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(54) Title: SOLID FORMS OF MOMELOTINIB SALTS AND IMPROVED PROCESSES FOR THE PREPARATION OF MOMELOTINIB

(57) Abstract: The present invention relates to the Amorphous Solid Dispersions (ASDs) of Momelotinib di-hydrochloride and processes for preparation thereof. Compared to a crystalline form, a stable amorphous form of Momelotinib di-hydrochloride enhances the solubility of the drug. The stable amorphous solid dispersions of Momelotinib di- hydrochloride reported herein can be easily reproduced and are amenable for processing into a dosage form. The present invention further provides processes for preparing Momelotinib salts and their use as means to purify the free base. Further, the process of preparation of Momelotinib free base via the neutralization of certain salt forms of Momelotinib significantly improves the chemical purity of the free base.

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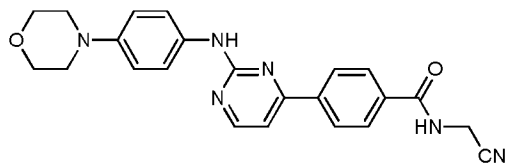
FIELD OF THE INVENTION

The present invention relates to the Amorphous Solid Dispersions (ASDs) of Momelotinib di-hydrochloride and processes for preparation thereof. Also, it relates to the processes of preparing Momelotinib salts and their use as means to purify the free base.

BACKGROUND OF THE INVENTION

The IUPAC name of drug, Momelotinib is N-(Cyanomethyl)-4-{2-[4-(morpholin-4-yl)anilino]pyrimidin-4-yl}benzamide, and is represented by the structure of formula below:



Momelotinib

Momelotinib is a potent, selective, and orally bioavailable JAK1, JAK2 & ACVR1 inhibitor which is being developed by Sierra Oncology, Inc. as a therapeutic agent in the treatment of myelofibrosis.

US 9809559 B2 discloses the PXRD and thermal characterization data for two forms of the di-hydrochloride salt (anhydrous Form I and monohydrate Form II) and two forms of the mono-hydrochloride salt (anhydrous Forms I and III).

It is very well known that crystalline solids normally require a significant amount of energy for dissolution due to their highly organized, lattice like structures. For example, the energy required for a drug molecule to escape from a crystal is more than from an amorphous or a non-crystalline form. It is also well known that the amorphous forms in a number of drugs exhibit different dissolution characteristics and, in some cases, different bioavailability patterns as compared to the crystalline form (*Chem. Pharm. Bull.* **1990**, *38*, 2003). For some therapeutic indications, one bioavailability pattern may be favored over another. Amorphous form of Cefuroxime axetil, Venetoclax and Apalutamide are good examples that exhibit higher

bioavailability than the crystalline form. Therefore, it is desirable to have amorphous forms of drugs with high purity to meet the needs of regulatory agencies and also have highly reproducible processes for their preparation.

Amorphous solid dispersions of drugs are known to generally improve the stability and solubility of drug products. However, such dispersions are generally unstable over time. Amorphous solid dispersions of drugs tend to convert to crystalline forms over time, which can lead to improper dosing due to differences of the solubility of crystalline drug material compared to amorphous drug material. In view of the above, it is therefore, desirable to prepare a stable amorphous form of Momelotinib salts, particularly Momelotinib di-hydrochloride. The present invention, however, provides stable amorphous dispersions of Momelotinib di-hydrochloride. Moreover, the present invention provides solid dispersions of Momelotinib di-hydrochloride which may be reproduced easily and is amenable for processing into a dosage form.

Momelotinib free base exhibits low to extremely low solubility in common organic solvents (such as methanol, ethyl acetate, isopropanol, ethanol, acetonitrile and dichloromethane) and is quite resistant to purification via usually employed techniques such as re-crystallization, trituration and column chromatography. US8486941B2 describes the synthesis and NMR characterization of Momelotinib free base and its hydrochloride, sulfate and methanesulfonate salts. The present inventors have observed that the process of preparation of Momelotinib free base via the neutralization of certain salt forms (e.g., hydrochloride, di-hydrochloride, besylate) of Momelotinib improves the chemical purity.

Finding a suitable excipient and process to form a stable ASD with Momelotinib di-hydrochloride is no way obvious. The process required the inventors to undertake extensive screening of excipients, solvents (that will dissolve both API and excipient) and conditions for solvent removal. For example, lyophilization of a solution of Momelotinib di-hydrochloride in water or water-acetonitrile did not afford a pure amorphous phase even after being ground together with Syloid. Similarly, a mixture of Momelotinib di-hydrochloride and PVP K-30, when taken in water alone,

led to an opalescent solution which soon started to flocculate. With regards to the purification of Momelotinib, it is apparent that not all salts of Momelotinib are serviceable for this purpose.

SUMMARY OF THE INVENTION

An aspect of the present invention provides an amorphous solid dispersion of di-hydrochloride salt of Momelotinib together with at least one pharmaceutically acceptable excipient.

Another aspect of the present invention provides a stable amorphous premix comprising an amorphous solid dispersion of di-hydrochloride salt of Momelotinib together with at least one pharmaceutically acceptable excipient and Syloid.

Another aspect of the present invention provides a process for the preparation of amorphous solid dispersion of di-hydrochloride salt of Momelotinib, comprising the steps of providing a solution of di-hydrochloride salt of Momelotinib together with at least one pharmaceutically acceptable excipient in a solvent and removing the solvent.

Yet another aspect of the present invention provides a process for the preparation of Momelotinib, comprising the step of releasing Momelotinib free base from its salt by neutralization.

Yet another aspect of the present invention provides the salt form of Momelotinib selected from the group consisting of *p*-toluenesulfonate (tosylate), benzenesulfonate (besylate) and trifluoromethanesulfonate (triflate) salts of Momelotinib.

Yet another aspect of the present invention provides a pharmaceutical composition comprising Momelotinib or its di-hydrochloride salt, obtained according to the processes of above aspects and at least one pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an illustrative X-ray powder diffraction pattern of amorphous solid dispersion of Momelotinib di-hydrochloride and PVP K-30 prepared by the method of Example No. 2(a).

Figure 2 is an illustrative X-ray powder diffraction pattern of premix of amorphous solid dispersion of Momelotinib di-hydrochloride and PVP K-30 with Syloid prepared by the method of Example No. 2(b).

Figure 3 is an illustrative X-ray powder diffraction pattern of amorphous solid dispersion of Momelotinib di-hydrochloride and Copovidone prepared by the method of Example No. 2(c).

Figure 4 is an illustrative X-ray powder diffraction pattern of premix of amorphous solid dispersion of Momelotinib di-hydrochloride and Copovidone with Syloid prepared by the method of Example No. 2(d).

Figure 5 is an illustrative X-ray powder diffraction pattern of Momelotinib di-hydrochloride prepared by the method of Example No. 3(a).

Figure 6 is an illustrative X-ray powder diffraction pattern of Momelotinib mesylate prepared by the method of Example No. 3(b).

Figure 7 is an illustrative X-ray powder diffraction pattern of Momelotinib tosylate prepared by the method of Example No. 3(c).

Figure 8 is an illustrative X-ray powder diffraction pattern of Momelotinib besylate prepared by the method of Example No. 3(d).

Figure 9 is an illustrative X-ray powder diffraction pattern of Momelotinib triflate prepared by the method of Example No. 3(e).

Figure 10 is an illustrative X-ray powder diffraction pattern of Momelotinib sulfate prepared by the method of Example No. 3(f).

Figure 11 is an illustrative X-ray powder diffraction pattern of Momelotinib hydrochloride prepared by the method of Example No. 3(g).

Figure 12 is an illustrative X-ray powder diffraction pattern of Momelotinib free base prepared by the method of Example No. 4(h).

DETAILED DESCRIPTION OF THE INVENTION

An aspect of the present invention provides an acid addition salt of Momelotinib, wherein salt is selected from a group comprising tosylate, besylate and triflate.

Another aspect of the present invention provides an acid addition salt of Momelotinib, wherein salt is selected from a group consisting tosylate, besylate and triflate.

Yet another aspect of the present invention provides a tosylate salt of Momelotinib, characterized by X-ray powder diffraction (XRPD) pattern comprising peaks at 4.46°, 10.38°, 13.90°, 14.74°, 16.53°, 23.07°, 20.33°, 23.92°, 26.34° and 27.78° ± 0.2° 2θ or an XRPD pattern as depicted in Figure 7.

Yet another aspect of the present invention provides the tosylate salt, wherein an XRPD pattern comprising peaks at 8.90°, 9.47°, 11.44°, 13.32°, 15.27°, 16.20°, 17.36°, 19.07°, 19.63°, 20.80° and 22.26° ± 0.2° 2θ.

Yet another aspect of the present invention provides the tosylate salt, wherein an XRPD pattern comprising peaks at 22.67°, 24.41°, 24.93°, 25.87°, 28.88°, 29.84°, 31.03°, 33.63°, 34.40°, 35.39°, 36.66° and 38.89° ± 0.2° 2θ.

Yet another aspect of the present invention provides a besylate salt of Momelotinib, characterized by an XRPD pattern comprising peaks at 4.77°, 14.61°, 15.15°, 16.09°, 17.54°, 18.11°, 19.19°, 23.10°, 23.70°, and 24.49° ± 0.2° 2θ or an XRPD pattern as depicted in Figure 8.

Yet another aspect of the present invention provides the besylate salt, wherein an XRPD pattern comprising peaks at 8.29°, 9.55°, 10.31°, 10.87°, 11.62°, 13.16°, 13.85°, 14.12°, 18.93°, 19.86°, 20.72°, 21.85°, 22.54°, 23.38° and 24.85° ± 0.2° 2θ.

Yet another aspect of the present invention provides the besylate salt, wherein an XRPD pattern comprising peaks at 25.78°, 26.35°, 27.22°, 28.06°, 28.80°, 29.92°, 31.08°, 31.60°, 33.05°, 33.63°, 34.70°, 34.87°, 35.55°, 36.88°, 37.28°, 38.37° and 39.02° ± 0.2° 2θ.

Yet another aspect of the present invention provides a triflate salt of Momelotinib, characterized by an XRPD pattern comprising peaks at 15.13°, 18.09°, 19.09°, 20.24°, 21.29°, 21.71°, 22.89°, 24.10°, 27.77° and 30.32° ± 0.2° 2θ or an XRPD pattern as depicted in Figure 9.

Yet another aspect of the present invention provides the triflate salt, wherein an XRPD pattern comprising peaks at 5.38°, 8.40°, 9.89°, 10.14°, 10.58°, 10.88°, 11.59°, 13.56°, 13.91°, 15.33°, 15.80°, 16.30°, 17.35°, 18.52° and 19.73° ± 0.2° 2θ.

Yet another aspect of the present invention provides the triflate salt, wherein an XRPD pattern comprising peaks at 23.51°, 25.23°, 25.64°, 26.60°, 27.33°, 28.12°, 28.56°, 30.74°, 31.38°, 32.17°, 35.16°, 36.34°, 37.86°, 38.25° and 38.85° ± 0.2° 2θ.

Yet another aspect of the present invention provides the salt, wherein the salt is crystalline.

Yet another aspect of the present invention provides a solid dispersion comprising momelotinib di-hydrochloride and at least one pharmaceutically acceptable excipient.

Yet another aspect of the present invention provides the solid dispersion, wherein the solid dispersion is amorphous solid dispersion.

