*

University of Washington (8)

2006 Kacey Claborn: *Chiro-optics of achiral compounds*

2007 Jason Benedict: *Dyeing crystals: 19th century phenomenology to 21st century technology*

2007 Kristin Wustholz: *Single-molecule orientations and photophysics in dyed salt crystals*

2008 Theresa Bullard: *Luminescence labeling and dynamics of growth active crystal surface structures*

2009 Erica Gunn: *Small molecule banded spherulites*

2011 Charles Branham: *The characterization and optimization of small oxygen sensors based on a porous phosphorescent metal complex*

2011 Eric Bott: *Unraveling dispersed kinetic behavior of single photoacid molecules in transparent crystal hosts*

2012 Erin Riley: *Single molecule photoluminescence intermittency: The role of the host*

New York University (11)

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1999

65 GA Crundwell, BA Cowan, JA Hopkins, JB Grutzner, B Kahr

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Chem. Mat. **1999**, *11*, 1312–1316

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Chemical Intelligencer, **1999**, April, 24–31

1998

59 ID Reingold, G Beckmann, AM Grannas, BD Williams, S Lovell, BE Kahr
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OPPI Briefs, **1998**, *30*, b29–b32

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Chirality **1998**, *10*, 66–77

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Acta Cryst. Sect C **1998**, 229–231

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Chem. Mat. **1998**, *10*, 2053–2057

55 CA Mitchell, R Gurney, B Kahr
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J. Am. Chem. Soc. **1998**, *120*, 9726–9727

1997

54 P Gopalan, G Crundwell, A Bakulin, ML Peterson, B Kahr
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51 JA Subramony, S-H Jang, B Kahr
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Structure and optical characterization of Rochelle salt dye inclusion crystals and the fluorescence detection of their phase transitions
Ferroelectrics, **1997**, *191*, 302–306

1996

49 B Kahr, S-H Jang, JA Subramony, L Bastin, MP Kelley
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1995

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Mol. Cryst. Liq. Cryst. **1995**, *272*, 147–152. doi: 10.1080/10587259508055282

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1994

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Structural Chem. **1994**, 5, 335–340. doi.org/10.1007/ BF02281225

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37 P Toma, MP Kelley, T Borchardt, SR Byrn, B Kahr
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J. Am. Chem. Soc. **1994**, *116*, 5519–5520

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J. Org. Chem. **1994**, *59*, 3230–3231

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33 JK Chow, M Kelley, B Kahr
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Mol. Cryst. Liq. Cryst. **1994**, *242*, 201–214

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31 S-H Jang, P Gopalan, JE Jackson, B Kahr
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1993

28 M Dudley, W Vetter, B Kahr
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National Synchrotron Light Source Report, SL Hurlburt, ML Lazarz, eds Brookhaven National Laboratories, Upton, New York, **1993**

27 S Dostal, SJ. Stoudt, P Fanwick, W Sereatan, B Kahr, JE Jackson
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26 ID Reingold, KS Kwong, BE Kahr, M Menard, G Cummings, JA Kowalski
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25 B Kahr, D Van Engen, P Gopalan
Crystal structure and magnetic susceptibility of a hydrocarbon free radical: Tris(3,5-di-*tert*-butylphenyl)methyl
Chem. Mat. **1993**, *5*, 729–732

24 P Gopalan, B Kahr
Reevaluating structures for mixed crystals of simple isomorphous salts: $Ba_xPb_{1-x}(NO_3)_2$
J. Solid State Chem. **1993**, *107*, 563-567

23 P Gopalan, M L Peterson, G Crundwell, B Kahr
Reevaluating structures for mixed crystals of simple isomorphous salts: $NaBr_xCl_{1-x}O_3$
J. Am. Chem. Soc. **1993**, *115*, 3366–3367

1992

22 S H Hoke II, J. Molstad, D Dilettato, MJ. Jay, B Kahr, RG Cooks
Reaction of fullerenes and benzyne
J. Org. Chem. **1992**, *57*, 5069–5071

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Mol. Cryst. Liq. Cryst. **1992**, *219*, 79–100

20 S-H Jang, R A Bertsch, JE Jackson, B Kahr
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Mol. Cryst. Liq. Cryst. **1992**, 211, 289–303

19 B Kahr, JE Jackson, DL Ward, S-H Jang, J. Blount
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J. Inorg. Organomet. Polymers, **1992**, *2*, 459–461

1991

15 SH Hoke II, J. Molstad, GL Payne, B Kahr, D Ben-Amotz, RG Cooks
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14 LM Roth, Y Huang, JT Schwedler, CJ Cassady, D Ben-Amotz, B Kahr, BS Freiser
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J. Am. Chem. Soc. **1991**, *113*, 5907–5908

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J. Am. Chem. Soc. **1991**, *113*, 5489–5490

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Occurrence and interconversion of high-mass fullerenes
Chem. Phys. Lett. **1991**, *183*, 149–152

1989

10 JM Chance, B Kahr, AB Buda, JS Siegel
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J. Am Chem. Soc. **1989**, *111*, 5940–5944

1988

9 A Mayr, KS Lee, B Kahr

Linkage of alkylidyne, carbonyl, and alkyne ligands at a tungsten center to form a metallacyclopentadienone and an eta^3-oxocyclobutenyl complex
Angew. Chem. Int. Ed. Engl. **1988**, *27*, 1730–1731

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J. Am. Chem. Soc. **1988**, *110*, 6670–6672

7 J. Chance, B Kahr, A B Buda, J. P Toscano, K Mislow
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J. Org. Chem. **1988**, *53*, 3226–3232

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J. Org. Chem. **1988**, *53*, 1687–1689

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J. Am. Chem. Soc. **1988**, *110*, 1917–1922

1987

4 B Kahr, SA Biali, W Schaefer, AB Buda, K Mislow
Molecular structure of hexakis(dichloromethyl)benzene
J. Org. Chem. **1987**, *52,* 3713–3717

1986

3 B Kahr, D Van Engen, K Mislow
The length of the ethane bond in hexaphenylethane and its derivatives
J. Amer. Chem. Soc. **1986**, *108,* 8305–8307

2 ID Reingold, HA Trujillo, BE Kahr
A new preparation of alpha-cycloheptatrienyl ketones
J. Org. Chem. **1986**, *51,* 1627–1629

1984

1 B. Kahr
The poisons of Ypres
The New York Times, March 30, **1984**

Lectures

Departments of Chemistry unless otherwise specified

1989

1. U. of California, Riverside, Riverside CA, Oct
2. San Francisco State U. San Francisco CA, Oct
3. Purdue U. West Lafayette IN, Nov
4. U. of Delaware, Newark DE, Nov

1990

5. U. of Minnesota, Minneapolis MN, Jan
6. U. of Chicago, Chicago IL, Jan
7. Colorado State U. Fort Collins CO, Feb
8. Pomona College, Claremont CA, Feb
9. 3rd Midwest Solid State Chemistry Symposium, Purdue U. West Lafayette IN, Jun
10. Purdue U. West Lafayette IN, Sep
11. Industrial Associates Meeting, Purdue U. West Lafayette IN, Oct
12. ACS Undergraduate Affiliates Meeting, Purdue U. West Lafayette IN, Nov

1991

13. Indiana Superconductivity Consortium, Physics, Purdue U. West Lafayette IN, Jun
14. Purdue U. West Lafayette IN, Sep
15. Indiana U. - Purdue U. at Indianapolis, Indianapolis IN, Sep
16. Juniata College, Huntington PA, Oct
17. ACS Undergraduate Affiliates Meeting, Purdue U. West Lafayette IN, Oct
18. Inorganic Chemistry Division, Purdue U. West Lafayette IN, Nov

1992

19. Dept. of Geophysical Sciences, U. of Chicago, Chicago IL, Mar
20. J. M. Chance Memorial Symposium, Vassar College, Poughkeepsie NY, Mar
21. Annual Meeting of American Society for Mass Spectrometry, Washington DC, Jun
22. 4th Midwest Solid State Organic Chemistry Symposium, U. of Nebraska, Lincoln NE, Jun
23. Annual Meeting of the American Crystallographic Association, Pittsburgh PA, Aug
24. 10th International Conference on Crystal Growth, San Diego CA, Aug

1993

25. Physical Division, Purdue U. West Lafayette IN, Jan
26. Analytical Division, Purdue U. West Lafayette IN, Apr
27. 11th International Conference on the Chemistry of the Organic Solid State, Jerusalem, Jul
28. Radicals in the Rockies, Telluride Summer Research Workshop, Telluride CO, Aug
29. ACS National Meeting, Chicago IL Aug
30. ACS Undergraduate Affiliates, Purdue U. West Lafayette IN, Sep
31. Indiana U. - Purdue U. Fort Wayne IN Oct
32. Dept. of Materials Science, State U. of New York, Stony Brook NY, Oct
33. Eastern Illinois U. Charleston IL, Oct
34. Organic Chemistry Division, Indiana U. Bloomington IN, Nov
35. Solid State Chemistry Seminar Program, Indiana U. Bloomington IN, Nov
36. Northern Illinois U. Dekalb IL, Nov

1994

37. Regional ACS Meeting, U. of Michigan, Ann Arbor MI, Jun
38. Annual Meeting of the American Crystallographic Association, Atlanta GA, Jun
39. Frontiers in Physical Organic Chemistry, ACS Meeting, Washington DC, Aug
40. Advance Research Workshop on Supramolecular Stereochemistry, Hveragerdi, Iceland, Sep
41. U. of Missouri, Columbia MO, Oct
42. U. of Colorado, Boulder CO, Nov

