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Novel polymorphs of Lorlatinib and their processes for the preparation thereof

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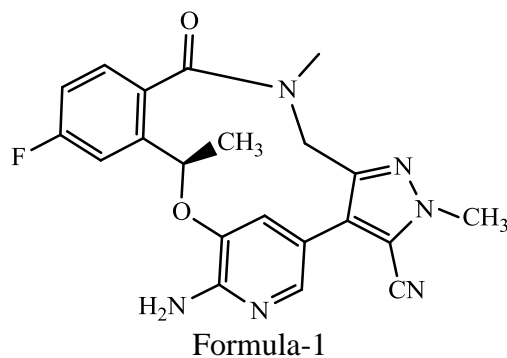
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Novel polymorphs of Lorlatinib and their processes for the preparation thereof

Field of the invention:

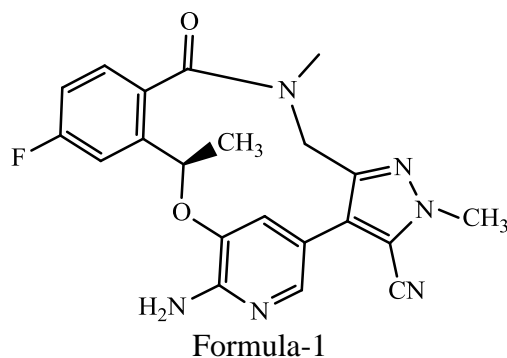
The present invention provides novel polymorphs of (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-methenopyrazolo[4,3-*h*] [2,5,11] benzoxa diazacyclotetradecine-3-carbonitrile represented by following structural formula-1 and their processes for the preparation thereof.



Formula-1

Background of the invention:

(10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-methenopyrazolo[4,3*h*][2,5,11] benzoxadiazacyclotetradecine-3-carbonitrile is commonly known as Lorlatinib, which was approved in US & Europe under the brand names of Lorbrena and Lorviqua respectively for the treatment of anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer.



Formula-1

Lorlatinib or pharmaceutically acceptable salts are described in US 8680111 B2.

US 9637500 B2 patent describes hydrated crystalline form 1, form 2 and acetic acid solvate form 3 of Lorlatinib and their process for the preparation.

WO2017175091A1 PCT publication describes crystalline anhydrous form 1 and

crystalline hydrate form 2 of Lorlatinib maleate and their processes for the preparation.

US 10420749 B2 patent describes anhydrous crystalline form-7 of Lorlatinib and its process for the preparation.

WO2019073347 A1 PCT publication describes hydrated crystalline form 24 of Lorlatinib and its process for the preparation.

WO2019209633A1 PCT publication describes crystalline form Z, form U1, form U2, form Gamma, form Epsilon, form X, form E1 and form E2 of Lorlatinib and its fumarate form F1, benzoate form B1, nicotinate form N1, mesylate form S1, tosylate form T1, hydrobromide form H1, L-malate form L1, citrate form C1, L-tartarate form R1 and maleate forms M1, M2, M4 and M5 and their process for the preparation.

There is a still develop further polymorphs of Lorlatinib to meet the pharmaceuticals requirements.

Since the development of new polymorphic forms of an active pharmaceutical ingredient provides new opportunity to improve the performance characteristics of pharmaceutical finished product, the development of new polymorphic forms is always encouraged.

Furthermore, solid state study of an active pharmaceutical ingredient aims to widen the variety of crystalline forms that a formulation scientist has available for designing a pharmaceutical dosage form with desired characteristics.

After numerous trials and earnest efforts, the present inventors found novel crystalline polymorphs of Lorlatinib, which are useful and suitable for the preparation of various pharmaceutical compositions.

Brief description of the invention:

The first embodiment of the present invention provides a novel crystalline form of Lorlatinib, herein after designated as crystalline form-M.

The second embodiment of the present invention provides a process for the preparation of crystalline form-M of Lorlatinib.