Yet another aspect of the present invention provides the solid dispersion, wherein the pharmaceutically acceptable excipient is selected from a group comprising polyvinyl pyrrolidone, povidone K-30, povidone K-60, Povidone K-90, polyvinylpyrrolidone, vinylacetate, co-povidone NF, polyvinylacetal diethylaminoacetate (AEA®), polyvinyl acetate phthalate, polysorbate 80, polyoxyethylene–polyoxypropylene copolymers (Poloxamer® 188), polyoxyethylene (40) stearate, polyethyene glycol, monomethyl ether, polyethyene glycol, poloxamer 188, pluronic F-68, methylcellulose, methacrylic acid copolymer (Eudragit or Eudragit-RLPO), hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate (HPMC-AS), hydroxypropylmethyl cellulose, hydroxypropyl cellulose-SSL (HPC-SSL), hydroxypropyl cellulose SL(HPC-SL), hydroxypropyl

cellulose L (HPC-L), hydroxyethyl cellulose, Soluplus® (polyvinyl caprolactam-polyvinyl acetatepolyethylene, glycol graft copolymer (PCL-PVAc-PEG)), gelucire 44/14, ethyl cellulose, D-alpha-tocopheryl polyethylene glycol 1000 succinate, cellulose acetate phthalate, carboxymethylethylcellulose, cyclodextrins, gelatins, hypromellose phthalates, sugars, polyhydric alcohols, water soluble sugar excipients, polyethylene oxides, polyoxyethylene derivatives, polyvinyl alcohols, propylene glycol derivatives and the like, organic amines such as alkyl amines and guanidine or its derivatives, colloidal silica, and mixtures thereof.

Yet another aspect of the present invention provides the process for preparation of solid dispersion comprising the step of combining momelotinib di-hydrochloride with at least one pharmaceutically acceptable excipient in the presence of a suitable solvent.

Yet another aspect of the present invention provides the process, wherein the solvent is selected from a group comprising methanol, ethanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 2-pentanol, 3-pentanol, tetrahydrofuran, 2-methyl-tetrahydrofuran, 1-4-dioxane, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, dimethylacetamide, methyl ethyl ketone, methyl isobutyl ketone, methyl acetate, ethyl acetate, isopropyl acetate, water, and mixtures thereof.

Yet another aspect of the present invention provides a process for the preparation of momelotinib free base, comprising preparing momelotinib salt and converting the momelotinib salt to momelotinib free base.

Yet another aspect of the present invention provides the process, wherein the salt is an acid addition salt.

Yet another aspect of the present invention provides the process, wherein the acid addition salt is selected from a group comprising hydrochloride, di-hydrochloride, bromide, sulfate, phosphate, perchlorate, formate, oxalate, trifluoroacetate, trichloroacetate, mesylate, tosylate, besylate, triflate, napsylate, camphorsulfonate and p-nitrobenzenesulfonate.

Yet another aspect of the present invention provides the process, wherein the acid addition salt of Momelotinib is selected from a group comprising tosylate, besylate, hydrochloride, di-hydrochloride or triflate.

Yet another aspect of the present invention provides the process, wherein the final momelotinib free base has a purity of more than about 98.5% by HPLC.

Yet another aspect of the present invention provides the process, wherein converting the momelotinib salt to momelotinib free base comprises neutralizing the momelotinib salt with a base.

Yet another aspect of the present invention provides the process, wherein the base is an inorganic base selected from a group comprising a hydroxide, an alkali metal carbonate, an alkali metal bicarbonate, and a combination thereof, or an organic base selected from a group comprising triethylamine, diisopropylethylamine, pyridine, 2,6-dimethylpyridine, and a combination thereof.

Yet another aspect of the present invention provides the process, wherein the neutralization is carried out in a solvent selected from a group comprising ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran, MTBE, dioxane, and dimethoxyethane; alcohols, such as methanol, ethanol, ethylene glycol, 1-propanol, 2-propanol, 2-methoxyethanol, 1-butanol, 2-butanol, iso-butyl alcohol, t-butyl alcohol, glycerol, and C_1-C_6 alcohols; halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride, and chlorobenzene; aromatic hydrocarbons, such as toluene; aliphatic hydrocarbons such as hexane and heptane; nitriles such as acetonitrile; esters such as ethyl acetate; polar aprotic solvents such as DMF, DMSO, DMAc; water and any mixtures of two or more thereof.

Yet another aspect of the present invention provides the process, wherein the solvent is water.

Yet another aspect of the present invention provides the process, wherein obtained momelotinib is crystalline.

Yet another aspect of the present invention provides a solid form of momelotinib free base characterized by an XRPD pattern comprising peaks at 4.21, 12.76, 15.26, 17.45, 20.01, 20.75, 21.72, 23.53, 26.13 and 28.02° ± 0.2° 2θ or an XRPD pattern as depicted in Figure 12.

Yet another aspect of the present invention provides the solid form, wherein an XRPD pattern comprising peaks at 8.36°, 10.15°, 11.13°, 11.96°, 13.96°, 15.99°, 16.37°, 18.69°, 24.12°, 24.53°, 25.53°, 27.11° and 29.30° ± 0.2° 2θ.

Yet another aspect of the present invention provides the solid form, wherein an XRPD pattern comprising peaks at 29.84°, 30.88°, 31.47°, 32.87°, 33.39°, 34.07°, 34.54°, 35.11°, 35.78°, 37.23°, 38.06° and 39.07° ± 0.2° 2θ.

Yet another aspect of the present invention provides the free base, wherein the free base is crystalline.

Yet another aspect of the present invention provides a pharmaceutical composition comprising an acid addition salt, or a solid dispersion, or a solid form, or a free base and optionally a pharmaceutically acceptable excipient.

Yet another aspect of the present invention provides a method of preventing or treating a condition or a disorder or a disease in a subject, comprising administering to the subject an effective amount of an acid addition salt, or a solid dispersion, or a solid form, or a free base or a pharmaceutical composition, wherein the condition or disorder or disease can be ameliorated with Janus kinase (JAK) inhibition.

Yet another aspect of the present invention provides an acid addition salt, or a solid dispersion, or a solid form, or a free base or a pharmaceutical composition, used for the condition or disorder or disease that can be ameliorated with Janus kinase (JAK) inhibition.

Yet another aspect of the present invention provides pharmaceutical composition or a solid form or a free base or a process, wherein at least one pharmaceutically acceptable excipient may be selected from the group consisting of polyvinyl pyrrolidone, povidone K-30, povidone K-60, Povidone K-90, polyvinylpyrrolidone vinylacetate, co-povidone NF, polyvinylacetal

diethylaminoacetate (AEA®), polyvinyl acetate phthalate, polysorbate 80, polyoxyethylene–polyoxypropylene copolymers (Poloxamer® 188), polyoxyethylene (40) stearate, polyethyene glycol monomethyl ether, polyethyene glycol, poloxamer 188, pluronic F-68, methylcellulose, methacrylic acid copolymer (Eudragit or Eudragit-RLPO), hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate (HPMC-AS), hydroxypropylmethyl cellulose, hydroxypropyl cellulose SSL (HPC-SSL), hydroxypropyl cellulose SL(HPC-SL), hydroxypropyl cellulose L (HPC-L), hydroxyethyl cellulose, Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (PCL-PVAc-PEG)), gelucire 44/14, ethyl cellulose, D-alpha-tocopheryl polyethylene glycol 1000 succinate, cellulose acetate phthalate, carboxymethylethylcelluloseand the like; cyclodextrins, gelatins, hypromellose phthalates, sugars, polyhydric alcohols, and the like; water soluble sugar excipients, preferably having low hygroscopicity, which include, but are not limited to, mannitol, lactose, fructose, sorbitol, xylitol, maltodextrin, dextrates, dextrins, lactitol and the like; polyethylene oxides, polyoxyethylene derivatives, polyvinyl alcohols, propylene glycol derivatives and the like; organic amines such as alkyl amines (primary, secondary, and tertiary), aromatic amines, alicyclic amines, cyclic amines, aralkyl amines, hydroxylamine or its derivatives, hydrazine or its derivatives, and guanidine or its derivatives, or any other excipient at any aspect of present application. The use of mixtures of more than one of the pharmaceutical excipients to provide desired release profiles or for the enhancement of stability is within the scope of this invention. Also, all viscosity grades, molecular weights, commercially available products, their copolymers, and mixtures are all within the scope of this invention without limitation. Solid dispersions of the present application also include the solid dispersions obtained by combining di-hydrochloride salt of Momelotinib with a suitable non-polymeric excipient by employing techniques known in the art or procedures described or exemplified in any aspect of the present invention.

Another aspect of the present invention provides a stable amorphous premix comprising an amorphous solid dispersion of di-hydrochloride salt of Momelotinib together with at least one pharmaceutically acceptable excipient and Syloid. Syloid may be Syloid 244 FP.

In another aspect of the present invention, the amorphous solid dispersion of di-hydrochloride salt of Momelotinib may be combined with Syloid or any other suitable additional pharmaceutically acceptable excipient to obtain premix of this aspect.

In another aspect of the present invention, the amorphous solid dispersion of di-hydrochloride salt of Momelotinib may be combined with Syloid or any other suitable additional excipient using a technique known in art or according to the previous aspects of the present invention such as grinding together in mortar-pestle.

Yet another aspect of the present invention provides a pharmaceutical composition comprising amorphous solid dispersion of di-hydrochloride salt of Momelotinib or premix thereof.

Yet another aspect of the present invention provides a process for the preparation of amorphous solid dispersion of di-hydrochloride salt of Momelotinib, comprising the step of providing a solution of di-hydrochloride salt of Momelotinib together with at least one pharmaceutically acceptable excipient in a solvent and removing the solvent.

In another aspect of the present invention, the process produces amorphous solid dispersion of di-hydrochloride salt of Momelotinib.

In another aspect of the present invention, the solvent may be selected from the group consisting of methanol, ethanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 2-pentanol, 3-pentanol, tetrahydrofuran, 2-methyl-tetrahydrofuran, 1-4-dioxane, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, dimethylacetamide, methyl ethyl ketone, methyl isobutyl ketone, methyl acetate, ethyl acetate, isopropyl acetate, water, and mixtures thereof.

In another aspect of the present invention, providing a solution may be carried out by dissolving di-hydrochloride salt of Momelotinib and at least one pharmaceutically acceptable excipient simultaneously or separately in same or different solvents.

In another aspect of the present invention, a solution of di-hydrochloride salt of Momelotinib and the excipient may be prepared at any suitable temperatures, such as about 0°C to about the reflux temperature of the solvent used. Stirring and heating may be used to reduce the time required for the dissolution process.

In another aspect of the present invention, a solution of di-hydrochloride salt of Momelotinib and the excipient may be filtered to make it clear and free of unwanted particles.

In another aspect of the present invention, the obtained solution may be optionally treated with an adsorbent material, such as carbon and/or hydrose, to remove colored components, etc., before filtration.

In another aspect of the present invention, removal of solvent may be carried out by methods known in the art or any procedure disclosed in the present inventio.

In another aspect of the present invention, removal of solvent may include, but not limited to solvent evaporation under atmospheric pressure or reduced pressure / vacuum such as a rotational distillation using Büchi® Rotavapor®, spray drying, freeze drying, agitated thin film drying and the like.

In a preferred aspect of the present invention, the solvent may be removed under reduced pressures, at temperatures of less than about 100 °C, less than about 80 °C, less than about 40 °C, less than about 20 °C, less than about 0 °C, less than about -20 °C, less than about -40 °C, less than about -60 °C, less than about -80 °C, or any other suitable temperatures.

In another aspect of the present invention, the isolation of an amorphous solid dispersion of di-hydrochloride salt of Momelotinib with excipient involves recovering the solid obtained. The solid may be recovered using techniques such as by scraping,

or by shaking the container, or triturating with a solvent to make slurry followed by filtration, or other techniques specific to the equipment used.