1995

43. Hope College, Hope MI, Mar
44. Calvin College, Grand Rapids MI, Mar
45. U. of Kentucky, Lexington KY, Mar
46. Dow - Analytical Sciences, Midland MI, Mar
47. 3rd International Synposium on Functional Dyes, U. of California Santa Cruz, Santa Cruz CA, Jul
48. NSF Workshop on Reactive Intermediates, Lake Tahoe CA, Aug
49. SUNY Geneseo, Geneseo, NY, Sep
50. Physics Dept. Purdue U. West Lafayette IN, Oct
51. Northwestern U. Evanston, IL, Oct
52. Dept. of Electrical Engineering, Purdue U. West Lafayette IN, Nov
53. Johns Hopkins U. Baltimore MD, Oct
54. Pacifichem, Honolulu HI, Dec

1996

56. Purdue U. West Lafayette IN, Jan
57. U. of Washington, Seattle WA, Mar
58. International Symposium On Ferroic Domains, Vienna, Austria, Mar
59. U. of Washington, Seattle WA, Apr
60-4. *Troisième* Cycle Lecturer, Universities of Bern and Geneva, May
65. The Ohio State U. Columbus OH, May

66. New York U. NYC NY, Jun
67. International Union for Crystallography, Seattle WA, Aug
68. Yale U. New Haven CT, Oct
69. NSF Materials Science Workshop, Philadelphia PA, Oct

1997

70. U. of Minnesota, Dept. of Chemical Engineering, Minneapolis, MN, Feb
71. Mayo Clinic, Rochester, MN Feb
72. Columbia U. New York City NY, Mar
73. U. of California, San Diego CA, Mar
74. U. of California, Los Angeles CA, Mar
75. International Conference on the Organic Solid State, Poland, Aug (declined)
76. Lawrence Livermore National Laboratory, Livermore CA, Nov

1998

77. California Institute of Technology, Pasadena CA, Jan
78. Nanotechnology Seminar Series, U. of Washington, Seattle WA, Feb
79. Dept. of Materials Science, U. of Washington, Seattle WA, Apr
80. International Conference on Reactive Intermediates, Anscona, Switzerland, Jul
81. Materials Research Society, Boston MA, Oct
82. NSF Japan-US Workshop, Lake Arrowhead CA, Dec

1999

83. James Flack Norris Awards Symposium, ACS, Anaheim CA Mar
84. Center for Fundamental Materials Research, Michigan State, East Lansing MI, Mar
85. Gordon Conference on Matrix Isolation, Plymouth NH, Jul
86. American Chemical Society Annual Meeting, New Orleans LA, Aug

2000

87. U. of Oregon, Eugene OR, Mar
88. Materials Research Society, San Francisco CA, Apr
89. Intra-sectoral Zoning, U. of Wisconsin, Madison WI, May
90. Annual Faculty Lecture, Chemistry, U. of Washington, Seattle WA, Nov
91. PACIFICHEM, Honolulu HI, Dec

2001

92. Transform Pharmaceuticals, Waltham MA, Mar
93. Midwest Conference on the Organic Solid State, Lincoln NE, Jun
94. ACS Regional Meeting, Seattle WA, Jun
95. International Conference on the Organic Solid State, XV, Mainz, Germany, Jul
96. *Dipartimento di Chimica Structurale*, Università di Milano, Milan, Italy, Aug
97. *École Supérieure de Chimie Physique Electronique de Lyon*, Lyon, France, Aug
98. U. of Wroclaw, Wroclaw, Poland, Aug
99. International Conference on Organic Crystal Chemistry, Rydzyna, Poland, Aug
100. 4th National Academy of Sciences Symposium on Japanese-American Frontiers of Science, Tokyo, Oct
101. U. of Michigan, Nov
102. H. H. King Lectureship, Kansas State U. Manhattan KS, Nov

2002

103. Simon Fraser U. Burnaby, Canada, Feb
104. American Association of Crystal Growth, Big Sky MT, Jun
105. 1st Royal Society Crystal Engineering Symposium, Bristol, UK, Jul
106. Transform Pharmaceuticals, Waltham MA, Aug

2003

107. Sigma Phi Upsilon Symposium on 50th Anniversary of DNA Structure, U. of Washington, Seattle WA, Feb
108. Western Washington U. Bellingham WA, May
109. U. of Washington, Seattle WA, May
110. 80th Birthday Symposium for Kurt Mislow, NYC NY, Jun

111. Symmetry 2003, Budapest Hungary Aug (declined)
112. Chirality 2003, Shizuoka Japan, Oct

2004

113. ACS Symposium on Polymorphism, Tampa FL, Feb
114. International Symposium on Amyloidosis, Tours, France, Apr
115. American Crystallographic Association, Chicago IL, Jul
116. 22nd Annual European Crystallography Meeting, Budapest, Hungary, Aug
117. Gordon Conference on Organic Materials, Les Diablerets, Switzerland, Oct
118. U. of Bern, Switzerland, Oct
119. Swiss Federal Materials Research Laboratory, Zürich, Switzerland, Oct
120. Regional ACS meeting, Kansas State U. Manhattan KS, Oct

2005

121. Brown U. Providence RI, Jan
122. New York U. New York City, NY Jan
123. American Crystallographic Association, Orlando FL May
124. Supramolecular Chemistry Gordon Conference, ME Jun
125. International Conference of the Chemistry of the Organic Solid State, UCLA, Los Angeles CA, Jul
126. UC Santa Barbara, Aug
127. ACS Meeting, Washington DC, Aug
128. National Institute of Standards and Technology, Washington DC, Aug
129. Georgetown U. Washington DC, Aug
130. U. of Washington, Materials Science, Seattle WA, Octobr

2006

131-3. *Université Louis Pasteur*, Strasbourg, France, Sep
134. U. of Padova, Padova, Italy, Sep
135. Italian Crystallographic Association, Ferrara, Italy, Sep
136. Larson Symposium, Princeton NJ, Oct
137. Tulane U. New Orleans LA, Nov

2007

138. U. of Denver, Denver CO, Feb
139. ACS Sympoium, Chicago IL, Mar
140. Faraday Discussions on Crystal Growth and Nucleation, London, Apr
141. Physical Organic Chemistry Gordon Conference, Holderness NH, Jun
142-3. American Crystallographic Association, Salt Lake City UT, Jul
144. International Outreach, U. of Washington, Seattle WA Aug
145. Washington State U. Physics, Spokane WA, Aug
146. 11th International Conference on Circular Dichroism, Groningen, Netherlands, Sep
147. U. of Massachusetts, Amherst MA, Oct

2008

148. Purdue U. West Lafayette IN, Jan
149. U. of Richmond, Richmond VA, Feb
150 U. of Washington, Graduate student club, Seattle WA, Mar
151. New York U. NYC NY, Mar
152. U. of Buffalo, SUNY, Buffalo NY, Mar
153. American Crystallographic Assn. Knoxville TN, Jun
154. Stereochemistry Gordon Conference, NH, Jul
155. Concordia U. Center for Self-Assembled Chemical Structures, Montreal, Canada, Sep
156. U. of Montreal, Center for Self-Assembled Chemical Structures, Montreal, Quebec, Canada, Sep
157. Southeast Regional Meeting of the ACS, Nashville TN, Nov

2009

158. Wiberg Lecture, Yale U. New Haven CT, Feb
159. Cornell U. Materials Science, Ithaca NY, Feb
160. Chirality, Breckenridge CO, Jul

161. American Crystal Growth Association, Fallen Leaf WI, Aug
162. European Crystallographic Association, Istanbul, Aug
163. Optical Society of American, San Jose CA, Oct
164. New York Nanotechnology Seminar Series, NYU, NYC NY, Oct
165. George Washington U. Washington DC, Nov

2010

166. City U. of New York Graduate Center, NYC NY, Feb
167. NYU/POLY, NYC NY, Feb
168. Crystal Growth School, Lago Gargnano, Italy, Apr (Icelandic volcano, could not fly)
169. NYU Medical Imaging Seminar Series, NYU Medical School, NYC NY, May
170. Draper Society, NYU, NYC NY, Nov
171. PacifiChem, Honolulu HI, Dec

2011

172. City U. of New York Graduate Center, physics, NYC NY, Feb
173. City U. of New York, Queens College, physics, NYC NY, Feb
174. International Conference on the Organic Solid State, Bangalore, India, Jun
175. U. of Hyderabad, Hyderabad, India, Jul
176. National Chemistry Laboratory, Pune, India, Jul
177. Indian Institute of Technology, Mumbai, India, Jul
176. American Association of Crystal Growth, Monterey CA, Aug
177. International Union for Crystallography, Madrid, Spain, Aug
178. Queens U. Kingston Ontario, Canada, Dec

2012

179. City U. of New York Photonic Initiative Symposium, NYC NY, Feb
180. American Crystallographic Association, Boston MA, Aug
181. 15th Society of Iodine Sciences Symposium. Chiba, Japan, Sep (declined)
182. Purdue U. West Lafayette IN, Sep
183. X-ray Diffraction Symposium, NYU, NYC NY Oct
184. Yale U. New Haven CT, Oct

2013

185. Long Island U. Brooklyn NY, Feb
186. College of Arts and Sciences Scholar's Lecture, NYU, NYC NY Feb
186. Tulane U. New Orleans LA, Apr
187. 14th International Conference on Chiroptical Spectroscopy, Nashville TN, Jun
188. Midwest Solid State Organic Chemistry Conference, Lexington KY, Jun
189. John Jay College, NYC NY, Dec