The third embodiment of the present invention provides a novel crystalline form of Lorlatinib, herein after designated as crystalline form-S.

The fourth embodiment of the present invention provides a process for the preparation of crystalline form-S of Lorlatinib.

The fifth embodiment of the present invention provides a novel crystalline form of Lorlatinib, herein after designated as crystalline form-N.

The sixth embodiment of the present invention provides a process for the preparation of crystalline form-N of Lorlatinib.

The seventh embodiment of the present invention provides a novel crystalline form of Lorlatinib, herein after designated as crystalline form-S1.

The eighth embodiment of the present invention provides a process for the preparation of crystalline form-S1 of Lorlatinib.

The ninth embodiment of the present invention is to provide a process for the preparation of amorphous form of Lorlatinib.

Brief description of the drawings:

Figure-1: Illustrates the powder X-Ray diffraction pattern of crystalline form-M of Lorlatinib.

Figure-2: Illustrates the powder X-Ray diffraction pattern of crystalline form-S of Lorlatinib.

Figure-3: Illustrates the powder X-Ray diffraction pattern of crystalline form-N of Lorlatinib.

Figure-4: Illustrates the powder X-Ray diffraction pattern of crystalline form-S1 of Lorlatinib.

Figure-5: Illustrates the powder X-Ray diffraction pattern of amorphous form of Lorlatinib.

Figure-6: Illustrates the powder X-Ray diffraction pattern of crystalline form-M of Lorlatinib obtained according to example-10.

Detailed description of the invention:

As used herein the term “suitable solvent” or solvent used in the present invention refers to “hydrocarbon solvents” such as n-hexane, n-heptane, cyclohexane, pet ether, benzene, toluene, pentane, cycloheptane, methyl cyclohexane, ethylbenzene, m-, o-, or p-xylene, or naphthalene and the like; “ether solvents” such as dimethoxymethane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, furan, diethyl ether, ethylene glycol dimethyl

ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, t-butyl methyl ether, 1,2-dimethoxy ethane and the like; “ester solvents” such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; “polar-aprotic solvents such as dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and the like; “chloro solvents” such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; “ketone solvents” such as acetone, methyl ethyl ketone, methyl isobutylketone and the like; “nitrile solvents” such as acetonitrile, propionitrile, isobutyronitrile and the like; “alcohol solvents” such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 1,2-propanediol (propylene glycol), 2-methoxyethanol, 1, 2-ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol and the like; “polar solvents” such as water or mixtures thereof.

The first embodiment of the present invention provides a novel crystalline form of Lorlatinib herein after designated as crystalline form-M.

In an aspect of first embodiment provides the crystalline form-M of Lorlatinib characterized by its Powder X-Ray diffractogram substantially in accordance with figure-1.

The second embodiment of the present invention provides a process for the preparation of crystalline form-M of Lorlatinib, comprising:

- a) dissolving Lorlatinib in 2-butanol,
- b) isolating crystalline form-M of Lorlatinib.

Dissolving the Lorlatinib in step-a) can be done at a temperature ranging from about 25°C to reflux temperature of the solvent used; isolating crystalline form-M in step-b) is by solvent removal by known techniques which are selected from filtration, cooling the mixture to lower temperatures to precipitate the solid followed by filtration of the mixture, crystallization; or by combining with an anti-solvent.

In the above process, step a) or step-b) optionally involve seeding with crystalline

form-M of Lorlatinib.

The third embodiment of the present invention provides a novel crystalline form of Lorlatinib, herein after designated as crystalline form-S.

In an aspect of third embodiment provides the crystalline form-S of Lorlatinib characterized by its powder X-Ray diffractogram as illustrated in figure-2.

The fourth embodiment of the present invention provides a process for the preparation of crystalline form-S of Lorlatinib, comprising:

- a) dissolving Lorlatinib in isopropanol,
- b) isolating crystalline form-S of Lorlatinib.