In another aspect of the present invention, the amorphous solid dispersion of di-hydrochloride salt of Momelotinib and excipient obtained may be optionally dried before or after isolating.

Yet another aspect of the present invention provides a process for the preparation of Momelotinib, comprising the step of releasing Momelotinib free base from its salt by neutralization.

In another aspect of the present invention, the neutralization of a salt of Momelotinib may be carried out by treating the salt with a base. Suitable bases may include, but are not limited to hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide, ammonium hydroxide, or the like; alkali metal carbonates, such as, for example, sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, or the like; alkali metal bicarbonates, such as, for example, sodium bicarbonate, potassium bicarbonate, or the like; organic bases, such as triethylamine, diisopropylethylamine, pyridine, 2,6-dimethylpyridine or the like.

In another aspect of the present invention, neutralization may be carried out at a suitable temperature of about 0 °C or above.

In yet another aspect of the present invention, the salt may be treated with a base at a suitable temperature of about 0 °C or above.

In another aspect of the present invention, Momelotinib may be obtained as solid directly on neutralization of the salt of Momelotinib.

In yet another aspect of the present invention, solid may be precipitated by cooling or addition of anti-solvent to the reaction mixture containing Momelotinib.

In another aspect of the present invention, the solid Momelotinib obtained according to the process of this aspect may be separated according suitable techniques such as filtration or centrifugation.

In another aspect of the present invention, the solid Momelotinib may be dried under suitable drying conditions such as suitable temperature and pressure.

In another aspect of the present invention, the solid form of Momelotinib obtained according to the process of this aspect may be in amorphous state.

In another aspect of the present invention, the solid form of Momelotinib obtained according to the process of this aspect may be any crystalline form reported in the literature.

In another aspect of the present invention, the inventors have identified that the process of preparation of Momelotinib through the neutralization of certain salt forms of Momelotinib surprisingly improves the chemical purity significantly as illustrated below.

Salt	**HPLC purity**		
	Free base input for salt formation	**Salt**	**Free base output from salt neutralization**
Besylate	98.21%	99.48%	99.01% (Na_2CO_3 was used for neutralization)
Besylate	98.21%	99.48%	98.52% (NH_4OH was used for neutralization)
Tosylate	98.21%	97.68%	97.67% (Na_2CO_3 was used for neutralization)
Mesylate	98.21%	99.20%	98.79% (Na_2CO_3 was used for neutralization)
Triflate	98.21%	98.53%	98.26% (Na_2CO_3 was used for neutralization)
Di-hydrochloride	98.21%	99.50%	99.62% (NH_4OH was used for neutralization)
Di-hydrochloride	98.21%	99.50%	99.47% (Na_2CO_3 was used for neutralization)

Hydrochloride	96.22%	98.79%	98.60% (NH_4OH was used for neutralization)

Yet another aspect of the present invention provides Momelotinib obtained according to the processes of the present invention, having a chemical purity of at least 99% or at least 99.5 or at least 99.9%, by HPLC.

In another aspect of present invention, Momelotinib or its pharmaceutically acceptable salt or free base may be prepared according to any of the methods known in the art (*J. Heterocycl. Chem.*, **2017**, *54*, 2902-2905 *and J. Chem. Res.*, **2016**, *40*, 511-513).

In another aspect of the present invention, ASDs of Momelotinib salt is used for the treatment of cancer such as myelofibrosis.

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the application in any manner. Variations of the described procedures, as will be apparent to those skilled in the art, are intended to be within the scope of the present application.

DEFINITIONS

The term "about" when used in the present application preceding a number and referring to it, is meant to designate any value which lies within the range of ±10%, preferably within a range of ±5%, more preferably within a range of ±2%, still more preferably within a range of ±1 % of its value. The term “inert solvent” when used in the present application is a solvent that does not react with the reactants or reagents under conditions that cause the chemical reaction indicated to take place.

"Substantially" amorphous denotes that 90 %, preferably 95 % or 99 %, more preferably all of the di-hydrochloride salt of Momelotinib being present in the solid dispersion, on the adsorbate or in the pharmaceutical composition is amorphous. In

other words, an "amorphous" Momelotinib di-hydrochloride salt composition denotes a Momelotinib di-hydrochloride salt-containing composition, which does not contain substantial amounts, preferably does not contain noticeable amounts, of crystalline portions of Momelotinib di-hydrochloride salt e.g., measurable upon X-ray powder diffraction analysis.

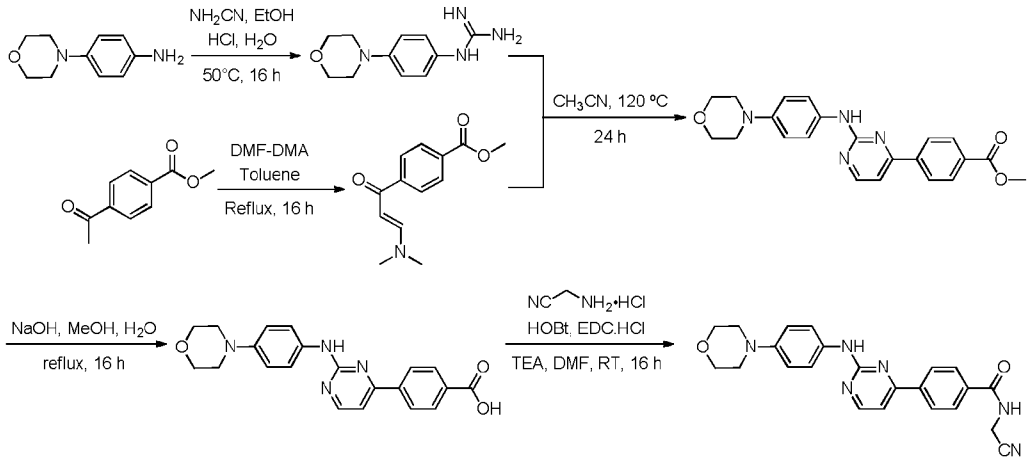
The term "solid dispersion" when used in the present application, denotes a state where most of the di-hydrochloride salt of Momelotinib, preferably 90%, 95% or all of the di-hydrochloride salt of Momelotinib of the solid dispersion, is homogeneously molecularly dispersed in a solid polymer matrix. Preferably solid dispersion, relates to a molecular dispersion where the API (active pharmaceutical ingredient) and polymer molecules are uniformly but irregularly dispersed in a non-ordered way. In other words, in a solid dispersion, the two components (polymer and API) form a homogeneous one-phase system, where the particle size of the API in the solid dispersion is reduced to its molecular size. In a preferred embodiment, in the solid dispersion according to the present invention no chemical bonds can be detected between the API and the polymer. In order to arrive at such a solid dispersion, preferably solid solution, it is required to have a substantial amount of API dissolved in a suitable solvent at least at one time point during preparation of said solid dispersion.

EXAMPLES

The scope of the present invention is illustrated by the following examples as disclosed herein which are not meant to restrict the scope of the invention in any manner whatsoever.

Example 1: Preparation of Momelotinib

Momelotinib may be prepared according to any of the methods known in the art such as *Heterocycl. Chem., 2017, 54, 2902-2905* and *J. Chem. Res., 2016, 40, 511-513* (Scheme 1).



Scheme 1

Example 2: Preparation of amorphous solid dispersion (ASD) of Momelotinib di-hydrochloride

2(a): Preparation of ASD with PVP K-30.

To a mixture of acetonitrile (5 mL) and DI-water (15 mL), Momelotinib di-hydrochloride (80 mg) followed by PVP K-30 (80 mg) were added at 27 °C. The resultant mixture was stirred at the same temperature for 15 minutes. The solution obtained was filtered and was then frozen at -78 °C. The frozen solution was lyophilized for 18 hours under reduced pressure to obtain 145 mg of the title compound. PXRD: Amorphous.

2(b): Preparation of ASD with PVP K-30, and its premix with Syloid

To a mixture of acetonitrile (5 mL) and DI-water (15 mL), Momelotinib di-hydrochloride (80 mg) followed by povidone K-30 (80 mg) were added at 27 °C. The resultant mixture was stirred at the same temperature for 15 minutes. The solution obtained was filtered and was then frozen at -78 °C. The frozen solution was lyophilized for 18 hours under reduced pressure to obtain 145 mg of the solid dispersion. The solid dispersion (40 mg) was mixed with Syloid 244 FP (40 mg) and

ground in a mortar-pestle for 10-15 minutes to obtain the title premix: PXRD: Amorphous.

2(c): Preparation of ASD with Copovidone.

To a mixture of acetonitrile (10 mL) and DI-water (20 mL), Momelotinib di-hydrochloride (80 mg) followed by Copovidone (80 mg) were added at 27 °C. The resultant mixture was stirred at the same temperature for 15 minutes. The solution obtained was filtered and was then frozen at -78 °C. The frozen solution was lyophilized for 18 hours under reduced pressure to obtain 148 mg of the title compound. PXRD: Amorphous.

2(d): Preparation of ASD with Copovidone, and its premix with Syloid

To a mixture of acetonitrile (10 mL) and DI-water (20 mL), Momelotinib di-hydrochloride (80 mg) followed by Copovidone (80 mg) were added at 27 °C. The resultant mixture was stirred at the same temperature for 15 minutes. The solution obtained was filtered and was then frozen at -78 °C. The frozen solution was lyophilized for 18 hours under reduced pressure to obtain 148 mg of the title compound as solid dispersion. The solid dispersion (40 mg) was mixed with Syloid 244 FP (40 mg) and ground in a mortar-pestle for 10-15 minutes to obtain the title premix. PXRD: Amorphous.

Example 3: Preparation of Momelotinib salts

3(a): Preparation of Momelotinib di-hydrochloride

To a stirred suspension of Momelotinib (1.5 g, HPLC purity: 98.21%) in methanol (135 mL), saturated IPA-HCl (6 mL) was added whereupon the suspension turned in to a clear solution. The reaction mixture turned in to a yellow colored suspension after 20-30 min, and the suspension was stirred for 2 h at room temperature. The suspension was filtered, washed with methanol (4.5 mL) and dried under reduced pressure at 45

°C for 3 h to obtain 1.4 g of the title compound as a yellow colored solid (HPLC purity: 99.50%, HCl content: 14.87% w/w)

3(b): Preparation of Momelotinib mesylate

To a stirred suspension of Momelotinib (500 mg, HPLC purity: 98.21%) in methanol (10 mL), methanesulfonic acid (266.6 mg) was added whereupon the suspension turned in to a clear solution momentarily before converting into a suspension again. The yellow colored suspension obtained was stirred for 2 h at room temperature. The suspension was filtered, washed with methanol (1.5 mL) and dried under reduced pressure at 45 °C for 3 h to obtain 580 mg of the title compound as a yellow colored solid (HPLC purity: 99.20%, methanesulfonic acid content: 31.86%).

3(c): Preparation of Momelotinib tosylate

To a stirred suspension of Momelotinib (500 mg, HPLC purity: 98.21%) in methanol (10 mL), *p*-toluenesulfonic acid (478 mg) was added whereupon the suspension turned in to a clear solution momentarily before converting into a suspension again. The yellow colored suspension obtained was stirred for 2 h at room temperature. The suspension was filtered, washed with methanol (1.5 mL) and dried under reduced pressure at 45 °C for 3 h to obtain 520 mg of the title compound as a yellow colored solid (HPLC purity: 97.68%, *p*-toluenesulfonic acid content: 44.53%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.28 (s, 6H), 3.48 (br. s, 4H), 3.93 (br. s, 4H), 4.36 (d, *J*= 5.6 Hz, 2H), 6.50 (br. s, 3 H), 7.13 (d, *J*=8.0 Hz, 4H), 7.50 (d, *J*=8.0 Hz, 5H), 7.55 (d, *J*=5.2 Hz,1H), 7.91 (d, *J*=8.4 Hz, 2H), 8.05 (d, *J*=8.4Hz, 2H), 8.30 (d, *J*=8.4 Hz, 2H), 8.62 (d, *J*=5.2 Hz, 1H), 9.36 (t, *J* =5.2 Hz, 1H), 9.99 (s, 1H).