2014

190. Curtin U. Perth Australia, Feb
191. Rigaku X-ray Symposium, Yale U. New Haven CT, Jun
192. NYU MRSEC Research Experience for Undergraduates, NYC NY, Jun
193. Bruker X-ray Symposium, NYU, NYC NY Jun
194. Dalhousie U. Halifax, Nova Scotia, Canada, Sep
195. ACS Regional Meeting, Portland OR, Sep
196. U. of Portland, Portland OR, Sep
197. Portland State U. Dean Ethics Endowment, Portland OR, Sep
198. Directional Nucleation and Growth of Molecular Crystals, Université Libre de Bruxelles, Brussels, Belgium, Nov
199. NSF Distinguished Lectureship, Washington DC, Dec

2015

200. Hebrew U. Jerusalem, Israel, Jan
201. Weizmann Institute of Science, Dept. of Materials and Interfaces, Rehovot, Israel, Jan
202. U. of Tel Aviv, Tel Aviv, Israel, Jan
203. Weizmann Institute of Science, Dept. of Structural Biology, Rehovot, Israel, Jan

204. Materials Research Society, San Francisco CA, Apr
205. St. Johns U. NYC NY Jun
206. Chirality 2015, Boston MA Jun
207. Crystal Growth and Assembly Gordon Conference, Biddeford ME, Jul
208. International Conference on Chemistry of the Organic Solid State 2015, Tokyo, Japan, Jul
209. Waseda U. Dept. of Applied Physics, Tokyo, Japan, Jul
210. Tokyo U. of Science, Tokyo Japan, Jul
211. Waseda U. Nanotechnology Institute, Tokyo, Japan, Jul
212. National Institute for Materials Science International Symposium, Tokyo, Japan, Jul
213. American Crystallographic Association, Philadelphia PA, Jul (Plenary Lecture declined)
214. 29th European Crystallography Conf. Rovinj, Croatia, Aug (declined)
215. Larson Symposium, Philadelphia PA, Oct
216. Pacifichem, Honolulu HI 2015, Dec (declined)

2016

217. Purdue U. Colloquium, W. Lafayette, IN, Mar
218. Purdue U. Physical Chemistry, W. Lafayette, IN, Mar
219. 1st Middle East Materials Science Symposium, NYU Abu Dhabi
220. U. of Texas, Austin TX, Mar
221. U. of Colorado, Boulder CO, Apr
222. ACS Regional Meeting, NYC, Jun
223. New York U./Tel Aviv U. Symposium, NYC, Jun
224. Crystal Engineering Gordon Conference, Jun
225-6. Waseda U. Tokyo, Japan, Jul
227. Brandeis U. Waltham MA, Sep
228. Substrate mediated polymorphism, Alexander von Humboldt U. Berlin, Oct

2017

229. U. of Hiroshima, Circular Dichroism workshop, Hiroshima, Japan, Feb
230. U. of Hiroshima, Synchrotron Radiation Conference, Hiroshima, Japan, Feb
231. Workshop on Chirality, Chiba U. Japan, Mar
232. Concordia U. Montreal, Mar
233-4. Math for America Teachers Workshops on Crystals, NYU, Mar & Jun
235. International Meeting on Circular Dichroism, Rennes, France, Jun
236. Computational Crystallography Symposium, NYU NYC, Jun
237. 2017 International Meeting on Chirality, Short Course, Tokyo, Jul
238. 2017 International Meeting on Chirality, Tokyo, Jul
239. American Physical Society Mid-Atlantic Section, Newark, NJ, Nov

2018

240. ACS National Meeting, Chiroptics Symposium, New Orleans, Mar
241. Mid-Hudson ACS Meeting, Vassar College, Poughkeepsie, Apr
242. Crystallization Workshop, Granada, Spain, May
243. Chirality 2018, Princeton NJ, Jun
244. NYU-Bruker X-ray Symposium, Jun
245. ACS National Meeting, Pasteur Symposium, Boston, Aug
246. Diamond Light Source, Oxfordshire UK, Sep
247. Kurt Mislow Memorial Symposium, Princeton NJ, Nov
248. 2nd Middle East Materials Science Symposium, NYU Abu Dhabi, Nov

2019

249. Stevens Institute of Technology, Dept. Chemical Engineering, Mar
250. Gordon Conference Seminar on Crystal Growth, Jun
251. Waseda University, Dept. Applied Physics, Mar
252. 24th International Conference on Chemistry of the Organic Solid State, NYC, Jun (co-organizer)
253. Gordon Research Symposium on Crystal Growth, Jun
254. Gordon Research Conference on Crystal Growth, Jun (session introduction/chair)
255. Temple University, Philadelphia, Oct

256. International Conference on Nanochirality, Ascona, Italy, Oct
257. University of Milan, Italy, Oct
258. Gerhard Schmidt Centennial Symposium, Weizmann Institute, Israel, Oct

2020

259. New Jersey Environmental Health Association, Atlantic City, NJ, Mar

----------COVID-19

260. ACS National Meeting, Polymorphism symposium, Philadelphia, Mar (CANCELLED)
261. East China Normal University, Shanghai, Aug (CANCELLED)
262. International Conference on Chirality, Tianjin China, Aug (CANCELLED)
263. Solvay Conference on Nucleation, Brussels, Belgium, Nov 2020 (CANCELLED)
264. Materials Chirality Asia, Tokyo, Oct (VIRTUAL)
265. PACIFICHEM, Honolulu, HI, Dec. (CANCELLED)

2021

266. Poincaré Webinar, Jan (VIRTUAL)
267. D'Arcy Thomson's Generative Influences. In Art, Design, and Architecture: From Forces to Forms, book launch, Mar (VIRTUAL)

267. ACS National Meeting, Polymorphism symposium, Mar (VIRTUAL)
268. ACS National Meeting, Crystal Growth Mechanisms symposium, Mar (VIRTUAL)
269. ChiralMat 2021, London, Mar (VIRTUAL)
270-1. International School of Crystallography, Molecular Crystal Engineering, Erice Italy, May/Jun (VIRTUAL)
271. Keynote Lecturer, *Centre Québécois sur les Matériaux Fonctionnels (CQMF)-Quebec Center for Advanced Materials (QCAM)*, Canada, May (VIRTUAL)
272. University of Delft, Netherlands, Jun (VIRTUAL)
273. Louisiana State University, Sep
274. Kona Soft Crystals, Honolulu, HI Dec (VIRTUAL)
275. Pacifichem, Honolulu, HI, Dec (VIRTUAL)

2022

276. STEAM Interdisciplinary Panel, Pratt Manhattan Gallery, NYC, Feb (VIRTUAL)
277. Hiroshima Chiroptics, Hiroshima, JAPAN, Mar (VIRTUAL)
278. International Conference on Chirality, Chicago, Jul
279. Chiroptical Spectroscopy, (co-organizer), NYC, Jul
280. Solvay Workshop on 'Nucleation: multiple pathways, multiple outcomes' Brussels, Belgium, Dec

JA-4

Comment

Cover illustration, created by Peter Zavalij, follows the content of the book. The illustration is inspired by Salvador Dali's painting "The Metamorphosis of Narcissus" where Narcissus [polycrystalline $(Au,Ni)Sn_4$, courtesy Lubov Zavalij] falls in love with his own reflection (diffraction pattern of LaB_6 collected on a Bruker Smart Apex CCD), transforms into an egg (reciprocal lattice), and then into a flower (crystal structure of $Mn_{7-x}(OH)_3(VO_4)_4$ in a physical space), which bears his name.

FUNDAMENTALS OF POWDER DIFFRACTION AND STRUCTURAL CHARACTERIZATION OF MATERIALS

by

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Dedication

This book is dedicated to our parents, some of whom did not live to see it published

is also a function of the triplet of Miller indices (*hkl*). Hence, in general the intensities of discrete points (*hkl*) in the reciprocal space are given as

$$I(hkl) \propto F^2(hkl)\frac{\sin^2 U_1 h\pi}{\sin^2 h\pi}\frac{\sin^2 U_2 k\pi}{\sin^2 k\pi}\frac{\sin^2 U_3 l\pi}{\sin^2 l\pi} \qquad (2.18)$$

The scattered intensity is nearly always measured in relative and not in absolute units, which necessarily introduces a proportionality coefficient, *C*. As we established before, when the phase angle is $n\pi$ (n is an integer), the corresponding interference functions in Eq. 2.18 are reduced to U_1^2, U_2^2 and U_3^2 and they become zero otherwise. Hence, assuming that the volume of a crystalline material producing a diffraction pattern remains constant (this is always ensured in a properly arranged experiment), the proportionality coefficient *C* can be substituted by a scale factor $K = CU_1^2U_2^2U_3^2$.

In addition to the scale factor, intensity scattered by a lattice is also subject to different geometrical effects,[1] *G*, which are various functions of the diffraction angle, θ. All things considered, the intensity scattered by a lattice may be given by the following equation:

$$I(hkl) = K \times G(\theta) \times F^2(hkl) \qquad (2.19)$$

This is a very general equation for intensity of the individual diffraction (Bragg) peaks observed in a diffraction pattern of a crystalline substance, and it will be discussed in details in section 2.10, while the geometry of powder diffraction, i.e. the directions in which discrete peaks can be observed, is discussed in the following two sections.

2.6 Geometry of diffraction by lattices

Both direct and reciprocal spaces may be used to understand the geometry of diffraction by a lattice. Direct space concepts are intuitive, and therefore, we will begin our consideration using physical space. Conversely, reciprocal space is extremely useful in the visualization of diffraction patterns in general and from powders in particular. In this section, therefore, we also show the relationships between geometrical concepts of diffraction in physical and reciprocal spaces.

[1] One of these geometrical effects is the polarization factor introduced earlier in the Thomson's equation, see section 2.5.1 and the corresponding footnote (No. 3 on page 140).