Dissolving the Lorlatinib in step-a) can be done at a temperature ranging from about 25°C to reflux temperature of the solvent used; isolating crystalline form-S in step-b) is by solvent removal by known techniques which are selected from cooling the mixture to lower temperatures to precipitate the solid followed by filtration of the mixture, crystallization; or by combining with an anti-solvent, wherein anti-solvent is selected from water.

In the above process, step a) or step-b) optionally involve seeding with crystalline form-S of Lorlatinib.

The fifth embodiment of the present invention provides a novel crystalline form of Lorlatinib, herein after designated as crystalline form-N.

In an aspect of fifth embodiment provides the crystalline form-N of Lorlatinib characterized by its powder X-Ray diffractogram as illustrated in figure-3.

The sixth embodiment of the present invention provides a process for the preparation of crystalline form-N of Lorlatinib, comprising:

- a) dissolving Lorlatinib in ethanol,
- b) isolating crystalline form-N of Lorlatinib.

Dissolving the Lorlatinib in step-a) can be done at a temperature ranging from about 25°C to reflux temperature of the solvent used; isolating crystalline form-N in step-b) is by solvent removal by known techniques which are selected from filtration, cooling the mixture to lower

temperatures to precipitate the solid followed by filtration of the mixture, crystallization; or by combining with an anti-solvent, wherein anti-solvent is selected from hydrocarbon solvents.

In the above process, step a) or step-b) optionally involve seeding with crystalline form-N of Lorlatinib.

The seventh embodiment of the present invention provides a novel crystalline form of Lorlatinib, herein after designated as crystalline form-S1.

In an aspect of seventh embodiment provides the crystalline form-S1 of Lorlatinib characterized by its powder X-Ray diffractogram as illustrated in figure-4.

The eighth embodiment of the present invention provides a process for the preparation of crystalline form-S1 of Lorlatinib, comprising:

- a) dissolving Lorlatinib in n-pentanol,
- b) isolating crystalline form-S1 of Lorlatinib.

Dissolving the Lorlatinib in step-a) can be done at a temperature ranging from about 25°C to reflux temperature of the solvent used; isolating crystalline form-S1 in step-b) is by solvent removal by known techniques which are selected from filtration, cooling the mixture to lower temperatures to precipitate the solid followed by filtration of the mixture, crystallization; or by combining with an anti-solvent, wherein anti-solvent is selected from hydrocarbon solvents.

In the above process, step a) or step-b) optionally involve seeding with crystalline form-S1 of Lorlatinib.

The ninth embodiment of the present invention provided a process for the preparation of amorphous form of Lorlatinib comprises:

- a) dissolving Lorlatinib to a solvent,
- b) isolating the amorphous form of Lorlatinib.

Dissolving the Lorlatinib in step-a) can be done at a temperature ranging from about 25°C to reflux temperature of the solvent used; solvent is selected from ketone solvents, ester solvents or mixtures thereof and the like; isolating amorphous form in step-b) is by solvent

removal by known techniques which are selected from distillation, filtration, cooling the mixture to lower temperatures to precipitate the solid followed by filtration of the mixture; or by combining with an anti-solvent selected from hydrocarbon solvents, water or mixtures thereof and the like.

In an aspect of the ninth embodiment provides amorphous form of Lorlatinib characterized by its powder X-Ray diffractogram substantially in accordance with figure-5.

The crystalline form-M, form-S, form-N, form-S1 and amorphous form of Lorlatinib of the present invention are prepared by the processes as illustrated in the present invention and they are useful for the preparation of various pharmaceutical compositions formulated in a manner suitable for the route of administration to be used where at least a portion of Lorlatinib is present in the composition in particular polymorphic form mentioned.

An embodiment of the present invention provides the use of crystalline form-M, form-S, form-N, form-S1 and amorphous form of Lorlatinib for the preparation of pharmaceutical formulations.