3(d): Preparation of Momelotinib besylate

To a stirred suspension of Momelotinib (500 mg, HPLC purity: 98.21%) in methanol (10 mL), benzenesulfonic acid (439 mg) was added whereupon the suspension turned in to a clear solution momentarily before converting into a suspension again. The

yellow colored suspension obtained was stirred for 2 h at room temperature. The suspension was filtered, washed with methanol (1.5 mL) and dried under reduced pressure at 45 °C for 3 h to obtain 680 mg of the title compound as a yellow colored solid (HPLC purity: 99.48%, benzenesulfonic acid content: 45.30%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.54 (br. s, 4H), 3.95 (br. s, 4H), 4.36 (d, J=5.2 Hz, 2H), 7.33-7.31 (m, 5H), 7.57 (d, J=5.2 Hz, 3H), 7.63-7.61 (m, 3H), 7.94 (d, J=8.8 Hz, 2H), 8.05 (d, J= 8.4Hz, 2H), 8.30 (d, J=8.4 Hz,2H), 8.63 (d, J=8.4 Hz, 1H), 9.38 (t, J =5.2 Hz, 1H), 10.0 (s, 3H).

3(e): Preparation of Momelotinib triflate

To a stirred suspension of Momelotinib (500 mg, HPLC purity: 98.21%) in methanol (10 mL), trifluoromethanesulfonic acid (416.4 mg) was added whereupon the suspension turned in to a clear solution momentarily before converting into a suspension again. The yellow colored suspension obtained was stirred for 2 h at room temperature. The suspension was filtered, washed with methanol (1.5 mL) and dried under reduced pressure at 45 °C for 3 h to obtain 620 mg of the title compound as a yellow colored solid (HPLC purity: 98.53%, triflic acid content: 41.51%). (400 MHz, DMSO-d_6): δ = 3.44 (br. s, 4H), 3.91 (br. s, , 4H), 4.36 (d, J=5.2 Hz, 2H), 6.4- 7.25 (br. s, 2H), 7.42 (d, J=5.6 Hz, 2H), 7.54 (d, J=5.2Hz, 2H), 7.89 (d, J=8.8 Hz, 2H), 8.05 (d, J=8.4 Hz, 2H), 8.30 (d, J =8.4 Hz, 2H), 8.62 (d, J =5.2 Hz, 2H), 9.35 (t, J = 5.2 Hz, 1H), 9.93 (s, 1H).

3(f): Preparation of Momelotinib sulfate

To a stirred suspension of Momelotinib (250 mg) in methanol (25 mL), concentrated sulfuric acid (1.0 mL) was added dropwise at 27 °C whereupon the suspension turned in to a clear brown solution. The reaction mixture turned in to a suspension after 5-10 min, and the suspension was stirred for 4 h at 27 °C. The suspension was filtered and dried under reduced pressure for 2 h to obtain 315 mg of the title compound as a pale yellow solid (HPLC purity: 96.95%, sulfuric acid content: 32.92%).

3(g): Preparation of Momelotinib hydrochloride

To a stirred suspension of Momelotinib (51 g, HPLC purity: 96.22%) in methanol (2.55 L), saturated IPA-HCl (204 mL) was added whereupon the suspension turned in to a clear solution. After completion of addition, the reaction mixture gradually turned in to a yellow colored suspension, and the suspension was stirred for 2-3 h at room temperature. The suspension was filtered, washed with methanol (2×100 mL), heptane (100 mL) and dried under reduced pressure at 45 °C for 3 h to obtain 44.9 g of the title compound as a yellow colored solid (HPLC purity: 98.79%, HCl content: 10.08% w/w).

Example 4: Preparation of Momelotinib free-base from salts

4(a): Preparation of Momelotinib free-base from Momelotinib triflate

To a stirred suspension of Momelotinib triflate (100 mg) in water (4 mL), Na_2CO_3 (45 mg) was added in a single portion whereupon the suspension turned in to a clear solution. After 5-10 min, the reaction mixture turned in to a yellow colored suspension which was stirred for 2 h at room temperature. The suspension filtered, washed with water (0.5 mL) and dried under reduced pressure at 45 °C for 3 h to afford 40 mg of Momelotinib free base as a yellow colored solid. HPLC purity: 98.26%

4(b): Preparation of Momelotinib free-base from Momelotinib besylate

To a stirred suspension of Momelotinib besylate (100 mg) in water (4 mL), Na_2CO_3 (44 mg) was added in a single portion whereupon the suspension turned in to a clear solution. After 5-10 min, the reaction mixture turned in to a yellow colored suspension which was stirred for 2 h at room temperature. The suspension filtered, washed with water (0.5 mL) and dried under reduced pressure at 45 °C for 3 h to afford 42 mg of Momelotinib free base as a yellow colored solid. HPLC purity: 99.01%.

4(c): Preparation of Momelotinib free-base from Momelotinib tosylate.

To a stirred suspension of Momelotinib tosylate (100 mg) in water (4 mL), Na_2CO_3 (42 mg) was added in a single portion whereupon the suspension turned in to a clear solution. After 5-10 min, the reaction mixture turned in to a yellow colored suspension which was stirred for 2 h at room temperature. The suspension filtered, washed with water (0.5 mL) and dried under reduced pressure at 45 °C for 3 h to afford 35 mg of Momelotinib free base as a yellow colored solid. HPLC purity: 97.67%

4(d): Preparation of Momelotinib free base from Momelotinib mesylate

To a stirred suspension of Momelotinib mesylate (100 mg) in water (4 mL), Na_2CO_3 (53 mg) was added in a single portion whereupon the suspension turned in to a clear solution. After 5-10 min, the reaction mixture turned in to a yellow colored suspension which was stirred for 2 h at room temperature. The suspension filtered, washed with water (0.5 mL) and dried under reduced pressure at 45 °C for 3 h to afford 48 mg of Momelotinib free base as a yellow colored solid. HPLC purity: 98.79%.

4(e): Preparation of Momelotinib free base from Momelotinib di-hydrochloride salt

To a stirred suspension of Momelotinib di-hydrochloride salt (400 mg) in water (16 mL), Na_2CO_3 (261 mg) was added in a single portion whereupon the suspension turned in to a clear solution. After 5-10 min, the reaction mixture turned in to a yellow colored suspension which was stirred for 2 h at room temperature. The suspension filtered, washed with water (2 mL) and dried under reduced pressure at 45 °C for 3 h to afford 300 mg of Momelotinib free base as a yellow colored solid. HPLC purity: 99.47%.

4(f): Preparation of Momelotinib free base from Momelotinib besylate

To a stirred suspension of Momelotinib besylate (100 mg) in water (4 mL) was added concentrated aqueous ammonia solution dropwise. Once the pH of the reaction mixture reaches ~10-12, the suspension momentarily turns in to a clear brown solution before becoming a yellow colored suspension again. The suspension was stirred for 2 h at

room temperature and then filtered. The solid obtained was washed with water (0.5 mL) and dried under reduced pressure at 45 °C for 3 h to obtain 43 mg of Momelotinib free base as a yellow colored solid. HPLC purity: 98.52%.

4(g): Preparation of Momelotinib freebase from Momelotinib di-hydrochloride salt using with ammonium hydroxide.

To a stirred suspension of Momelotinib di-hydrochloride salt (400 mg) in water (16 mL) was added concentrated aqueous ammonia solution dropwise. Once the pH of the reaction mixture reaches ~10-12, the suspension momentarily turns in to a clear brown solution before becoming a yellow colored suspension again. The suspension was stirred for 2 h at room temperature and then filtered. The solid obtained was washed with water (2 mL) and dried under reduced pressure at 45 °C for 3 h to obtain 298 mg of Momelotinib free base as a yellow colored solid. HPLC purity: 99.62%.

4(h): Preparation of Momelotinib freebase from Momelotinib hydrochloride salt using with ammonium hydroxide.

To a stirred suspension of Momelotinib hydrochloride (44.4 g) in water (1.776 L) was added 25% aqueous ammonia solution (310 mL) dropwise. Once the pH of the reaction mixture reaches ~12, the suspension momentarily turns in to a clear solution before becoming a yellow colored suspension again. The suspension was stirred for 2-3 h at room temperature and then filtered. The solid obtained was washed with water (2×133 mL) and dried under reduced pressure at 45 °C for 30-40 min to obtain 40.4 g of Momelotinib free base as a yellow colored solid. HPLC purity: 98.60%.

WE CLAIM

1. An acid addition salt of Momelotinib, wherein salt is selected from a group comprising tosylate, besylate and triflate.

2. A tosylate salt of Momelotinib, characterized by X-ray powder diffraction (XRPD) pattern comprising peaks at 4.46°, 10.38°, 13.90°, 14.74°, 16.53°, 23.07°, 20.33°, 23.92°, 26.34° and 27.78° ± 0.2° 2θ or an XRPD pattern as depicted in Figure 7.

3. The tosylate salt as claimed in claim 1 or 2, characterized by an XRPD pattern comprising peaks at 8.90°, 9.47°, 11.44°, 13.32°, 15.27°, 16.20°, 17.36°, 19.07°, 19.63°, 20.80°, and 22.26° ± 0.2° 2θ.

4. The tosylate salt as claimed in claim 1 or 2, characterized by an XRPD pattern comprising peaks at 22.67°, 24.41°, 24.93°, 25.87°, 28.88°, 29.84°, 31.03°, 33.63°, 34.40°, 35.39°, 36.66°, and 38.89° ± 0.2° 2θ.

5. A besylate salt of Momelotinib, characterized by an XRPD pattern comprising peaks at 4.77°, 14.61°, 15.15°, 16.09°, 17.54°, 18.11°, 19.19°, 23.10°, 23.70°, and 24.49° ± 0.2° 2θ or an XRPD pattern as depicted in Figure 8.

6. The besylate salt as claimed in claim 5, characterized by an XRPD pattern comprising peaks at 8.29°, 9.55°, 10.31°, 10.87°, 11.62°, 13.16°, 13.85°, 14.12°, 18.93°, 19.86°, 20.72°, 21.85°, 22.54°, 23.38°, and 24.85° ± 0.2° 2θ.

7. The besylate salt as claimed in claim 5 or 6, characterized by an XRPD pattern comprising peaks at 25.78°, 26.35°, 27.22°, 28.06°, 28.80°, 29.92°, 31.08°, 31.60°, 33.05°, 33.63°, 34.70°, 34.87°, 35.55°, 36.88°, 37.28°, 38.37°, and 39.02° ± 0.2° 2θ.

8. A triflate salt of Momelotinib, characterized by an XRPD pattern comprising peaks at 15.13°, 18.09°, 19.09°, 20.24°, 21.29°, 21.71°, 22.89°, 24.10°, 27.77° and 30.32° ± 0.2° 2θ or an XRPD pattern as depicted in Figure 9.

9. The triflate salt as claimed in claim 8, characterized by an XRPD pattern comprising peaks at 5.38°, 8.40°, 9.89°, 10.14°, 10.58°, 10.88°, 11.59°, 13.56°, 13.91°, 15.33°, 15.80°, 16.30°, 17.35°, 18.52°, and 19.73° ± 0.2° 2θ.