2.6.1 Laue equations and Braggs' law

The geometry of diffraction from a lattice, or in other words the relationships between the directions of the incident and diffracted beams, was first given by Laue (see the footnote on page 31) in a form of three simultaneous equations, which are commonly known as Laue equations:

$$\begin{aligned} a(\cos\psi_1 - \cos\varphi_1) &= h\lambda \\ b(\cos\psi_2 - \cos\varphi_2) &= k\lambda \\ c(\cos\psi_3 - \cos\varphi_3) &= l\lambda \end{aligned} \qquad (2.20)$$

Here *a*, *b* and *c* are the dimensions of the unit cell; $\psi_{1\text{-}3}$ and $\varphi_{1\text{-}3}$ are the angles that the incident and diffracted beams, respectively, form with the parallel rows of atoms in three independent directions; the three integer indices *h*, *k* and *l* have the same meaning as in Eq. 2.18, i.e. they are unique for each diffraction peak and define the position of the peak in the reciprocal space (also see Chapter 1, section 1.15), and λ is the wavelength of the used radiation. The cosines, $\cos\psi_i$ and $\cos\varphi_i$, are known as the direction cosines of the incident and diffracted beams, respectively. According to the formulation given by Laue, sharp diffraction peaks can only be observed when all three equations in 2.20 are satisfied simultaneously.

Laue equations once again indicate that a periodic lattice produces diffraction maxima at specific angles, which are defined by both the lattice repeat distances (*a*, *b*, *c*) and the wavelength (λ). Laue equations give the most general representation of a three-dimensional diffraction pattern and they may be used in the form of Eq. 2.20 to describe the geometry of diffraction from a single crystal.

More useful in powder diffraction is the law formulated by W.H. Bragg and W.L. Bragg (see the footnote on page 31). It was introduced above (e.g. see Eq. 2.11) without an explanation, and we already know that it establishes certain relationships among the diffraction angle (Bragg angle), wavelength and interplanar spacing.

According to the Braggs, diffraction from a crystalline sample can be explained and visualized by using a simple notion of mirror reflection of the incident x-ray beam from a series of crystallographic planes. As established earlier (see Chapter 1, section 1.14.1), all planes with identical triplets of Miller indices are parallel to one another and they are equally spaced. Thus, each plane in a set (*hkl*) may be considered as a separate scattering object. The set is periodic in the direction perpendicular to the planes and the repeat distance in this direction is equal to the interplanar distance d_{hkl}. Diffraction from a set of equally spaced objects is only possible at specific angle(s) as

we already saw in section 2.5. The possible angles, θ, are established from Braggs' law, which is derived geometrically in *Figure 2.26*.

Consider an incident front of waves with parallel propagation vectors, which form an angle θ with the planes (*hkl*). In a mirror reflection, the reflected wavefront will also consist of parallel waves, which form the same angle θ with all planes. The path differences introduced between a pair of waves both before and after they are reflected by the neighboring planes, Δ, are determined by the interplanar distance as $\Delta = d_{hkl}\sin\theta$. The total path difference is 2Δ, and the constructive interference is observed when $2\Delta = n\lambda$, where n is integer and λ is the wavelength of the incident wavefront. This simple geometrical analysis results in the Braggs' law:

$$2d_{hkl}\sin\theta_{hkl} = n\lambda \tag{2.21}$$

The integer n is known as the order of reflection. Its value is taken as 1 in all calculations, since orders higher than one ($n > 1$) can always be represented by first order reflections ($n = 1$) from a set of different crystallographic planes with indices that are multiples of n because

$$d_{hkl} = nd_{nh,nk,nl} \tag{2.22}$$

and for any $n > 1$, Eq. 2.21 is simply transformed as follows:

$$2d_{hkl}\sin\theta_{hkl} = n\lambda \Rightarrow 2d_{nh,nk,nl}\sin\theta_{nh,nk,nl} = \lambda \tag{2.23}$$

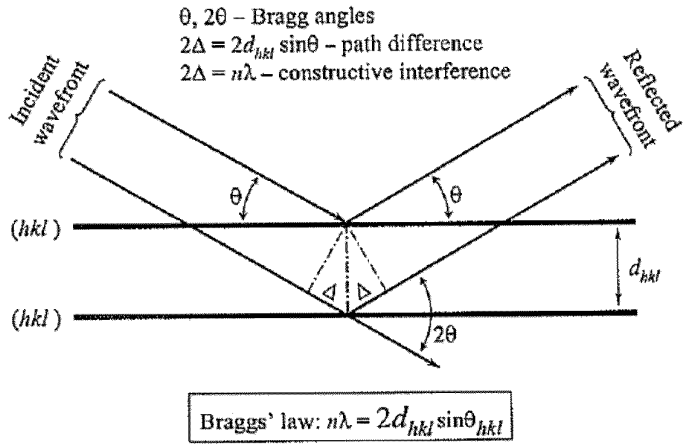

Figure 2.26. Geometrical illustration of the Braggs' law.

2.6.2 Reciprocal lattice and Ewald's sphere

The better visual representation of the phenomenon of diffraction has been introduced by Ewald (see the footnote on page 50). Consider an incident wave with a certain propagation vector, $\mathbf{k}_0$, and a wavelength, λ. If the length of $\mathbf{k}_0$ is selected as the inverse of the wavelength

$$|\mathbf{k}_0| = 1/\lambda \tag{2.24}$$

then the entire wave is fully characterized, and it is said that $\mathbf{k}_0$ is its wavevector. When the primary wave is scattered elastically, the wavelength remains constant. Thus, the scattered wave is characterized by a different wavevector, $\mathbf{k}_1$, which has the same length as $\mathbf{k}_0$:

$$|\mathbf{k}_1| = |\mathbf{k}_0| = 1/\lambda \tag{2.25}$$

The angle between $\mathbf{k}_0$ and $\mathbf{k}_1$ is 2θ (*Figure 2.27*, left). We now overlap these two wavevectors with a reciprocal lattice (*Figure 2.27*, right) such that the end of $\mathbf{k}_0$ coincides with the origin of the lattice. As shown by Ewald, diffraction in the direction of $\mathbf{k}_1$ occurs only when its end coincides with a point in the reciprocal lattice. Thus, considering that $\mathbf{k}_0$ and $\mathbf{k}_1$ have identical lengths regardless of the direction of $\mathbf{k}_1$ (the direction of $\mathbf{k}_0$ is fixed by the origin of the reciprocal lattice), their ends are equidistant from a common point and all possible orientations of $\mathbf{k}_1$ delineate a sphere in three dimensions. This sphere is called the Ewald's sphere, and it is shown schematically in *Figure 2.28*. Obviously, the radius of the Ewald's sphere is $1/\lambda$.

The simple geometrical arrangement of the reciprocal lattice, Ewald's sphere, and three vectors ($\mathbf{k}_0$, $\mathbf{k}_1$, and $\mathbf{d}^*_{hkl}$) in a straightforward and elegant fashion yields Braggs' equation. From both *Figure 2.27* and *Figure 2.28*, it is clear that vector $\mathbf{k}_1$ is a sum of two vectors, $\mathbf{k}_0$ and $\mathbf{d}^*_{hkl}$:

$$\mathbf{k}_1 = \mathbf{k}_0 + \mathbf{d}^*_{hkl} \tag{2.26}$$

Its length is known ($1/\lambda$) and its orientation, i.e. angle θ, is found by a simple algebraic transformation after recalling that $|\mathbf{d}^*| = 1/d$:

$$|\mathbf{k}_1|\sin\theta = |\mathbf{k}_0|\sin\theta = \frac{|\mathbf{d}^*|}{2} \Rightarrow 2d\sin\theta = \lambda \tag{2.27}$$

JA-5.1

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/635,207	09/17/2013	Vimal Kumar Shrawat	ID-PAW-0631	3019

122584 7590 02/25/2015
SHILPA MEDICARE LIMITED
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INDIA

EXAMINER
BROOKS, CLINTON A

ART UNIT	PAPER NUMBER
1671	

MAIL DATE	DELIVERY MODE
02/25/2015	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 13/635,207	Applicant(s) SHRAWAT ET AL.	
	Examiner CLINTON BROOKS	Art Unit 1671	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/7/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *7-12* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *7-12* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *9/14/2012* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☒ All b)☐ Some** c)☐ None of the:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *2*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Status of Claims

In view of the amendment received 11/07/2014, claims 7-12 are currently pending.

Priority

The instant application, United States Application Serial No. 13/635207, filed September 17, 2013 claims priority as follows:

** CONTINUING DATA **********
This application is a 371 of PCT/IN2011/000586 08/29/2011
** FOREIGN APPLICATIONS **********
INDIA 3563/CHE/2010 11/25/2010

The certified foreign document is present in the file and is in the English language, thus, the 11/25/2010 date is granted.

Restriction Election

In the response received 11/07/2014, Applicant elects group II, claims 7-12 with traverse. Applicant traverses based on the argument that the special technical feature is Fingolimod Polymorphs and their processes. However, the art teaches solid forms of these compounds, thus, some forms are present in the art. Thus, Applicant argument is not persuasive.

The restriction is deemed proper and therefore made **FINAL**.

Applicant cancelled the not elected claims.

Information Disclosure Statement

All references from the IDS received September 28, 2012 and September 28, 2012 have been considered unless marked with a strikethrough.

Claim Rejections – 112 First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-12 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for DMF, THF and 2-methoxy ethanol as solvents and acetone and acetonitrile as co-solvents does not reasonably provide enablement for all organic solvents and all co-solvents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The Nature of the Invention

The claims are drawn to a process for producing a specific form of Fingolimod HCl.

