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Novel polymorph of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-4 tetradecine-3-carbonitrile and its process for the preparation thereof

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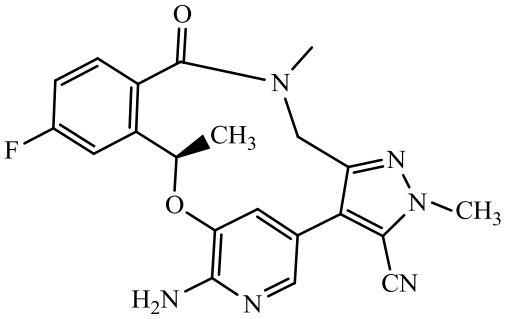
Novel polymorph of (10*R*)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-methenopyrazolo[4,3-*h*][2,5,11]Benzoxadiazacyclo tetradecine-3-carbonitrile and its process for the preparation thereof

Field of the invention:

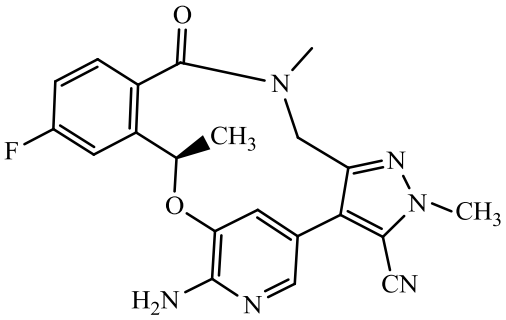
The present invention provides novel polymorph of (10*R*)-7-amino-12-fluoro-2,10, 16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-methenopyrazolo[4,3*h*] [2,5,11] benzoxa diazacyclotetradecine-3-carbonitrile represented by following structural formula-1 and its process for the preparation thereof.



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. This

patent also discloses the process for the preparation of Lorlatinib.

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 Ul, form U2, form Gamma, form Epsilon, form X, form El and form E2 of Lorlatinib and its fumarate form Fl, benzoate form Bl, nicotinate form Nl, mesylate form Sl, tosylate form Tl, hydrobromide form Hl, L-malate form Ll, citrate form Cl, L-tartarate form Rl and maleate forms Ml, 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 polymorph 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-S2.

The second embodiment of the present invention provides process for the preparation of crystalline form-S2 of Lorlatinib.

Brief description of the drawings:

Figure-1: Illustrates the powder X-Ray diffraction pattern of crystalline form-S2 of Lorlatinib.

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, l, 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-S2.

The first aspect of first embodiment provides the crystalline form-S2 of Lorlatinib characterized by its Powder X-Ray diffractogram substantially in accordance with figure-1.

The second aspect of the first embodiment provides the use of crystalline form-S2 of Lorlatinib for the preparation of pharmaceutical formulations.

The third aspect of the first embodiment provides pharmaceutical composition comprising crystalline form-S2 of Lorlatinib 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.

The fourth aspect of the first embodiment provides a pharmaceutical composition comprising crystalline form 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.

The second embodiment of the present invention provides a process for the preparation of crystalline form-S2 of Lorlatinib, comprising:

a) dissolving Lorlatinib in hexanoic acid,
b) isolating crystalline form-S2 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-S2 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-S2 of Lorlatinib.

In the above process, the solution obtained in step-a) optionally heating to 40-70°C.

The crystalline form-S2 of Lorlatinib of the present invention is prepared by the process as illustrated in the present invention and is 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.

Crystalline form-S2 of Lorlatinib obtained according to the present invention is having a purity of >98%, preferably >99%, more preferably >99.5% by HPLC.

Crystalline form-S2 of Lorlatinib produced by the process 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 form-S2 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 form-S2 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 CuKα radiation of wavelength 1.5406A° and at a continuous scan speed of 0.03°/min.

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

Example:

Example-1: Preparation of crystalline form-S2 of Lorlatinib

Dissolved Lorlatinib (500 mg) in hexanoic acid (4 ml) at 25-30°C and stirred for 10 minutes at the same temperature. Heated the solution to 60-65°C and stirred for 1 hour at the same temperature. Filtered the precipitated solid and dried to get the title compound.

Yield: 350 mg. PXRD of the obtained compound is as illustrated in figure-1.

Drawings

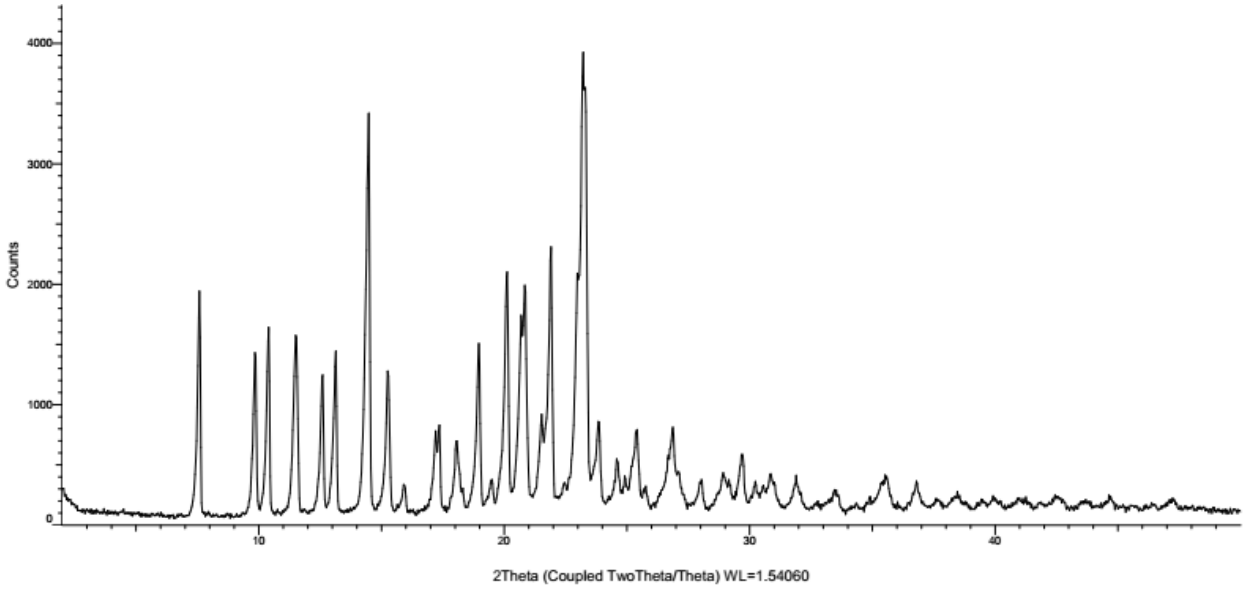


Figure-1

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