10. The triflate salt as claimed in claim 8 or 9, characterized by an XRPD pattern comprising peaks at 23.51°, 25.23°, 25.64°, 26.60°, 27.33°, 28.12°, 28.56°, 30.74°, 31.38°, 32.17°, 35.16°, 36.34°, 37.86°, 38.25°, and 38.85° ± 0.2° 2θ.

11. The salt as claimed in any of claims 1 to 10, wherein the salt is crystalline.

12. A solid dispersion comprising momelotinib dihydrochloride and at least one pharmaceutically acceptable excipient.

13. The solid dispersion as claimed in claim 12, wherein the solid dispersion is amorphous solid dispersion.

14. The solid dispersion as claimed in claim 12 or 13, wherein the pharmaceutically acceptable excipient is selected from a group comprising polyvinyl pyrrolidone, povidone K-30, povidone K-60, Povidone K-90, polyvinylpyrrolidone, vinylacetate, co-povidone NF, polyvinylacetal diethylaminoacetate (AEA®), polyvinyl acetate phthalate, polysorbate 80, polyoxyethylene–polyoxypropylene copolymers (Poloxamer® 188), polyoxyethylene (40) stearate, polyethyene glycol, monomethyl ether, polyethyene glycol, poloxamer 188, pluronic F-68, methylcellulose, methacrylic acid copolymer (Eudragit or Eudragit-RLPO), hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate (HPMC-AS), hydroxypropylmethyl cellulose, hydroxypropyl cellulose-SSL (HPC-SSL), hydroxypropyl cellulose SL(HPC-SL), hydroxypropyl cellulose L (HPC-L), hydroxyethyl cellulose, Soluplus® (polyvinyl caprolactam-polyvinyl acetatepolyethylene, glycol graft copolymer (PCL-PVAc-PEG)), gelucire 44/14, ethyl cellulose, D-alpha-tocopheryl polyethylene glycol 1000 succinate, cellulose acetate phthalate, carboxymethylethylcellulose, cyclodextrins, gelatins, hypromellose phthalates, sugars, polyhydric alcohols, water soluble sugar excipients, polyethylene oxides, polyoxyethylene derivatives, polyvinyl alcohols, propylene glycol derivatives

and the like, organic amines such as alkyl amines and guanidine or its derivatives, colloidal silica, and mixtures thereof.

15. The process for preparation of solid dispersion as claimed in any of claims 12 to 14, comprising the step of combining momelotinib dihydrochloride with at least one pharmaceutically acceptable excipient in the presence of a suitable solvent.

16. The process as claimed in claim 15, wherein the solvent is selected from a group comprising methanol, ethanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 2-pentanol, 3-pentanol, tetrahydrofuran, 2-methyl-tetrahydrofuran, 1-4-dioxane, acetone, acetonitrile, dimethylsulfoxide, dimethylformamide, dimethylacetamide, methyl ethyl ketone, methyl isobutyl ketone, methyl acetate, ethyl acetate, isopropyl acetate, water, and mixtures thereof.

17. A process for the preparation of momelotinib free base, comprising preparing momelotinib salt and converting the momelotinib salt to momelotinib free base.

18. The process as claimed in claim 17, wherein the salt is an acid addition salt.

19. The process as claimed in claim 17 or 18, wherein the acid addition salt is selected from a group comprising hydrochloride, dihydrochloride, bromide, sulfate, phosphate, perchlorate, formate, oxalate, trifluoroacetate, trichloroacetate, mesylate, tosylate, besylate, triflate, napsylate, camphorsulfonate and p-nitrobenzenesulfonate.

20. The process as claimed in claim 19, wherein the acid addition salt of Momelotinib is selected from a group comprising tosylate, besylate, hydrochloride, dihydrochloride or triflate.

21. The process as claimed in any of claims 17 to 20, wherein the final momelotinib free base has a purity of more than about 98.5% by HPLC.

22. The process as claimed in claim 17, wherein converting the momelotinib salt to momelotinib free base comprises neutralizing the momelotinib salt with a base.

23. The process as claimed in claim 17, wherein the base is an inorganic base selected from a group comprising a hydroxide, an alkali metal carbonate, an alkali metal

bicarbonate, and a combination thereof, or an organic base selected from a group comprising triethylamine, diisopropylethylamine, pyridine, 2,6-dimethylpyridine, and a combination thereof.

24. The process as claimed in claim 22 or 23, wherein the neutralization is carried out in a solvent selected from a group comprising ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran, MTBE, dioxane, and dimethoxyethane; alcohols, such as methanol, ethanol, ethylene glycol, 1-propanol, 2-propanol, 2-methoxyethanol, 1-butanol, 2-butanol, iso-butyl alcohol, t-butyl alcohol, glycerol, and C_1-C_6 alcohols; halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride, and chlorobenzene; aromatic hydrocarbons, such as toluene; aliphatic hydrocarbons such as hexane and heptane; nitriles such as acetonitrile; esters such as ethyl acetate; polar aprotic solvents such as DMF, DMSO, DMAc; water and any mixtures of two or more thereof.

25. The process as claimed in claim 24, wherein the solvent is water.

26. The process as claimed in any of claims 17 to 25, wherein obtained momelotinib is crystalline.

27. A solid form of momelotinib free base characterized by an XRPD pattern comprising peaks at 4.21, 12.76, 15.26, 17.45, 20.01, 20.75, 21.72, 23.53, 26.13 and 28.02° ± 0.2° 2θ or an XRPD pattern as depicted in Figure 12.

28. The solid form as claimed in 27, wherein an XRPD pattern comprising peaks at 8.36°, 10.15°, 11.13°, 11.96°, 13.96°, 15.99°, 16.37°, 18.69°, 24.12°, 24.53°, 25.53°, 27.11°, and 29.30° ± 0.2° 2θ.

29. The solid form as claimed in 27, wherein an XRPD pattern comprising peaks at 29.84°, 30.88°, 31.47°, 32.87°, 33.39°, 34.07°, 34.54°, 35.11°, 35.78°, 37.23°, 38.06°, and 39.07° ± 0.2° 2θ.

30. The free base as claimed in any of claims 27 to 29, wherein the free base is crystalline.

31. A pharmaceutical composition comprising an acid addition salt as claimed in any of claims 1 to 11, or a solid dispersion as claimed in any of claims 12 to 14, or a solid

form as claimed in any of claim 27 to 29, or a free base as claimed in claim 30 and optionally a pharmaceutically acceptable excipient.

32. A method of preventing or treating a condition or a disorder or a disease in a subject, comprising administering to the subject an effective amount of an acid addition salt as claimed in any of claims 1 to 11, or a solid dispersion as claimed in any of claims 12 to 14, or a solid form as claimed in any of claim 27 to 29, or a free base as claimed in claim 30 or a pharmaceutical composition as claimed in claim 31, wherein the condition or disorder or disease can be ameliorated with Janus kinase (JAK) inhibition.

33. An acid addition salt as claimed in any of claims 1 to 11, or a solid dispersion as claimed in any of claims 12 to 14, or a solid form as claimed in any of claim 27 to 29, or a free base as claimed in claim 30 or a pharmaceutical composition as claimed in claim 31, used for the condition or disorder or disease that can be ameliorated with Janus kinase (JAK) inhibition.