The State of the Prior Art and the Predictability or lack thereof in the art

The state of the prior art is one of synthesizing a specific polymorphic form. The prior art shown in the rejections below show that various solvents have been used to produce crystals of Fingolimod HCl. However, it is unclear which solvents produce which specific polymorphic forms of the salts.

The amount of direction or guidance present and the presence or absence of working examples

The specification discloses specific solvents that are used to produce different forms. For example the specification discloses that DMF, THF and 2-methoxy ethanol can be used as a solvent, and that acetone and acetonitrile can be used as a co-solvent.

The breadth of the claims

The claim is extremely broad in that it is drawn to the use of any organic solvent and any co-solvent for claim 11. Claim 12 contains classes of ketones, nitriles, or alcohols whereas the examples do not support such classes.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art/formulation art, it is noted that each embodiment of the inventions is required to be individually assessed.

Thus, the specification fails to provide sufficient support of the broad method of making the crystalline form, as a result necessitating one of skill to perform a search for which solvent combinations would provide the specific form.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what solvents, would be effective providing the specific crystalline form.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instantly claimed methods. In view of the breadth of the claim, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which solvents would provide a the specific crystalline form, with no assurance of success.

An amendment to claim 12 that required the co-solvent to be acetone or acetonitrile would overcome this rejection.

Claim Rejections – 112 Second Paragraph

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. The claim includes the language "substantially according to Fig-3 and DSC isothermanl pattern substantially according to Fig-4." It is unclear where the metes and bounds of "substantially" begin or end. Further, it is unclear which aspects of the Figure are substantial and which ones are not. Thus, the claim has multiple interpretations.

Claim 7-12 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. The claims only require 4 peaks in an X-ray diffraction pattern. The specific peaks are insufficient to differentiate one form from another. For example other forms have similar peaks within the degree of error (see instant Figures for evidence).

Claim Rejections -- 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7-10 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by the article to Kiuchi et al. ("Kiuchi", made of record on the IDS).

See page 2953 right column paragraph 1 for example.

Kiuchi discloses a solid form or a crystalline form of Fingolimod chloride. The patent office is not a scientific laboratory and thus the patent office cannot differentiate the forms in the claims from the forms in Kiuchi.

Conclusions

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CLINTON BROOKS whose telephone number is (571)270-7682. The examiner can normally be reached on Monday-Friday 8:00 AM to 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, FEREYDOUN SAJJADI can be reached on (571)272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for

unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CLINTON BROOKS/

Primary Examiner, Art Unit 1621

JA-5.2

S/N 13/635,207 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Vimal Kumar Shrawat et al. Examiner: Brooks, Clinton A
Serial No.: 13/635,207 Group Art Unit: 1671
Filed: September 17, 2013 Confirmation No.: 3019
Title: FINGOLIMOD POLYMORPHS AND THEIR PROCESSES

Declaration by Dr. Vimal Kumar Shrawat, Ph.D. Under 37 CFR §1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir,

I, Dr. Vimal Kumar Shrawat, Ph.D., currently residing in Raichur, India, hereby declare the following:

I received a Ph.D. in Synthetic Organic Chemistry from the from Center of Advance studies, Department of Chemistry, Delhi University located in Delhi, India. Currently I hold the position of Chief Operating Officer (COO); Corporate Operations, Shilpa Medicare Limited in Raichur, India. I have worked in the field of Synthetic Organic Chemistry for more than 30 years, including the research carried out as part of my graduate work. Through my education and experience I have a very good knowledge of Synthetic Organic Chemistry theory and practice, particularly as applied to the optimization and parameterization of small molecule synthesis and crystallization processes.

I am an inventor of the US patent application 13/635,027. I am accordingly familiar with the subject matter of this application.

During prosecution of the US patent application No. 13/635,027. We conducted experiment to repeat the procedure as disclosed in Page 2953 of Kiuchi et al.

The work done to repeat this experiment was carried out either by me or under my supervision. This experiment was carried out so as to faithfully reproduce the experiment as disclosed above. A copy of the experimental procedure for repetition Kiuchi et al process as disclosed in Page 2953 is submitted as Exhibit – A

A copy of a side by side XRPD's showing the powder X-ray diffractogram of Kiuchi et al. and Form β of the present invention is attached hereto as Exhibit B. I believe that the powder X-ray diffraction analysis of the products obtained by reproducing the process disclosed in Kiuchi et al using ethanol and ethyl acetate in a ratio of 1:1 show that neither of the product obtained in that experiment corresponds to the crystal form recited in the claims of the present invention.

I, Dr. Vimal Kumar Shrawat, Ph.D, declare under penalty of perjury that the above statements are true and correct to the best of my knowledge, information, and belief. I understand that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon.

Dated: 14/05/2015

Dr. Vimal Kumar Shrawat

Exhibit A: A copy of the experimental procedure for repetition of Kiuchi et al process as disclosed in Page 2953.

Confidential Document

Innovating for affordable healthcare

Experiment Reference Number: RR/FM-III/03/01/15 Date: April 04, 2015

Objective: To conduct experiment in view of our US patent application (US 2013/0281739) prosecution with respect to requirement of requirement of PXRD comparison with respect to SML patented process (As per instruction received from IPM department)

Process Reference: Preparation of Fingolimod Hydrochloride as disclosed in Page 2953 (Paragraph 1) Journal of Medicinal Chemistry 2000, vol.43.No.15 2953

S.No	Name of Raw Material	Quantity
1	2-Acetamido-2{2-(4-octylphenyl)ethyl]propane -1,3-diol diacetate (FM-I)	10.0 gm
2	Methanol	122.0 ml
3	2N LiOH	97.56ml
4	Ethyl acetate	100.0 ml+100.0 ml + 6 ml
5	Saturated-Sodium chloride Solution	50 .0 ml
6	Sodium sulfate	10.0 gm
7	1N Hydrochloric acid + ether	7.15 ml +7.15 ml
8	Ethanol	14.3 ml + 6 ml

Operations:

1. In a three necked RB flask ,charged FM-1(10.0g), Methanol (122.0 ml)and stir at room temperature for 15-30 min to get the clear solution
2. Add 2N LiOH (97.56) ml at room temperature and slowly raised the temperature to reflux and maintained for two hours.
3. Recover the methanol completely at 45-50°C and extracted with ethyl acetate (2 X 100.0 ml).
4. Combined the ethyl acetate layer and washed with brine solution (50.0 ml)
5. Finally dried over anhydrous sodium sulfate and recovered the ethyl acetate completely to get the residue.
6. The residue obtained (2.0gram) was converted in to hydrochloride salt by treatment with ethanol (14.3 ml) and 1N HCL solution in ether(14.3 ml)
7. Recrystallized from Ethyl acetate (6 ml)/ethanol (6 ml) to give the Fingolimod Hydrochloride salt
8. Dried the material at room temperature for 4-5 hours under vacuum and sample submitted for HPLC purity, XRPD, IR and 1H-NMR (DMSO-d6)

Reaction performed By

Signature with date 04/04/2015

Shilpa Medicare Limited, Raichur, Chemical Research Lab

Checked By

Signature with date 04/04/2015

Exhibit-B: Powder X-ray diffraction data for products obtained as per the present invention (Fingolimod Hydrochloride Form β) (Fig-1) and the product(Fingolimod Hydrochloride) obtained as disclosed in Page 2953 of Kiuchi et al. (Fig-2)

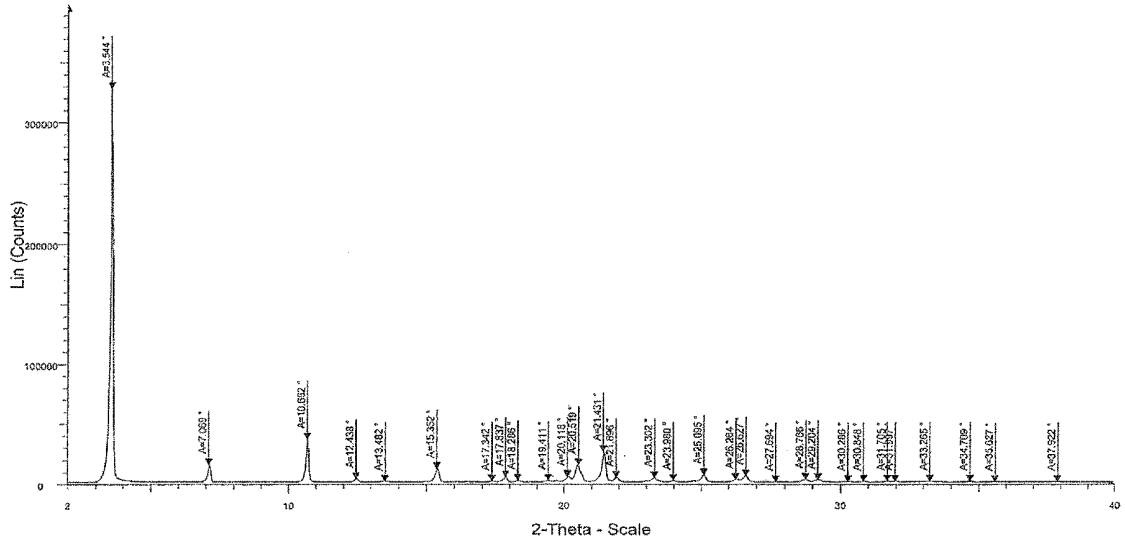

Fig-1: Showing the PXRD of crystalline Fingolimid hydrochloride Form β as claimed in the present invnetion.