The other embodiment of the present invention provides pharmaceutical composition comprising crystalline form-M or form-N or form-S or form-S1 or amorphous of Lorlatinib or mixture thereof and at least one pharmaceutically acceptable excipient. As used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

In an aspect of the present invention provides a pharmaceutical composition comprising crystalline forms or amorphous prepared according to the present invention and one or more pharmaceutically acceptable carriers for the treatment of anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer.

Crystalline forms or amorphous form of Lorlatinib obtained according to the present invention is having a purity of >98%, preferably >99%, more preferably >99.5% by HPLC.

Crystalline forms or amorphous form of Lorlatinib produced by the processes of the present invention can be further micronized or milled to get desired particle size to achieve

desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction include but not limited to single or multi-stage micronization using cutting mills, pin/cage mills, hammer mills, jet mills, fluidized bed jet mills, ball mills and roller mills. Milling or micronization may be performed before drying or after drying of the product.

Crystalline forms or amorphous form of Lorlatinib obtained according to the present invention has particle size of less than about 250 μm or less than about 200 μm or less than about 150 μm or less than about 100 μm or less than about 50 μm or any other suitable particle sizes.

Lorlatinib used as an input for the preparation of crystalline forms or amorphous form of Lorlatinib obtained according to the present invention is prepared by any of the processes disclosed in literature such as US 8680111 B2 or other references.

PXRD (Powder X-Ray diffractogram) Method of Analysis:

The PXRD analysis of compounds of the present invention was carried out by using BRUKER-Axis/D8 ADVANCE (DAVINCI) X-Ray diffractometer using $\text{CuK}\alpha$ radiation of wavelength 1.5406\AA and at a continuous scan speed of $0.03^\circ/\text{min}$.

The best mode of carrying out the present invention is illustrated by the below mentioned examples. These examples are provided as illustration only and hence should not be considered as limitation of the scope of the invention.

Examples:

Example-1: Preparation of crystalline form-M of Lorlatinib

Dissolved Lorlatinib (500 mg) in 2-butanol (5 ml) at $95\text{-}100^\circ\text{C}$ and stirred for 10 minutes at the same temperature. Cooled the solution to $0\text{-}5^\circ\text{C}$ and stirred for 15 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 400 mg. PXRD of the obtained compound is as illustrated in figure-1.

Example-2: Preparation of crystalline form-S of Lorlatinib

Dissolved Lorlatinib (1 g) in isopropanol (4 ml) at 80-85°C and stirred for 10 minutes at the same temperature. Water (200 µl) was added to resultant solution, cooled the mixture to 0-5°C and stirred for 80 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 800 mg. PXRD of the obtained compound is as illustrated in figure-2.

Example-3: Preparation of crystalline form-S of Lorlatinib

Dissolved Lorlatinib (2 g) in isopropanol (10 ml) at 80-85°C and stirred for 10 minutes at the same temperature. Cooled the resultant solution to 25-30°C and stirred for 30 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 1.8 g. PXRD of the obtained compound is similar to figure-2.

Example-4: Preparation of crystalline form-N of Lorlatinib

Dissolved Lorlatinib (2 g) in ethanol (20 ml) at 25-30°C. The resultant solution was added to pre-cooled n-heptane (300 ml) at 0-5°C and stirred for 30 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 1500 mg. PXRD of the obtained compound is as illustrated in figure-3.

Example-5: Preparation of crystalline form-S1 of Lorlatinib

Dissolved Lorlatinib (2 g) in n-pentanol (100 ml) at 80-85°C. The resultant solution was added to pre-cooled n-heptane (300 ml) at 0-5°C and stirred for 20 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 1 g. PXRD of the obtained compound is as illustrated in figure-4.

Example-6: Preparation of Amorphous form of Lorlatinib

Dissolved Lorlatinib (500 mg) in 2-pentanone (1 ml) at 25-30°C. The resultant solution was cooled to 0-5°C. n-Heptane (30 ml) was added to the above solution at 0-5°C and stirred for 90 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 460 mg. PXRD of the obtained compound is as illustrated in figure-5.