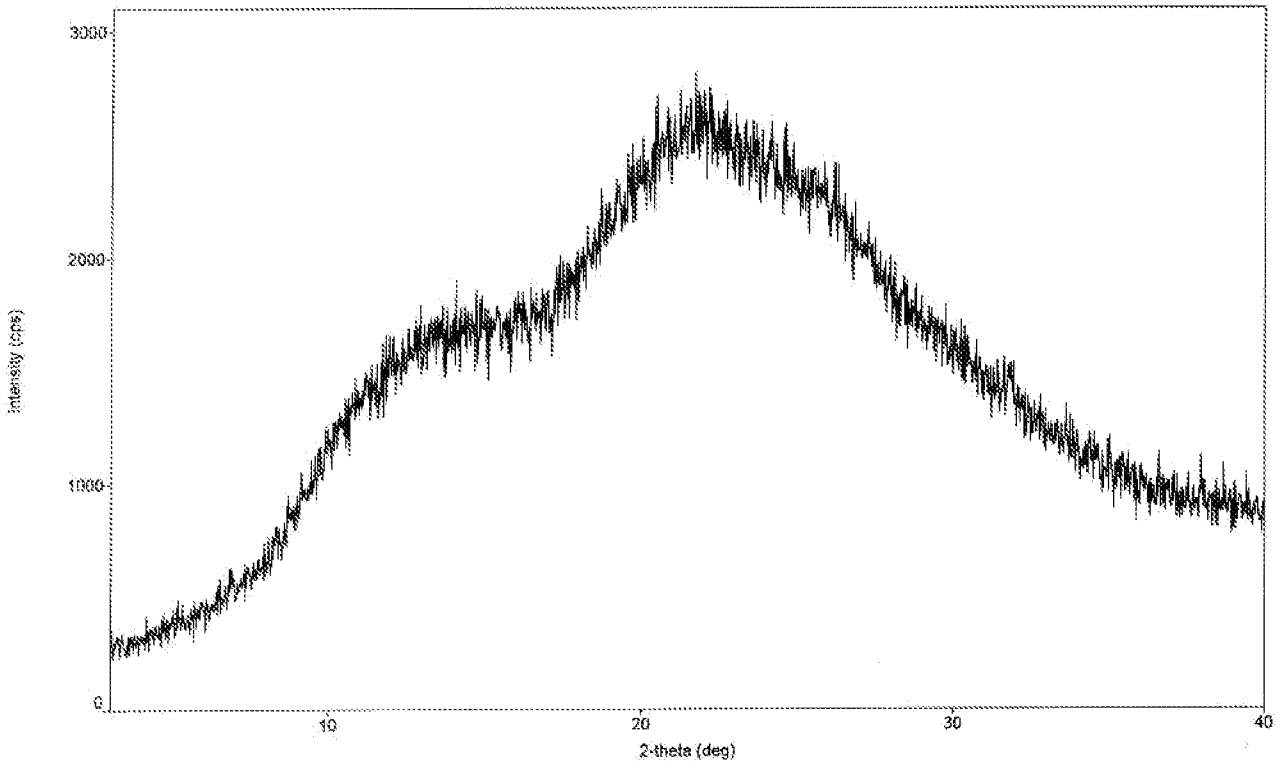


Figure 1

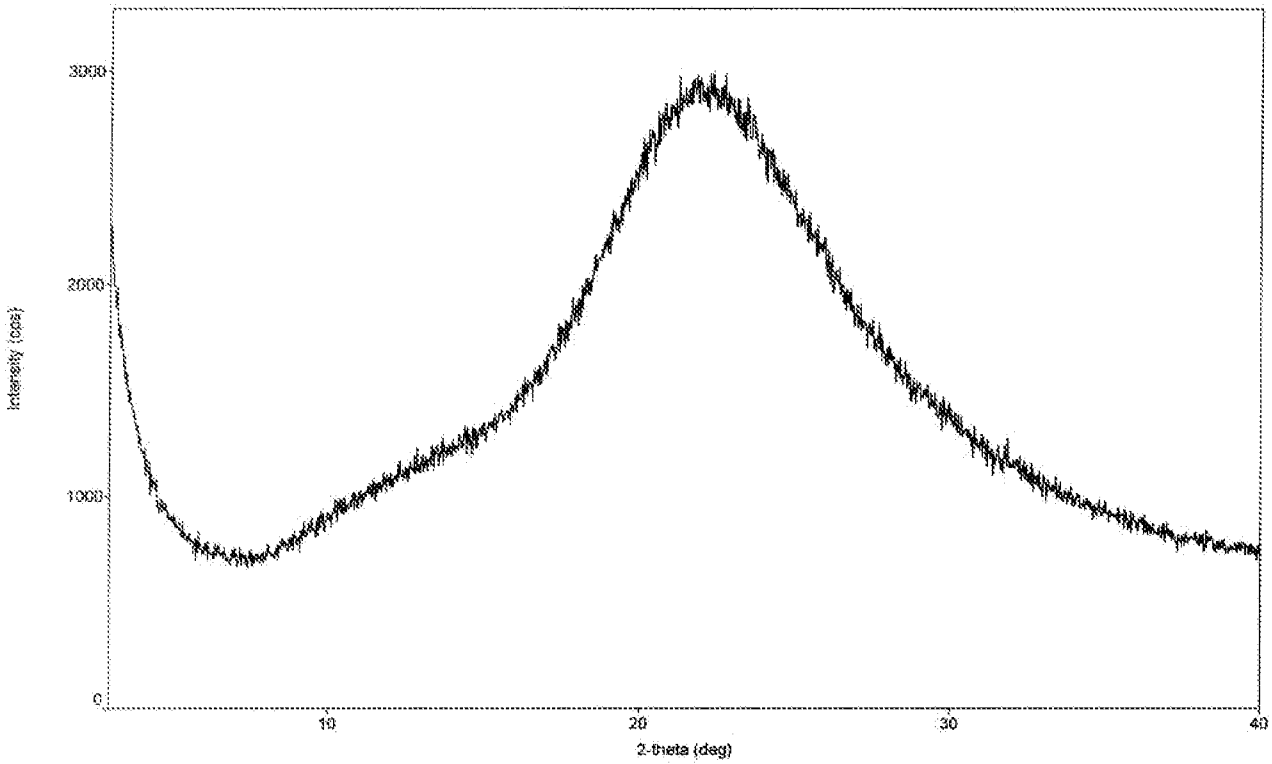


Figure 2

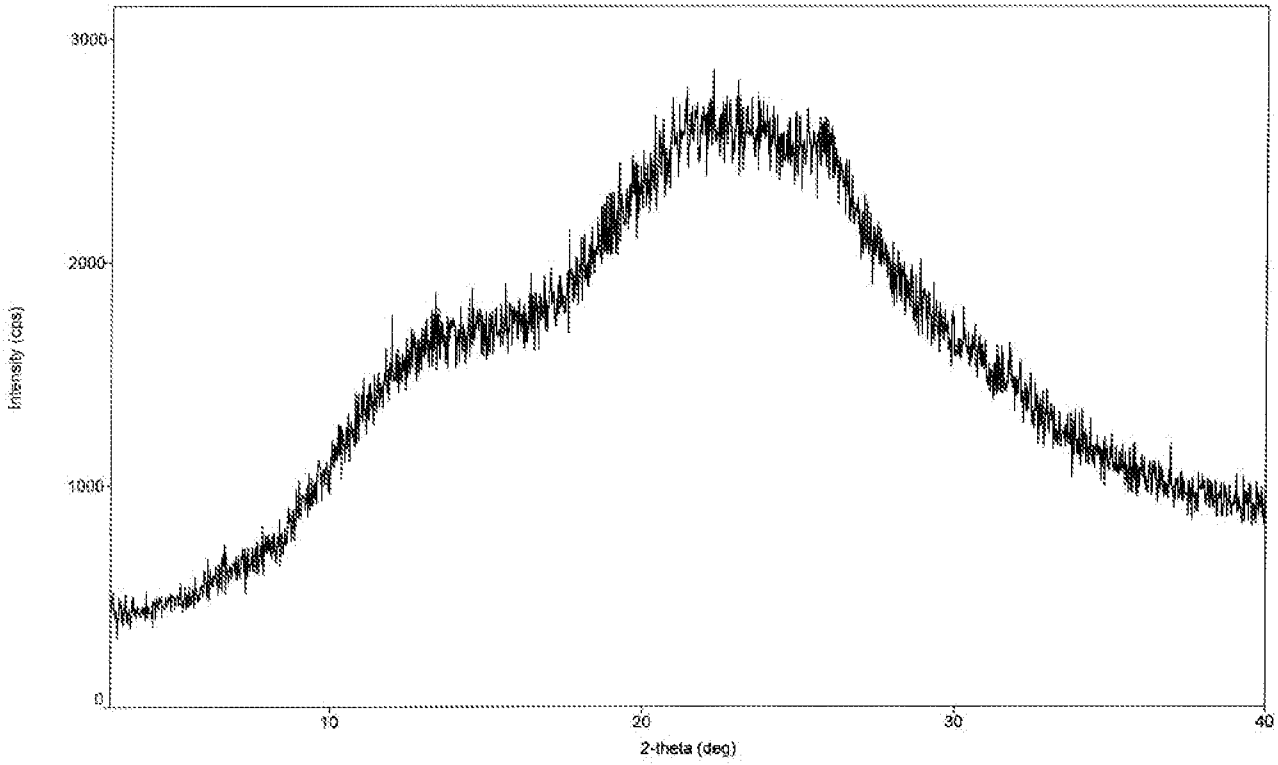


Figure 3

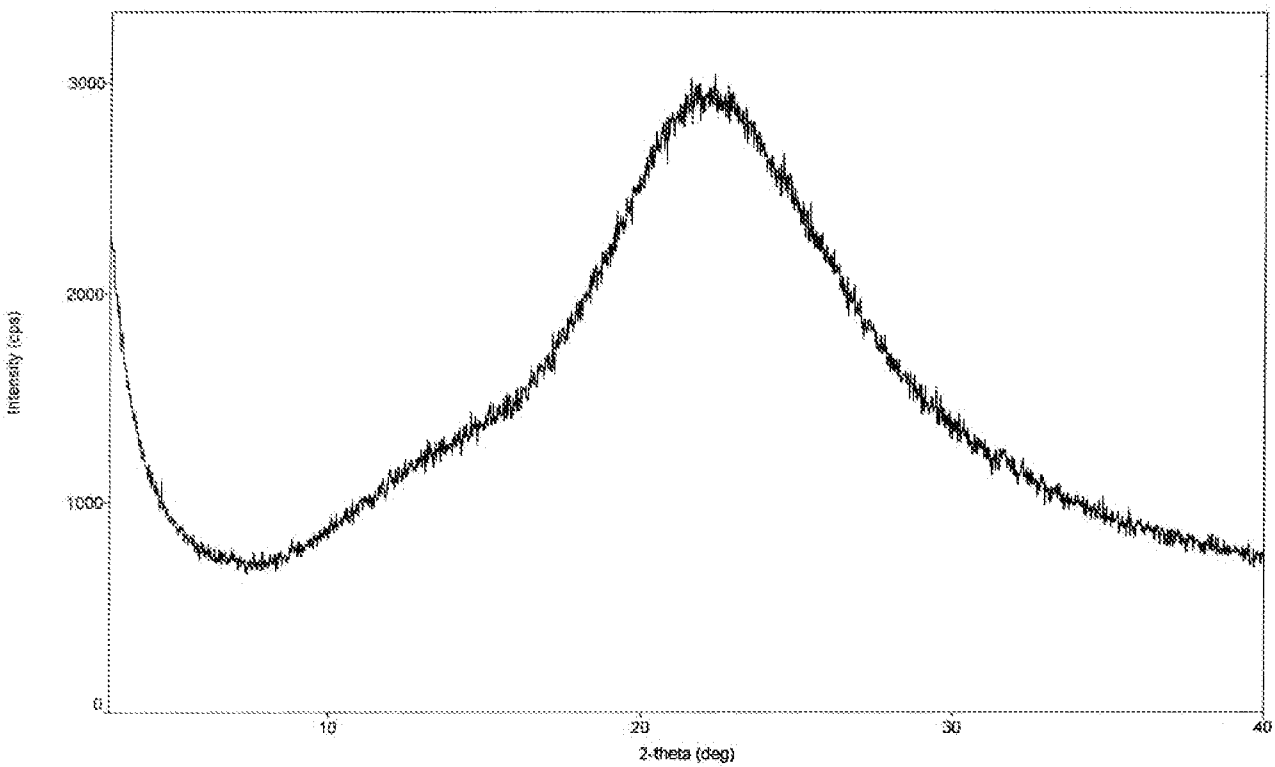


Figure 4

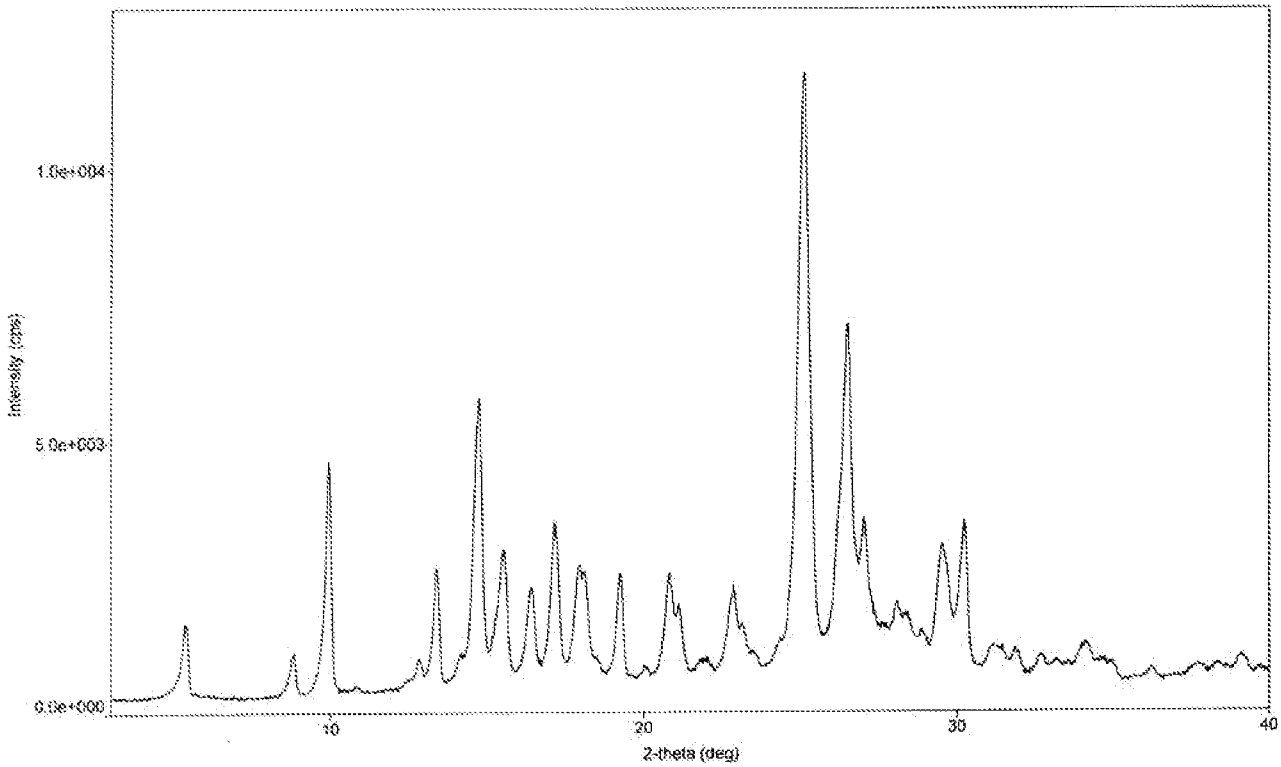


Figure 5

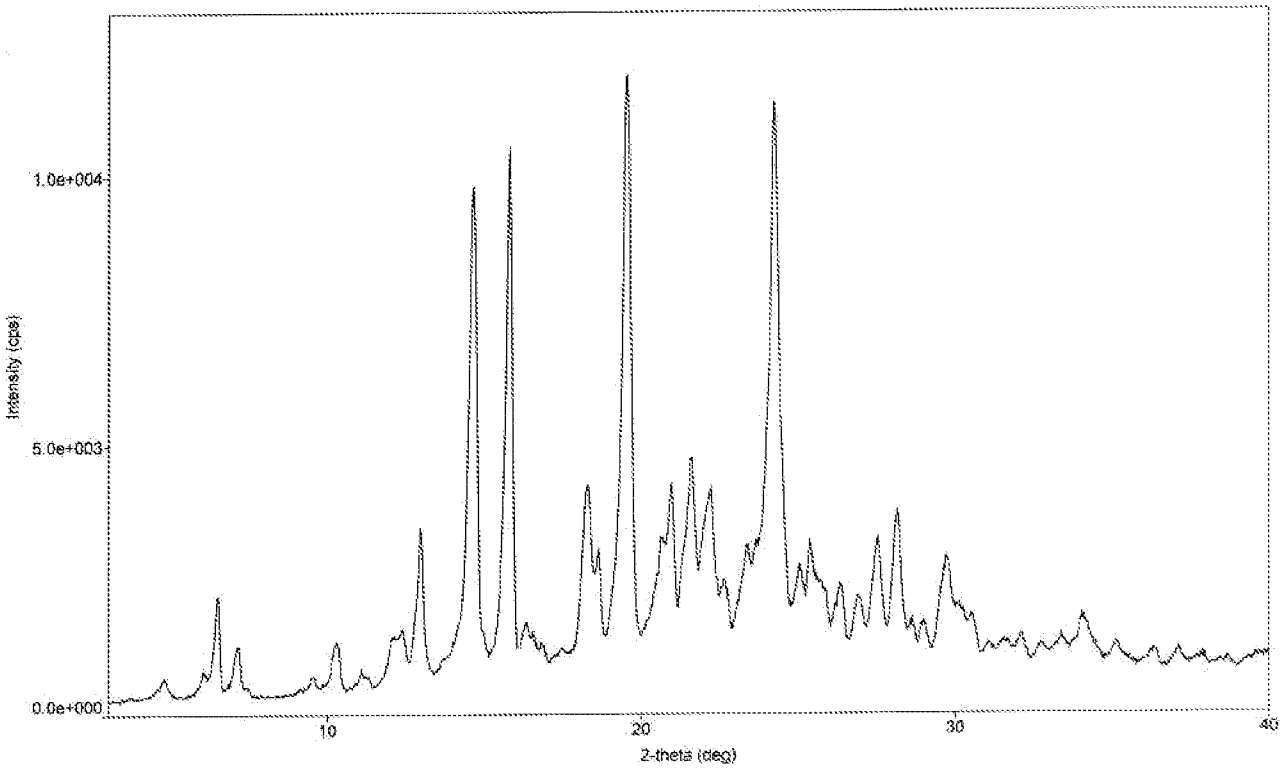


Figure 6

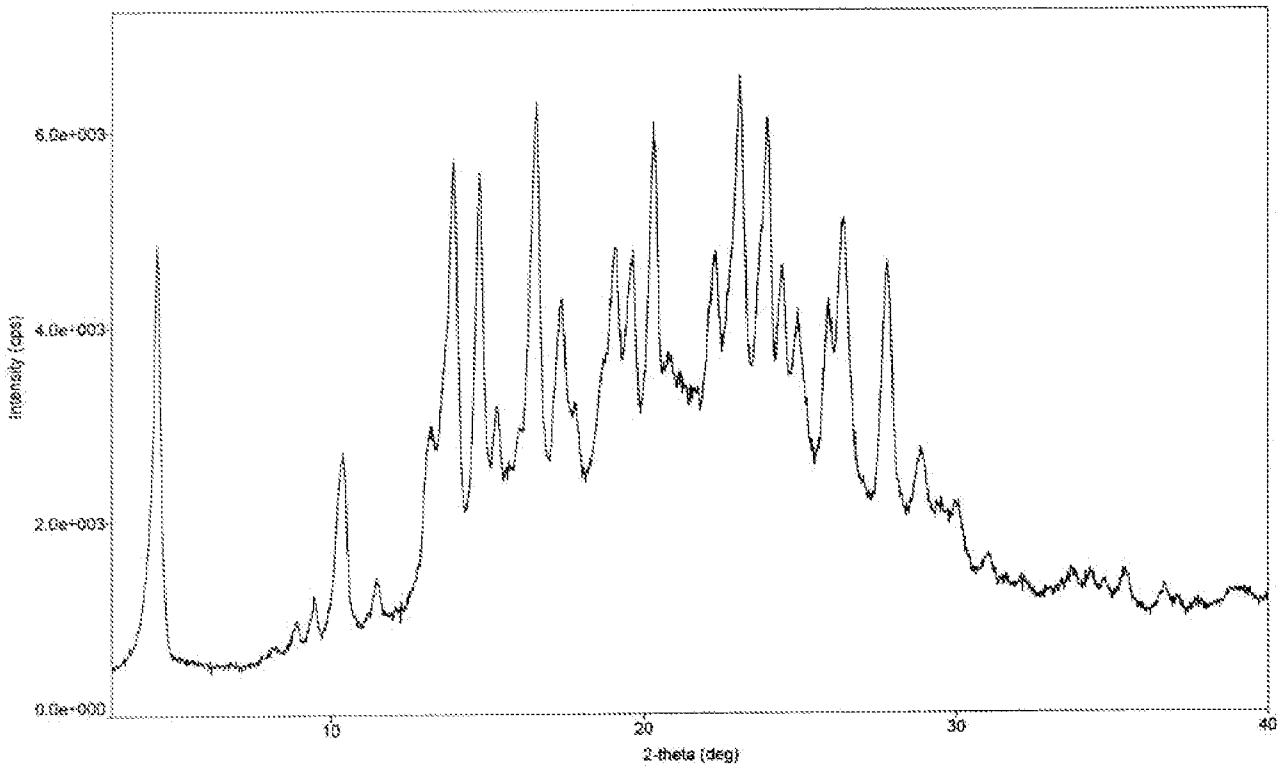


Figure 7

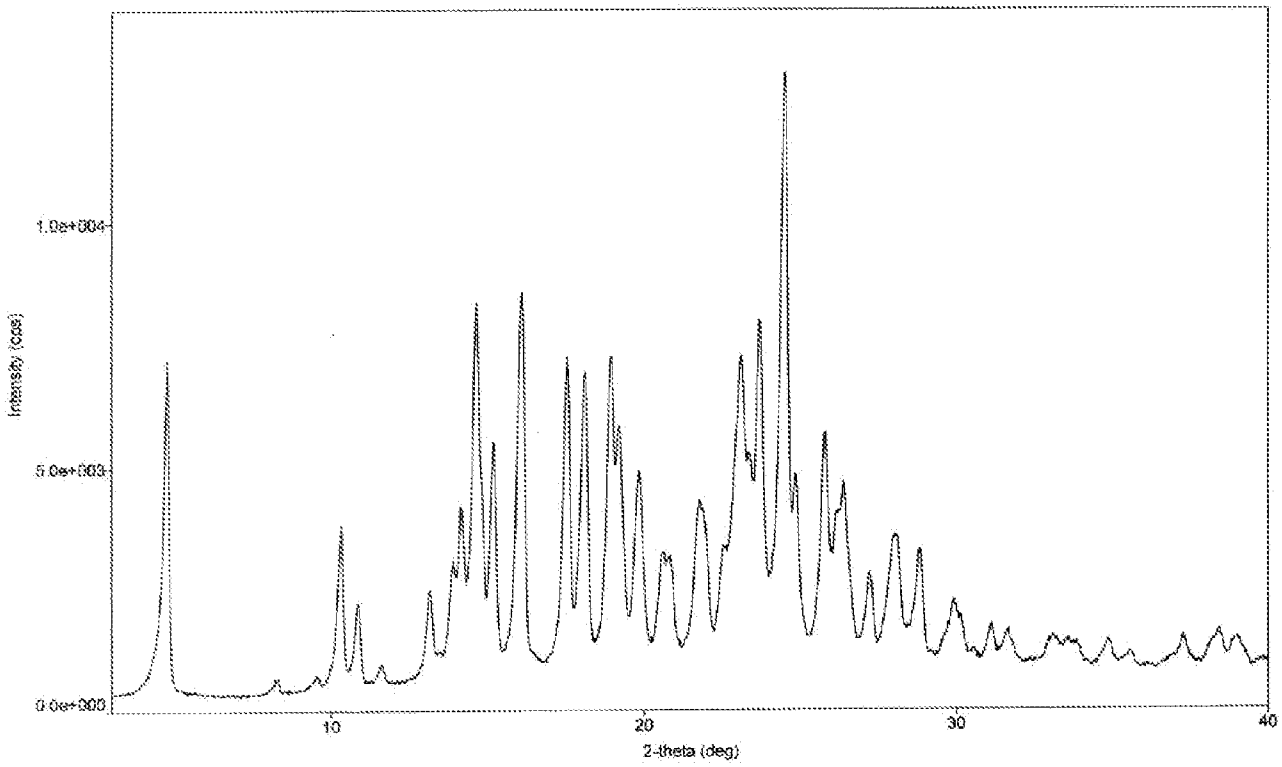


Figure 8

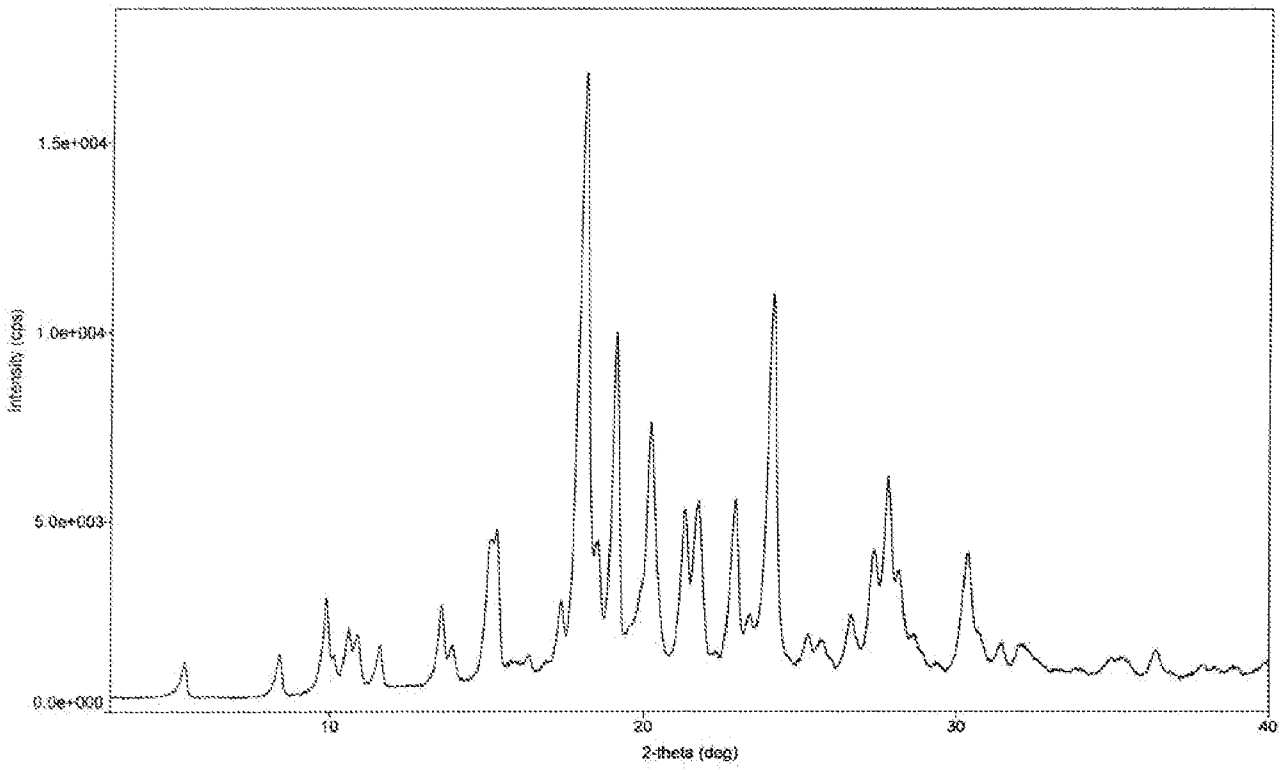


Figure 9

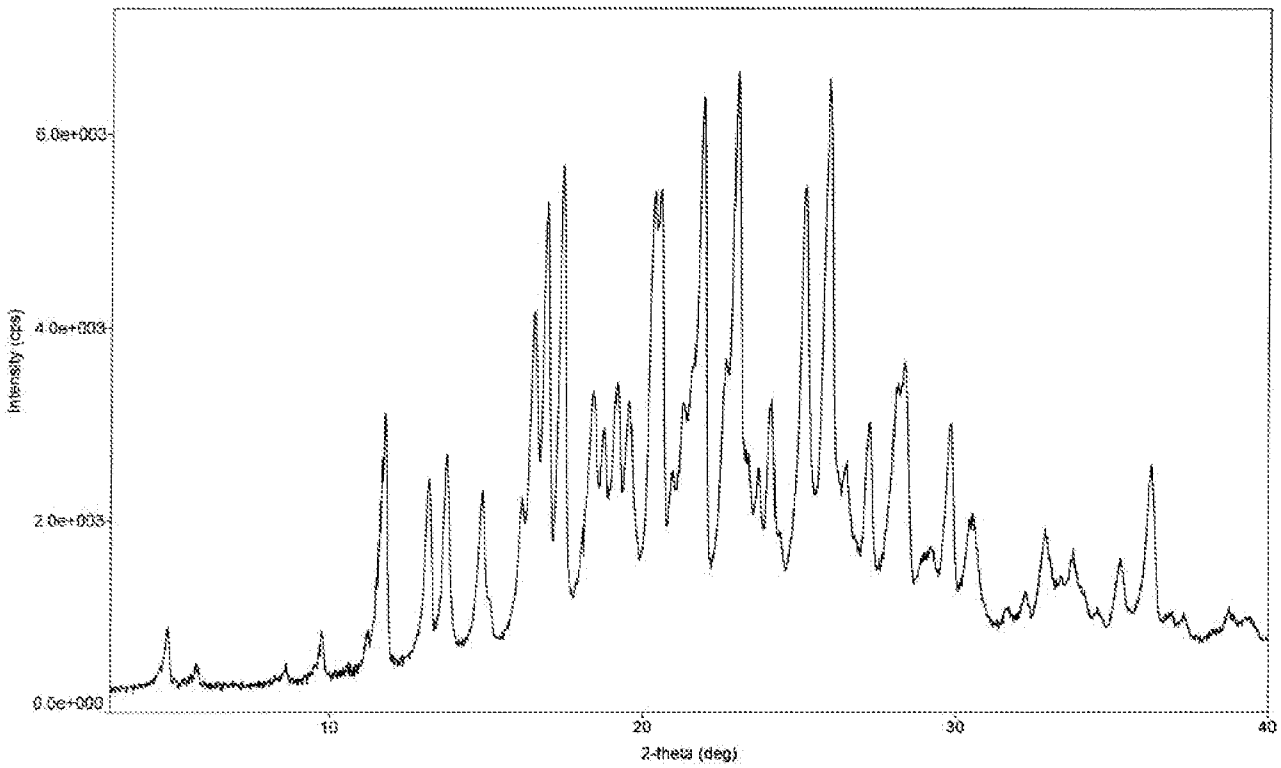


Figure 10

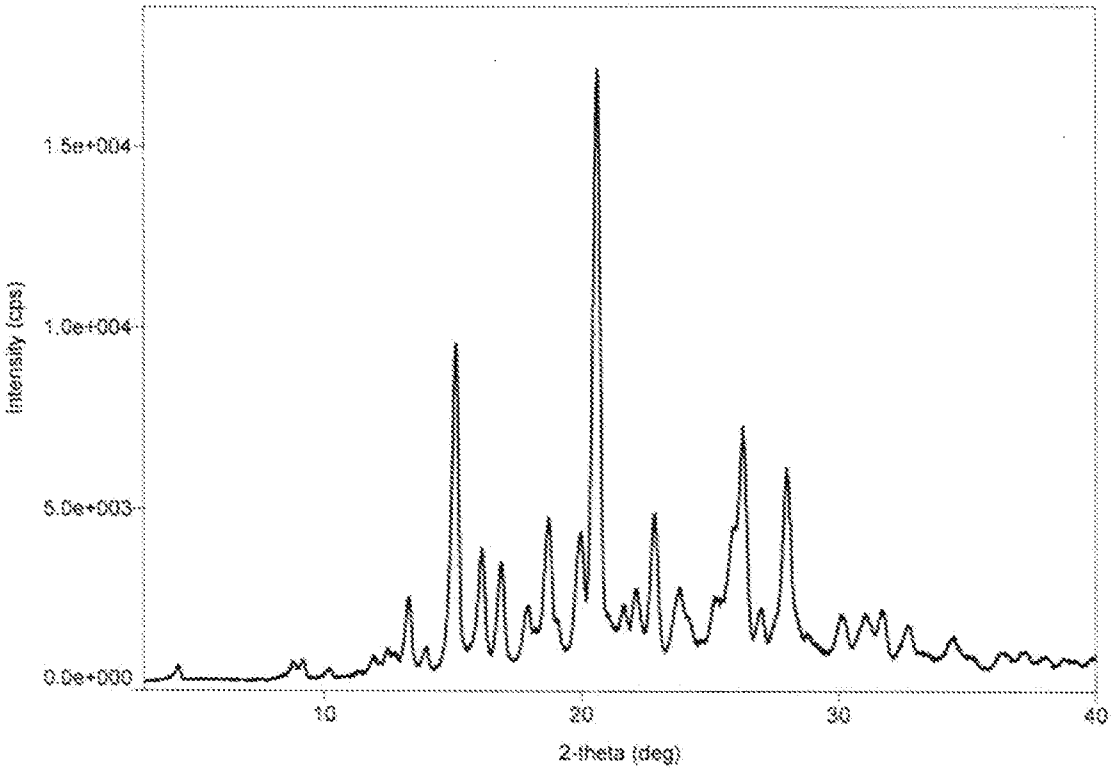


Figure 11

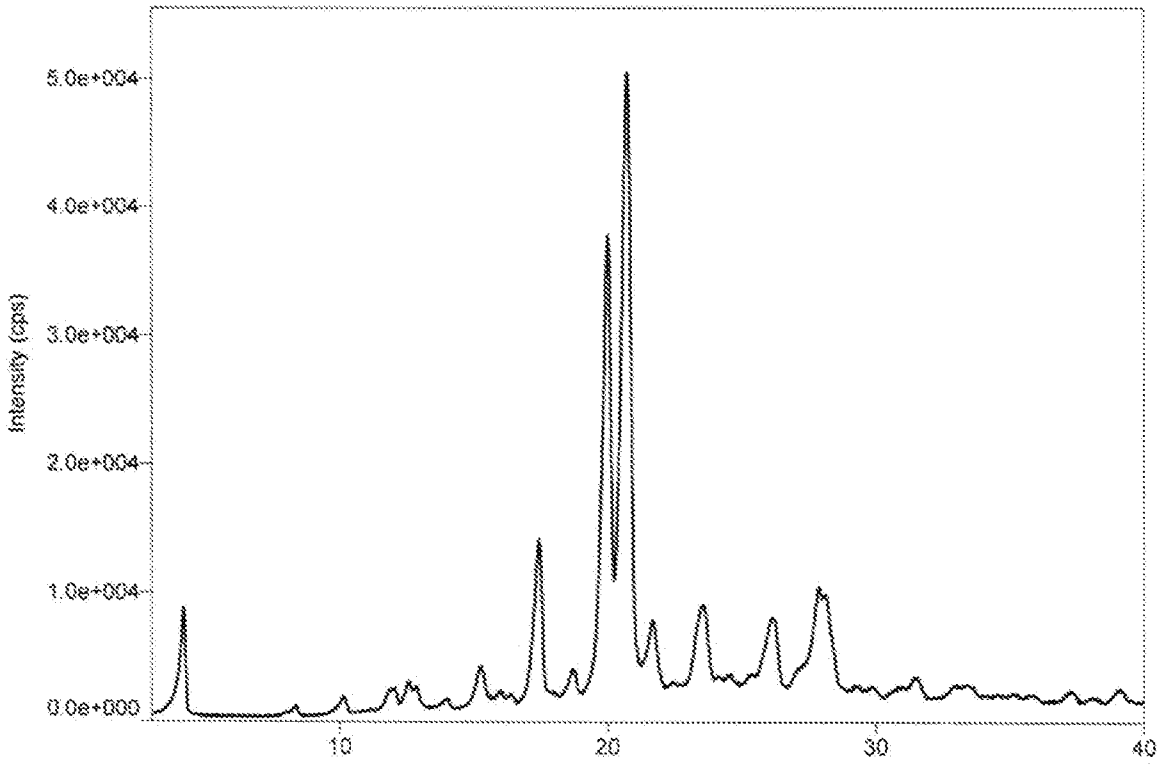


Figure 12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2023/050151