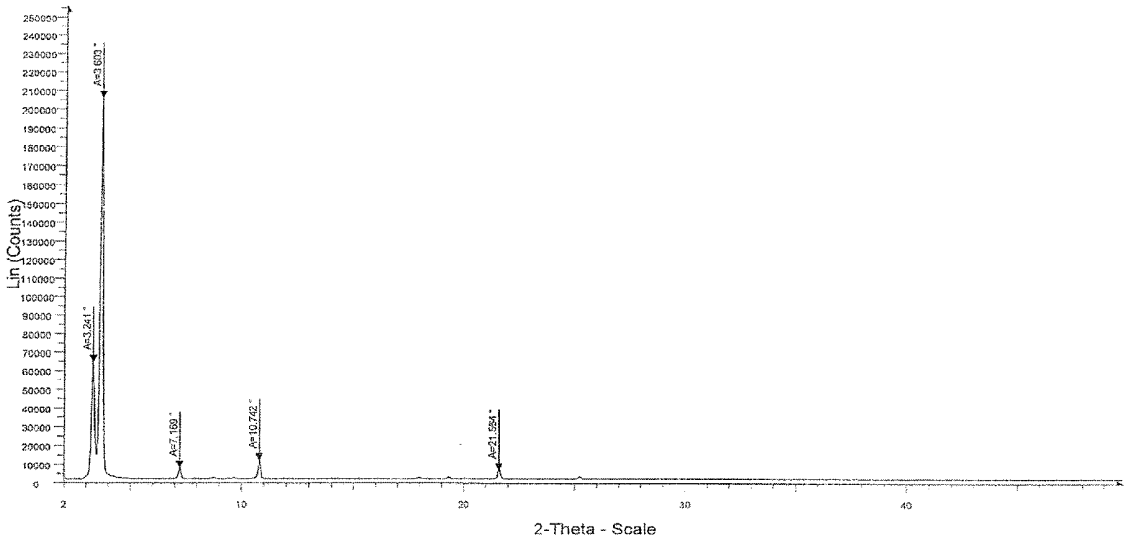

Fig-2: Showing the PXRD of Fingolimid hydrochloride crystalline Form obtained as per the experiment disclosed in Page 2953 of Kiuchi et al.

S/N 13/635,207 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Vimal Kumar Shrawat et al.
Serial No.: 13/635,207
Filed: September 17, 2013
Title: FINGOLIMOD POLYMORPHS AND THEIR PROCESSES

Examiner: Brooks, Clinton A
Group Art Unit: 1671
Confirmation No.: 3019

AMENDMENT & RESPONSE UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In response to the Office Action dated February 25, 2015, the following amendments are respectfully submitted:

Amendments to the claims are reflected in the listing of the claims which begins on page 2 of this document.

Remarks begin from page 4 onwards of this document.

Inventor's Declaration in view of incorporating the side-by-side experimentation results in compliance to show the difference between present invention and Kiuchi et al.

Amendments to the Claims

This listing of claims will replace all prior versions and listings of claims in the application

Listing of claims

1-6) - (Cancelled)

7) (Currently amended) Fingolimod hydrochloride crystalline Form-β characterized by X-ray powder diffraction pattern consisting ~~comprising at least 4~~ characteristic 2Θ° peaks selected from the XRPD peak set of 3.54, 7.07,10.66,15.35, 20.52, 21.43 and 25.10 ±0.1 2Θ°.

8). (Currently amended) Fingolimod hydrochloride crystalline Form- β according to claim-7, which is further characterized by DSC isotherm consisting ~~comprising at least three~~ endothermic peaks ranging between-

a. Peak -1- Between 40 to 45°C
b. Peak -2- Between 65 to 70°C
c. Peak -3- Between 107 to 115°C
d. Peak -4- Between 265 to 270°C

9) (Currently amended) Fingolimod hydrochloride crystalline Form-β characterized by X-ray powder diffraction pattern consisting ~~comprising at least 4~~ characteristic 2Θ° peaks selected from the XRPD peak set of 3.54, 7.07, 10.66, 15.35, 20.52, 21.43 and 25.10 ± 0.1 2Θ° and DSC isotherm consisting ~~comprising~~ the endothermic peaks ranging between 40 to 45°C (Peak -1), 65 to 70°C (Peak -2), 107 to 115°C (Peak-3) and/or 265 to 270°C (Peak-4)

10) (Currently amended) Fingolimod hydrochloride crystalline Form-β according to claim-9, characterized by X-ray powder diffraction pattern as disclosed in ~~substantially according to~~ Fig-3 and DSC isothermal pattern as disclosed in ~~substantially according to~~ Fig-4.

11) (Currently amended) A process for preparing Fingolimod hydrochloride crystalline Form-β comprising the steps of-

a. combining the Fingolimod hydrochloride with organic solvent selected from dimethylformamide, dimethylacetamide, tetrahydrofuran and 2-methoxyethanol;
b. optionally heating upto about 40- 50°C followed by cooling; and
c. isolating the crystalline Form-β using another co-solvent selected from acetone or acetonitrile by recrystallization

12) (Currently amended) A process for preparing Fingolimod hydrochloride crystalline Form- β according to claim 11, wherein organic solvent may be selected from dimethylformamide, dimethylacetamide , tetrahydrofuran, 2-methoxyethanol and co-solvent selected from acetone or acetonitrile ~~ketone or nitrile or alcohol~~.

13-15) (Cancelled)

REMARKS

Applicants have received the Office Action dated February 25, 2015. By way of response, Applicant has suitably amended the claims 7-12 in order to comply the requirements. No new matter is added thereby.

For the reasons given below, Applicants respectfully submit that the pending claims are in condition for allowance and notification to that effect is earnestly solicited.

The Rejection of Claims under § 112- First Paragraph

Claims 11-12 are rejected under 35 U.S.c. 112(a) or 35 U.S.c. 112 (pre-AIA), first paragraph, because the specification, while being enabling for DMF, THF and 2-methoxy ethanol as solvents and acetone and acetonitrile as co-solvents does not reasonably provide enablement for all organic solvents and all co-solvents.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

We respectfully submit that proposed amended set of claim shall comply with the requirements in clearly pointing out and distinctly claiming the subject matter of the instant invention.

Though the applicant amended the claims to comply with the requirements of the examiner, applicant likes to inform the examiner that the examples disclosed in the patent specification "which are provided by way of illustration only and should not be construed as limiting the scope of the invention in any manner" and the same is clearly disclosed before example 1 of the patent specification.

Applicants like to inform the examiner that it is not obligatory to disclose each and every part of the claim as the person skilled in the art may understand how to perform the experimentation using a different solvent following the procedure as disclosed for another solvent.

The claims with respect to solvent are being enabled with paragraph [0073], wherein it clearly mentions that "Combining the Fingolimod hydrochloride with as Organic solvents for preparing Form-β comprise either mixing or suspending or making solution with organic solvent selected from dimethylformamide, dimethylacetamide, tetrahydrofuran, 2-methoxyethanol."

The claims with respect to co-solvent are further being enabled with paragraph [0077], wherein it clearly mentions that "Reaction mass can be cooled up to 0-30° C. and subjected to stir for about 1-2 hrs. The product may be isolated from the reaction mass by combining with co-solvent selected from ketone (C3 to C8) or nitrile (C2 to C4) or alcohol (C1 to C4), followed by conventional processes including filtering and optional drying, which may be carried out at room temperature for the suitable durations to retain the crystalline polymorphic form characteristics"

Polymorphism has been given importance in the recent literatures owing to its relevance to the drugs having oral dosage forms due to its apparent relation to dose preparation/suitability in composition steps/ bioavailability and other pharmaceutical profiles, stable polymorphic form of a drug has often remained the clear choice in compositions due to various reasons of handling, mixing and further processing including bioavailability and stability.

Polymorphism is the ability of a solid material to exist in more than one form or crystal structure. Polymorphism can potentially be found in any crystalline material, which refers to chemical elements. When polymorphism exists as a result of difference in crystal packing, it is called packing polymorphism.

Polymorphs have different stabilities and may spontaneously convert from a metastable form (unstable form) to the stable form at a particular temperature. They also exhibit different

melting points, solubility's (which affect the dissolution rate of drug and consequently its bioavailability in the body), X-ray crystal and diffraction patterns.

Person skilled in the art may know the importance of the solvent used in the reaction, conditions and reagents used in the reaction in the formation of crystal packing of the material. However, polymorphism is a unique property of a molecule to exist in different crystalline packing pattern or in disordered arrangement of molecules (amorphous). A molecule may not also have tendency to exist in multiple crystalline shape/packing pattern. If there are many crystalline forms (polymorphism) exists for a molecules, they may not necessarily be all useful or thermodynamically stable. Hence, concluding a polymorphic form as new and useful is an uphill task for an inventor unless adequate due diligence and studies were performed in laboratory in order to conclude. Further, besides the change in the solvent system - specific process conditions in the recrystallization step mainly varies the crystal packing of the material, if polymorphism exists in the molecule, which accordingly changes the polymorphic nature of the crystalline form. The temperature maintained in the reaction and the nature of the reaction, whether it is acidic or basic also plays an important role in crystal packing of the material.

In view of the above it is abundantly clear that the no - prior art disclosed the specific conditions as claimed in the present patent application. The present inventors surprisingly found that the crystalline form β by performing exhaustive work on the process development for the preparation of stable and pure Fingolimod HCl.

The present invention is clearly elaborated in the specification for the preparation of Fingolimod crystalline form β from paragraph [0067] to paragraph [0077]. For a person skilled in the art this data is sufficient to prepare Fingolimod in a crystalline form β consistently.