Example-7: Preparation of Amorphous form of Lorlatinib

Dissolved Lorlatinib (500 mg) in acetone (3 ml) at 25-30°C. The resultant solution was added to pre-cooled mixture of n-heptane and water (60 ml) at 0-5°C and stirred for 90

minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 450 mg.

Example-8: Preparation of Amorphous form of Lorlatinib

Dissolved Lorlatinib (200 mg) in ethyl acetate (3 ml) at 70-75°C. The resultant solution was cooled to 0-5°C. n-Heptane (30 ml) was added to above solution at 0-5°C and stirred for 10 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 150 mg.

Example-9: Preparation of Amorphous form of Lorlatinib

Dissolved Lorlatinib (200 mg) in methyl isobutyl ketone (3 ml) at 95-100°C. The resultant solution was cooled to 0-5°C. n-Heptane (30 ml) was added to above solution at 0-5°C and stirred for 10 minutes at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 150 mg.

Example-10: Preparation of crystalline form-M of Lorlatinib

Dissolved Lorlatinib (15 g) in 2-butanol (150 ml) at 95-100°C. Cooled the solution to 0-5°C and stirred for 1 hour at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 12 g. PXRD of the obtained compound is as illustrated in figure-6.

Drawings

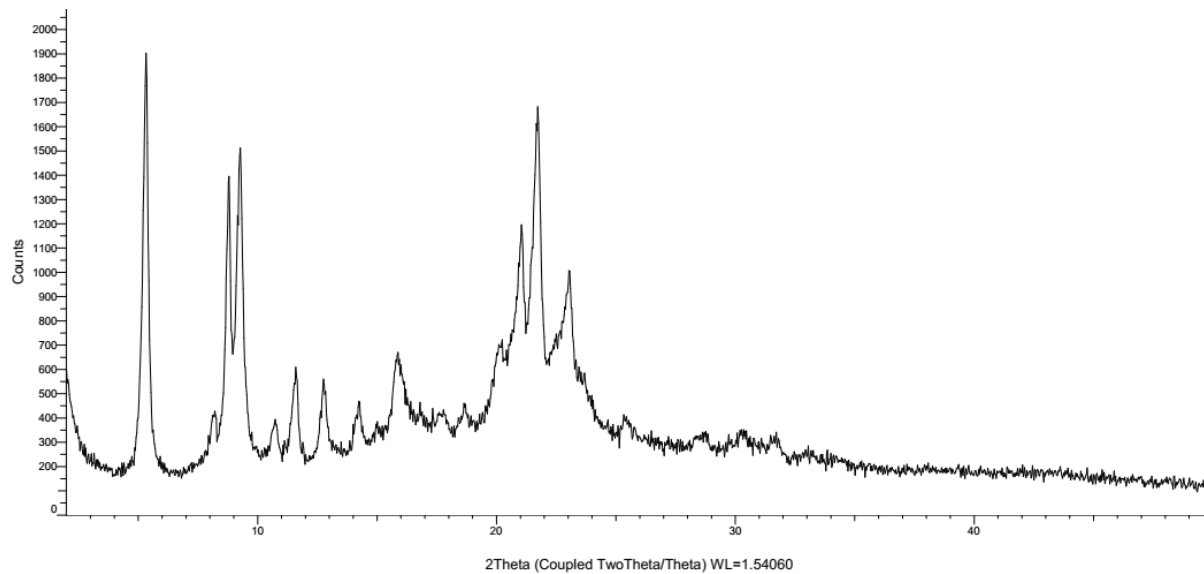


Figure-1

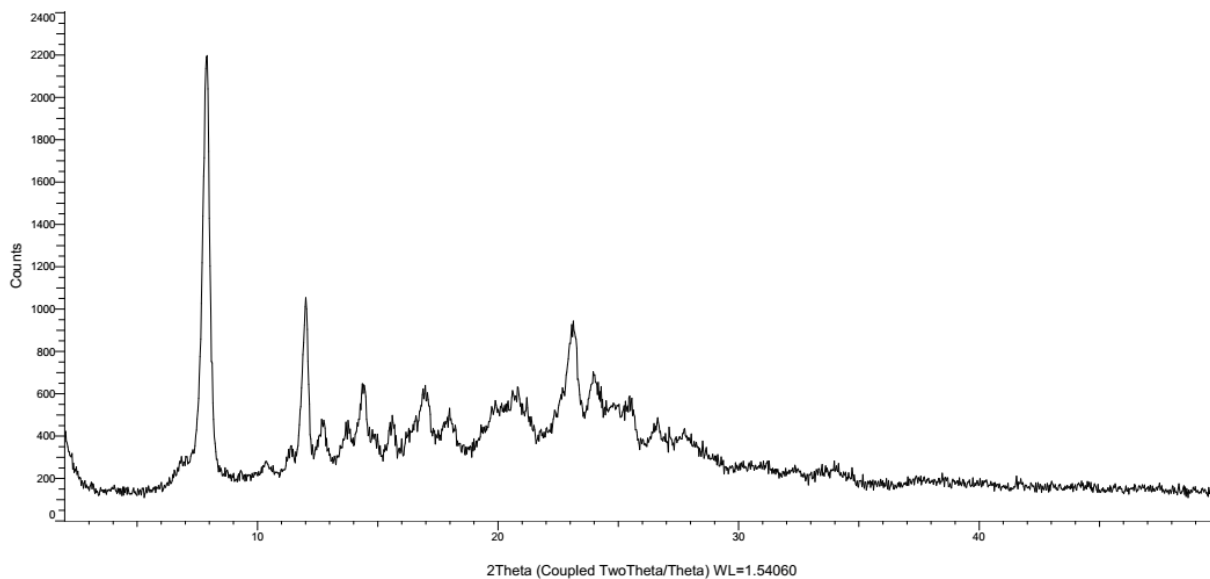


Figure-2

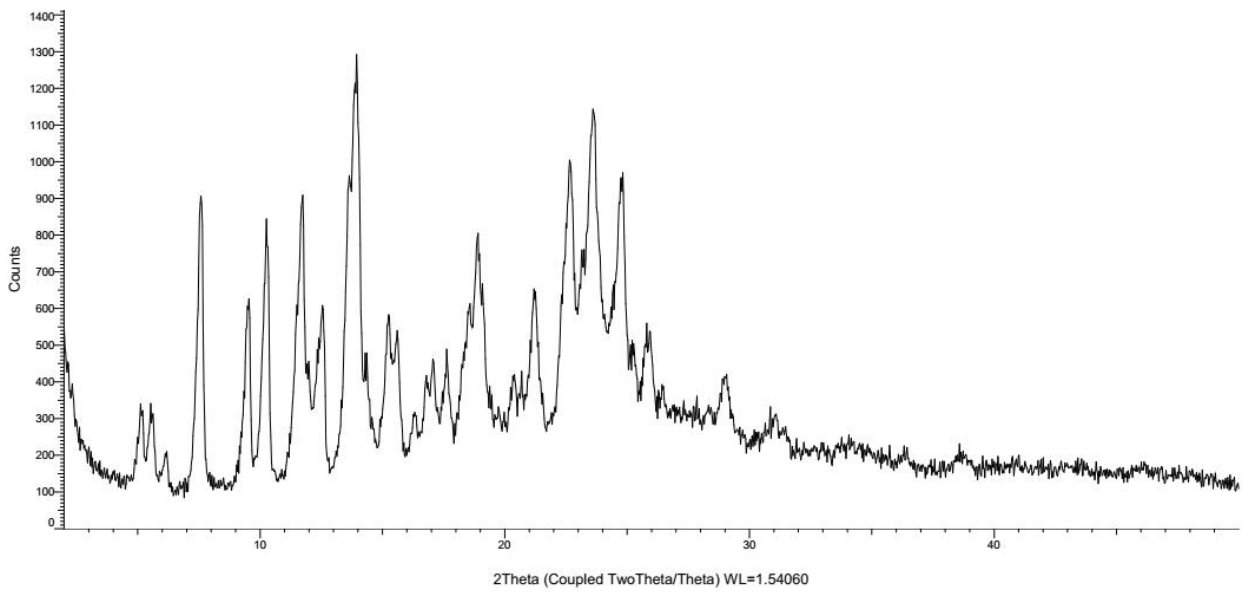


Figure-3

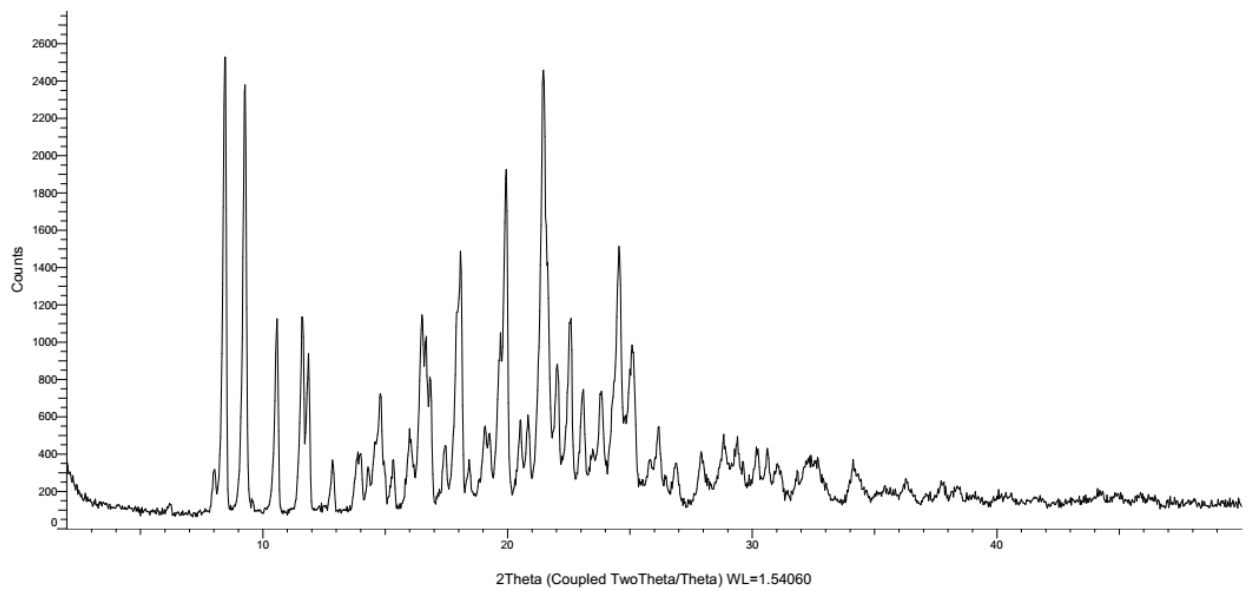


Figure-4

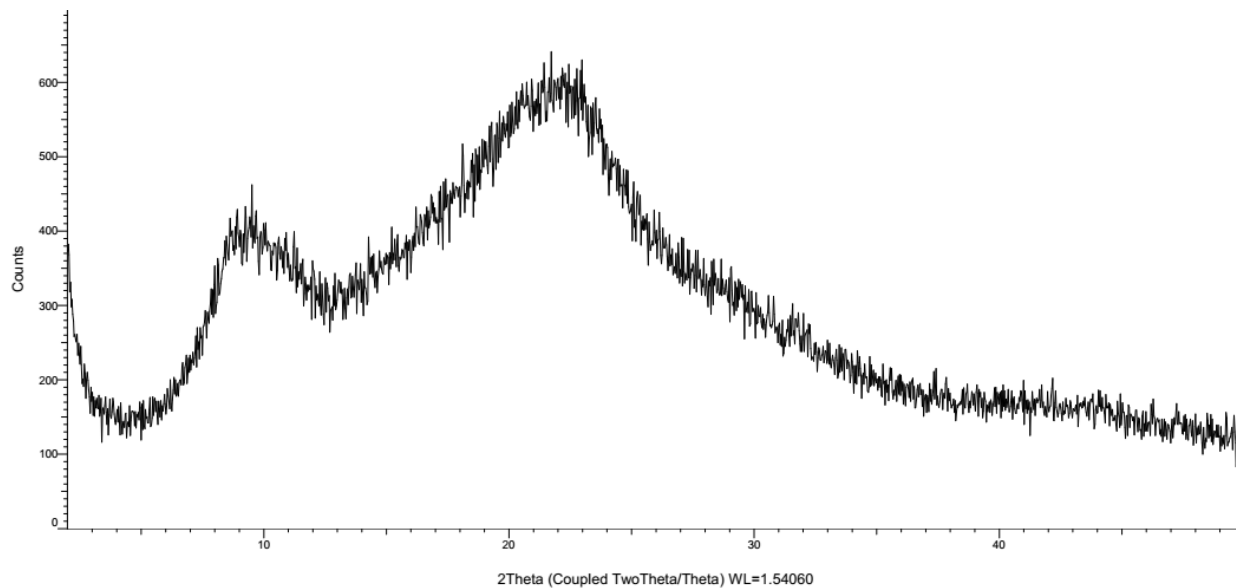


Figure-5

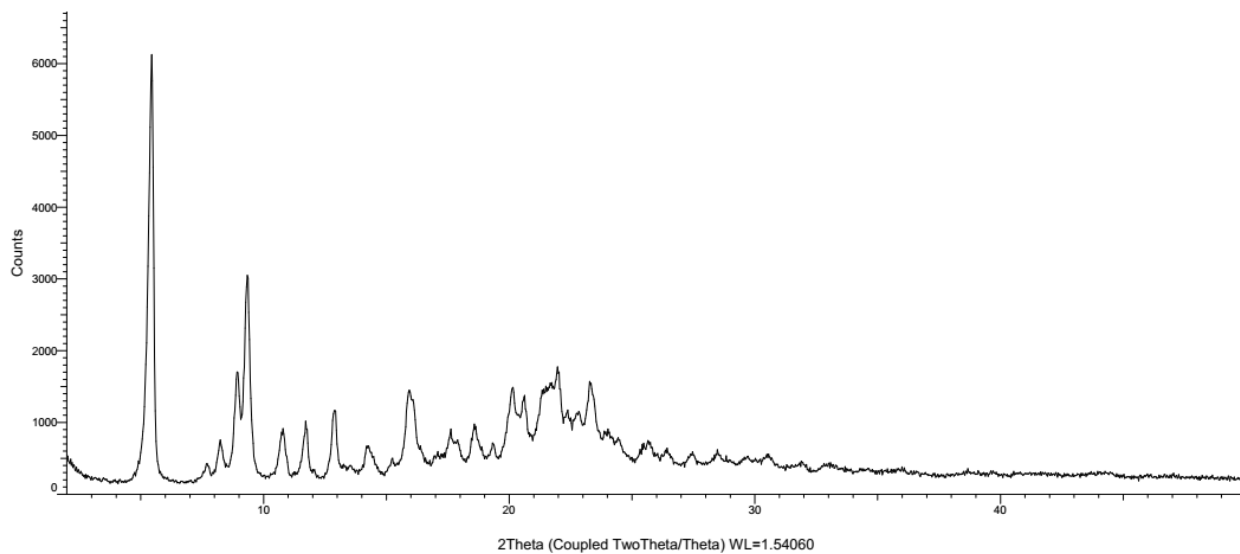


Figure-6