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/5377,A61P35/00,A61K09/14,C07D417/12,A61P07/00 Version=2023.01

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K; A61P;C07D

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015191846 A1 (GILEAD SCIENCES INC [US]); 17 Dec 2015; Abstract, Claims 1-23, Figs 1-15, Tables 1-5, Exapmles 1-8	1-31
Y	CN 101861313 B (YM BIOSCIENCES AUSTRALIA PTY LTD); 04 Jun 2014; Abstract, Claims 1-18, Examples 1-6, Tables 1-2	1-31

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05-06-2023	05-06-2023

Name and mailing address of the ISA/	Authorized officer
Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Kamalesh Kumar Patel Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2023/050151

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 32-33
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claims 32-33 relates to Janus kinase (JAK) inhibition for the treatment of the human or animal body, which does not require an international search by the ISA in accordance with PCT
Article 17(2)(a)(i) and [Rule 39.1(iv)].

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2023/050151

Citation	Pub.Date	Family	Pub.Date
WO 2015191846 A1	17-12-2015	AU 2015274554 A1	24-11-2016
		BR 112016028749 A2	22-08-2017
		CN 106458929 A	22-02-2017
		EP 3154950 A1	19-04-2017
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CN 101861313 B	04-06-2014	AU 2008226327 A1	18-09-2008
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		JP 2010520892 A	17-06-2010
		KR 20090128478 A	15-12-2009
		WO 2008109943 A1	18-09-2008