Further, it is clear for a person skilled in the art that the combination of organic solvent selected from dimethylformamide, dimethylacetamide, tetrahydrofuran, 2-methoxyethanol and a co-solvent selected from selected from ketone (C3 to C8) or nitrile (C2 to C4) or alcohol (C1 to C4) will clearly using the procedure as disclosed in the specification clearly results in Fingolimod in a crystalline form β and no ambiguity is observed.

In view of the above remarks, we respectfully submit that amended set of claims, wherein claims claim 11 and 12 are narrowed down by limiting the organic solvents and co-solvents to overcome the rejections and reconsideration and withdrawal of these rejections are requested.

We respectfully submit the amended set of claims while complying with the requirements of 35 USC§112 in entirety, by clearly enabling the claimed subject matter of the instant invention. Accordingly, it is respectfully submitted that the rejections have been overcome by the above amendments. We humbly request for the reconsideration of the same and withdrawal of the rejections.

The Rejection of Claims under § 112- Second Paragraph

Claim 10 *is rejected under 35 U.S.c. 112(b) or 35 U.S.c. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. The claim includes the language "substantially according to Fig-3 and DSC isothermal pattern substantially according to Fig-4." It is unclear where the metes and bounds of "substantially" begin or end. Further, it is unclear which aspects of the Figure are substantial and which ones are not. Thus, the claim has multiple interpretations.*

We respectfully submit that amended set of claim shall comply with the requirements in clearly pointing out and distinctly claiming the subject matter of the instant invention.

As per the present amended claims the word "substantially" is removed to overcome the objection raised by the examiner. In view of these amendments, applicant likes to inform the examiner that now there is no ambiguity in interpretation of claims with respect to the amended set of claims.

Though the applicant amended the claims to comply with the requirements of the examiner, wherein as per the present amended claims the word "substantially" is removed to overcome the rejections. Applicant likes to inform the examiner that the word "substantially" is

used to show the presence of single crystalline form, which is free of process related impurities and other polymorphic forms. Further, in the present application in paragraph [0060] it is clearly mentioned that the "A substantially pure product having purities more than 99% (by HPLC) can be obtained by the process of the present invention". For a person skilled in the art, it is clear from this sentence that Fingolimod, which is in crystalline form β having a purity of greater than 99% (by HPLC).

Further, the present inventors found that the Fingolimod crystalline form β is substantially pure, which means it is having a purity of greater than 99 % and free of process related impurities.

In view of the above remarks, we respectfully submit that amended set of claims, wherein claim 10 is amended by removing the word "substantially" to overcome the rejections and reconsideration and withdrawal of these rejections are requested.

Claim 7-12 *is rejected under 35 U.S.c. 112(b) or 35 U.S.c. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. The claims only require 4 peaks in an X-ray diffraction pattern. The specific peaks are insufficient to differentiate one form from another. For example other forms have similar peaks within the degree of error (see instant Figures for evidence).*

We respectfully submit that amended set of claim shall comply with the requirements in clearly pointing out and distinctly claiming the subject matter of the instant invention.

As per the present amended claims the claims are narrowed down by incorporating "consisting of" instead of "comprising at least 4" to overcome the rejections and reconsideration and withdrawal of these rejections are requested.

In view of these amendments, applicant likes to inform the examiner that this data is sufficient to differentiate the claimed from other forms. From the presently amended claim, for a person skilled in the art it is clear that crystalline polymorphic form of Fingolimod HCl designated as Form-β, if and only if every peak in the claim is present the XRPD.

Unexpected Results: Form β of Fingolimod has several unexpected advantages over previously discovered crystalline Form of Fingolimod. Form β is the most thermodynamically stable polymorphic form of Fingolimod under processing and storage conditions, when compared to compound obtained as per prior art discovered forms. Such improved properties are important for better tablet processing and manufacturing.

In view of the above remarks, we respectfully submit that amended set of claims, wherein claim 7-12 is amended to overcome the rejections and reconsideration and withdrawal of these rejections are requested.

The Rejection of Claims under § 102

Claims 7-10 are rejected under pre-AIA 35 U.S.c. 102(b) as being anticipated by the article to Kiuchi et al. ("Kiuchi", made of record on the IDS). See page 2953 right column paragraph 1 for example. Kiuchi discloses a solid form or a crystalline form of Fingolimod chloride. The patent office is not a scientific laboratory and thus the patent office cannot differentiate the forms in the claims from the forms in Kiuchi.

In response, the Applicants respectfully submit that the presently claimed invention is not obvious over Kiuchi et al. in view of the cited references. The Office is incorrectly assuming that the existence of crystalline Form suggests the existence of Form β of the present invention. It is clear to those skilled in the art of pharmaceutical crystallization and solid-state chemistry that the existence of polymorphism, as well as the existence of specific polymorphs, cannot be predicted. "Polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformation of the molecules. As a result, the polymorphic solids have different unit cells and hence display different physical properties" (Brittain et al., Polymorphism of Pharmaceutical Solids, Page 2). The present invention is not

JA-5.3

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/635,207	09/17/2013	Vimal Kumar Shrawat	ID-PAW-0631	3019

122584 7590 09/09/2015

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INDIA

EXAMINER
BROOKS, CLINTON A

ART UNIT	PAPER NUMBER
1671	

MAIL DATE	DELIVERY MODE
09/09/2015	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 13/635,207	Applicant(s) SHRAWAT ET AL.	
	Examiner CLINTON BROOKS	Art Unit 1671	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/15/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *7-12* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☒ Claim(s) *11 and 12* is/are allowed.

7)☒ Claim(s) *7-10* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *9/14/2012* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☒ All b)☐ Some** c)☐ None of the:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *2*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

This action is **FINAL.**

Status of Claims

In view of the amendment received 11/07/2014, claims 7-12 are currently pending.

Response to Applicant Amendment/Consideration of Affidavit

In view of Applicant amendment, the 112 first paragraph rejection is withdrawn.

In view of Applicant, the 112 second paragraph rejection over claim 10 is withdrawn, and the 112 second paragraph rejection over claims 7-12 is withdrawn.

In view of the affidavit the 102(b) rejection is withdrawn. Applicant uses different solvent system to crystallize the hydrochloride salt arriving at a unique polymorph.

Applicant amendment necessitated addition issues.

New Rejections Necessitated By Amendment

Claim Rejections – 112 Fourth Paragraph

The following is a quotation of 35 U.S.C. 112(d):

> (d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), fourth paragraph:

> Subject to the [fifth paragraph of 35 U.S.C. 112 (pre-AIA)], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

Claim 10 is rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. The claim increases the scope of 9. Since claim 9 uses "consisting" transitional language only the peaks listed must be present. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

Claim Rejections – 112 First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. In

view of the amendment to "consisting" language a new issue is introduced. Applicant was clearly in possession of a pattern which "comprises" the peaks, but Applicant did not possess a pattern that only had the peaks listed in the claim. The "consisting" transition phrase is the issue. The Figures referernced had more peaks than the peaks listed in the claim.

Claim Objections

Claim 7-10 are objected to because of the following informalities: Applicant improperly amended the claims. Applicant improperly added the word "consisting" to each of the claims without marking it with an underline. Appropriate correction is required. This amendment should not have been entered, but a notice of non-compliance is not being sent out in order to expedite prosecution.

Conclusions

Claims 11-12 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CLINTON BROOKS whose telephone number is (571)270-7682. The examiner can normally be reached on Monday-Friday 8:00 AM to 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, FEREYDOUN SAJJADI can be reached on (571)272-3311. The fax phone number

for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CLINTON BROOKS/

Primary Examiner, Art Unit 1621

JA-5.4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Vimal Kumar Shrawat et al.
Serial No.: 13/635,207
Filed:September 17, 2013
Title: FINGOLIMOD POLYMORPHS AND THEIR PROCESSES

Examiner: Brooks, Clinton A
Group Art Unit: 1671
Confirmation No.: 3019

AMENDMENT & RESPONSE UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In response to the Office Action dated September 09, 2015, the following amendments are respectfully submitted:

Amendments to the claims are reflected in the listing of the claims which begins on page 2 of this document.

Remarks begin from page 4onwards of this document.

Amendments to the Claims

This listing of claims will replace all prior versions and listings of claims in the application

Listing of claims

1-6)- (Cancelled)

7) **(Currently amended)** Fingolimod hydrochloride crystalline Form-β characterized by X-ray powder diffraction pattern ~~consisting~~ comprising characteristic 2Θ° peaks selected from the XRPD peak set of 3.54, 7.07,10.66,15.35, 20.52, 21.43 and 25.10 ±0.1 2Θ°.

8). (Currently amended) Fingolimod hydrochloride crystalline Form- β according to claim-7, which is further characterized by DSC isotherm ~~consisting~~ comprising endothermic peaks ranging between-

a. Peak -1- Between 40 to 45°C
b. Peak -2- Between 65 to 70°C
c. Peak -3- Between 107 to 115°C
d. Peak -4- Between 265 to 270°C

9) (Currently amended) Fingolimod hydrochloride crystalline Form-β characterized by X-ray powder diffraction pattern ~~consisting~~ comprising characteristic 2Θ° peaks selected from the XRPD peak set of 3.54, 7.07, 10.66, 15.35, 20.52, 21.43 and 25.10 ± 0.1 2Θ° and DSC isotherm ~~consisting~~ comprising the endothermic peaks ranging between 40 to 45°C (Peak -1), 65 to 70°C (Peak -2), 107 to 115°C (Peak-3) and/or 265 to 270°C (Peak-4)

10) (Previously Presented) Fingolimod hydrochloride crystalline Form-β according to claim-9, characterized by X-ray powder diffraction pattern as disclosed in Fig-3 and DSC isothermal pattern as disclosed in Fig-4.

11) (Previously Presented) A process for preparing Fingolimod hydrochloride crystalline Form-β comprising the steps of-

a. combining the Fingolimod hydrochloride with organic solvent selected from dimethylformamide, dimethylacetamide, tetrahydrofuran and 2-methoxyethanol;
b. optionally heating upto about 40- 50°C followed by cooling; and
c. isolating the crystalline Form-β using another co-solvent selected from acetone or acetonitrile by recrystallization

12)(Previously Presented) A process for preparing Fingolimod hydrochloride crystalline Form- β according to claim 11, wherein organic solvent may be selected from dimethylformamide, dimethylacetamide , tetrahydrofuran, 2-methoxyethanol and co-solvent selected from acetone or acetonitrile.

13-15) (Cancelled)

REMARKS

Applicants have received the Office Action dated September 09, 2015. By way of response, Applicant has suitably amended the claims 7-9 in order to comply the requirements. No new matter is added thereby. Further, applicant appreciates the examiner for allowing the claims 11-12 and withdrawing the previous rejections.

For the reasons given below, Applicants respectfully submit that the pending claims are in condition for allowance and notification to that effect is earnestly solicited.

The Rejection of Claims under§112- Fourth Paragraph

Claim 10 is rejected under 35 U.S.c. 112(d) or pre-AIA 35 U.S.c. 112, 4th paragraph, asbeing of improper dependent form for failing to further limit the subject matter of the claim uponwhich it depends, or for failing to include all the limitations of the claim upon which it depends.The claim increases the scope of 9. Since claim 9 uses "consisting" transitional language onlythe peaks listed must be present. Applicant may cancel the claim(s), amend the claim(s) to placethe claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present asufficient showing that the dependent claim(s) complies with the statutory requirements.

We respectfully submit that proposed amended set of claims shall comply with the requirements in clearly pointing out and distinctly claiming the subject matter of the instant invention.

Though the applicant amended the claims to comply with the requirements of the examiner, applicant would like to inform the examiner that the enabling disclosure as Figure 3 and Figure 4 of the specification specifically discloses the said PXRD and DSC isothermal pattern of Fingolimod hydrochloride crystalline Form-β as claimed in the instant invention.

Applicant has suitably amended the claim 9 as suggested by the examiner by replacing the word "consisting" with "comprising", which is well supported by the specification. In this regard, we respectfully submit the amended set of claims, which will comply with the requirements of 35 USC§112 in entirety, by clearly possessing the dependency of claim 10 on claim 9. Accordingly, it is respectfully submitted that the rejections have been overcome by the above amendments. We humbly request for the reconsideration of the same and withdrawal of the rejections.

The Rejection of Claims under§112- First Paragraph

***Claims** 7-10are rejected under 35 U.S.c. 112(a) or 35 U.S.c. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention. In view of the amendment to consisting" language a new issue is introduced. Applicant was clearly in possession of a pattern which "comprises" the peaks, but Applicant did not possess a pattern that only had the peaks listed in the claim. The "consisting" transition phrase is the issue. The Figures referenced had more peaks than the peaks listed in the claim.*

We respectfully submit that amended set of claim shall comply with the requirements in clearly pointing out and distinctly claiming the subject matter of the instant invention.

As per the present amended claims the word "consisting" is replaced with "comprising" to overcome the objection raised by the examiner. In view of these amendments, applicant would like to inform the examiner that now there appears to be no ambiguity in interpretation of claims with respect to the amended set of claims.

Claim 7-10 are objected to because of the following informalities: Applicant improperly amended the claims. Applicant improperly added the word "consisting" to each of the claims without marking it with an underline. Appropriate correction is required. This amendment

should not have been entered, but a notice of non-compliance is not being sent out in order to expedite prosecution.

Applicant hereby submitting the new amended set of claims, wherein applicant properly amended the claims by marking the changes with underlines (additions) and strike through (eliminations).

We respectfully submit that amended set of claim shall comply with the requirements in clearly pointing out and distinctly claiming the subject matter of the instant invention.

In view of the above remarks, we respectfully submit that amended set of claims, wherein claim 7-9are amended to overcome the rejections and reconsideration and withdrawal of these rejections are requested.

CONCLUSION

In view of the above amendments and remarks, Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. If the Examiner has any other unclear or unresolved matter in this connection, the Examiner is invited to telephone/fax/e-mail the undersigned, to facilitate advancement of the present application.

Respectfully submitted,

/

Dated: October 28, 2015

Dr. Akshay Kant Chaturvedi
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JA-5.5

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

122584 7590 11/23/2015

SHILPA MEDICARE LIMITED
10/80, Second Floor,
Rajendra Gunj
Raichur, Karnataka, 584102
INDIA

EXAMINER
BROOKS, CLINTON A

ART UNIT	PAPER NUMBER
1671	

DATE MAILED: 11/23/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/635,207	09/17/2013	Vimal Kumar Shrawat	ID-PAW-0631	3019

TITLE OF INVENTION: FINGOLIMOD POLYMORPHS AND THEIR PROCESSES

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	02/23/2016

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

122584 7590 11/23/2015
SHILPA MEDICARE LIMITED
10/80, Second Floor,
Rajendra Gunj
Raichur, Karnataka, 584102
INDIA

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/635,207	09/17/2013	Vimal Kumar Shrawat	ID-PAW-0631	3019

TITLE OF INVENTION: FINGOLIMOD POLYMORPHS AND THEIR PROCESSES

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	02/23/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
BROOKS, CLINTON A	1671	564-360000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/635,207	09/17/2013	Vimal Kumar Shrawat	ID-PAW-0631	3019

122584 7590 11/23/2015

SHILPA MEDICARE LIMITED
10/80, Second Floor,
Rajendra Gunj
Raichur, Karnataka, 584102
INDIA

EXAMINER	
BROOKS, CLINTON A	
ART UNIT	PAPER NUMBER
1671	

DATE MAILED: 11/23/2015

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 13/635,207	Applicant(s) SHRAWAT ET AL.	
	Examiner CLINTON BROOKS	Art Unit 1671	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *10/28/2015*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *7-12*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☒ All b) ☐ Some *c) ☐ None of the:
   1. ☒ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☒ Other *After Final "OK to Enter"*.

/CLINTON BROOKS/ Primary Examiner, Art Unit 1671	11/16/2015

The present application is being examined under the pre-AIA first to invent provisions.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance:

In view of the amendment, the rejections and objections of record are withdrawn. Applicant previously presented an affidavit distinguishing the instant polymorph from the art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CLINTON BROOKS whose telephone number is (571)270-7682. The examiner can normally be reached on Monday-Friday 8:00 AM to 5:00 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, FEREYDOUN SAJJADI can be reached on (571)272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CLINTON BROOKS/
Primary Examiner, Art Unit 1671

JA-6

From: Love, Jane M. <JLove@gibsondunn.com>
Sent: Thursday, March 17, 2022 4:55 PM
To: Saliba, Raja; Ranney, Christine; Eve H. Ormerod; Dzwonczyk, Michael R.; Rachuba, L Roman; Neal C. Belgam
Cc: Trenchard, Robert W.; Glandorf, David; Parks, Allyson; Shapiro, Russell O; 'Silver, Daniel'; 'Joyce, Alexandra'; Boland, Mark; Love, Jane M.
Subject: RE: Shilpa / Novartis Case No. 21-558-MN - 6pmET exchange of rebuttal claim terms and constructions

Hi Raja,

We can adjust the briefing as you suggest. To confirm, that makes Shilpa's opening brief due on March 25, and Novartis's answering brief on April 22.

As for indefiniteness, on our call today I explained our position in response to your questions and we did agree to disagree on the merits. Also, our claim chart further cites intrinsic evidence on the point. As I said on our call, we believe that the claim fails to identify a unique polymorph using appropriately characteristic peaks. We appreciate you disagree, but we have provided enough information for Shilpa to address the point in the opening brief, and saving arguments for reply would be inappropriate. Of course, arguments may evolve during briefing, but we feel we have provided enough for Shilpa to address the indefiniteness problem at the beginning of briefing.

Best,
Jane

Jane M. Love, Ph.D.

GIBSON DUNN

Gibson, Dunn & Crutcher LLP
200 Park Avenue, New York, NY 10166-0193
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JLove@gibsondunn.com • www.gibsondunn.com

From: Saliba, Raja
Sent: Thursday, March 17, 2022 4:17 PM
To: Love, Jane M. ; Ranney, Christine ; Eve H. Ormerod ; Dzwonczyk, Michael R. ; Rachuba, L Roman ; Neal C. Belgam
Cc: Trenchard, Robert W. ; Glandorf, David ; Parks, Allyson ; Shapiro, Russell O ; 'Silver, Daniel' ; 'Joyce, Alexandra' ; Boland, Mark
Subject: RE: Shilpa / Novartis Case No. 21-558-MN - 6pmET exchange of rebuttal claim terms and constructions

[WARNING: External Email]

Dear Jane,

Thank you for today's call. We look forward to receiving your proposed revisions to the joint claim construction chart and hopefully we will be able to agree to an overall reduction in the number of terms that the Court needs to construe. With respect to the indefiniteness positions that Novartis raised for several

terms, we are not entirely clear as to the basis, but will plan to respond to your arguments in Shilpa's reply brief after having the opportunity to consider your arguments in Novartis' answering brief.

We have one request regarding the briefing schedule. Given that we are still conferring on terms, we would like to extend the deadlines for the opening and answering briefs by two days, leaving the reply and sur-reply deadlines intact. Please let us know if you would agree to this schedule change and we can have a stipulation sent over for your review.

Best,
Raja