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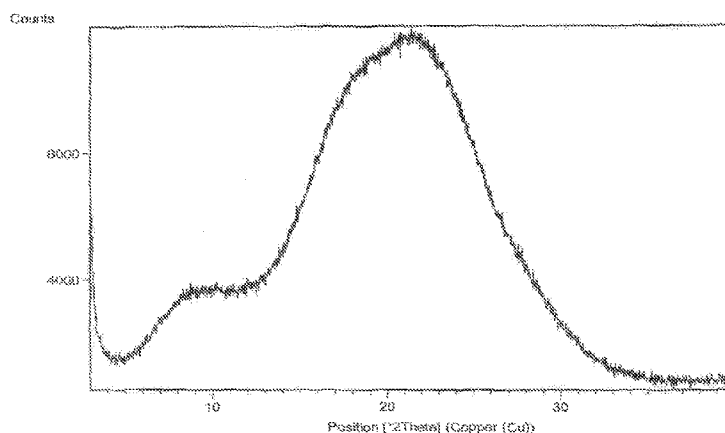


Figure 1

(57) **Abstract:** Aspects of the present application relate to Amorphous Lumacافتor, its amorphous solid dispersion and pharmaceutical compositions thereof. Further aspects relate to processes for the preparation of crystalline and amorphous Lumacافتor and solid dispersions thereof. Other aspects of the present application include a complex of Lumacافتor and Ivacافتor, its crystalline and amorphous phase, their preparative processes and pharmaceutical compositions thereof.

AMORPHOUS AND CRYSTALLINE SOLID FORMS OF LUMACAFTOR OR ITS COMPLEX AND PREPARATIVE PROCESSES THEREOF

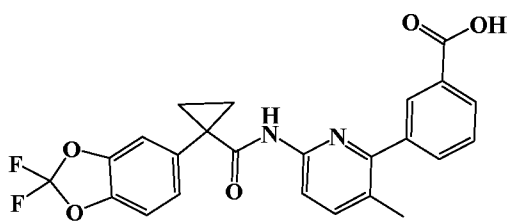
PRIORITY

The present application claims priority of Indian patent applications. 201641000118, 201641008639 & 201641011174 filed on 04 January 2016, 11 March 2016 & 30 March 2016, respectively and the whole content of which is hereby incorporated by reference herein.

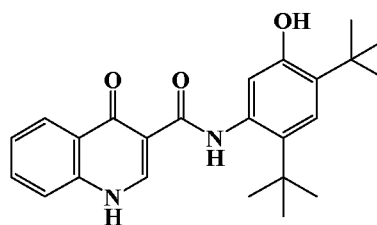
INTRODUCTION

Aspects of the present application relate to Amorphous Lumacaftor, its amorphous solid dispersion and pharmaceutical compositions thereof. Further, aspects relate to processes for the preparation of crystalline and amorphous Lumacaftor and solid dispersions thereof. Other aspects of the present application relate to the complex of Lumacaftor and Ivacaftor, amorphous phase of Lumacaftor and Ivacaftor, their preparative processes and pharmaceutical compositions thereof.

ORKAMBI is approved in US and Europe as a fixed dose combination (FDC) pink immediate-release film-coated tablet for oral administration. The active ingredients in ORKAMBI tablets are Lumacaftor, which has the chemical name: 3-[6-({[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropyl]carbonyl}amino)-3-methylpyridin-2-yl] benzoic acid, and Ivacaftor, a CFTR potentiator, which has the chemical name: N-(2,4-di-tertbutyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide.



Lumacaftor



Ivacaftor

Orkambi contains 200 mg of Lumacaftor and 125 mg of Ivacaftor as active substances. US FDA label prescribes two tablets to be taken orally every 12 hours for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene. Lumacaftor partially corrects the fundamental molecular defect caused by F508del-CFTR to increase the amount of

functional F508del-CFTR at the cell surface, resulting in enhanced chloride transport. The channel gating activity of F508del-CFTR delivered to the cell surface by Lumacaftor can be potentiated by Ivacaftor to further enhance chloride transport. When added to F508del/F508del-HBE, the magnitude of chloride transport observed with the combination of Lumacaftor and either acute or chronic Ivacaftor treatment was greater than that observed with Lumacaftor alone.

BACKGROUND

US 8993600 B2 discloses Lumacaftor as compound-396, its pharmaceutical use for the treatment of cystic fibrosis. Further, it discloses preparative methods for the preparation of compounds disclosed therein including Lumacaftor by reacting N-(6-chloro-5-methylpyridin-2-yl)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropane carboxamide with 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid. However, it is not disclosed about the nature of compound prepared by the process disclosed therein.

US 8507534 B2 discloses Lumacaftor in crystalline Form I characterized by one or more peaks at 15.2 to 15.6 degrees, 16.1 to 16.5 degrees, and 14.3 to 14.7 degrees in an X-ray powder diffraction obtained using Cu K alpha radiation. Lumacaftor Form I was prepared either by dispersing or dissolving a salt form, such as HCl, of Lumacaftor in an appropriate solvent for an effective amount of time (or) directly by treating t-butyl ester intermediate of Lumacaftor with an appropriate acid, such as formic acid. US 8507534 B2 further discloses the reaction of tert-butyl-3-(6-amino-3-methylpyridin-2-yl) benzoate with 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-cyclopropanecarbonyl chloride in the presence of base for the preparation of Lumacaftor.

US 8507687 B2 discloses the crystalline Form A of Lumacaftor, which is a isostructural solvate with methanol, ethanol, 2-propanol, acetone, acetonitrile, tetrahydrofuran, methyl acetate, 2-butanone, ethyl formate, 2-methyl tetrahydrofuran and a crystalline Form A of Lumacaftor HCl salt.

US 7495103 B2 discloses Ivacaftor or a pharmaceutically acceptable salt thereof, its pharmaceutical composition and its use for treating or lessening the severity of cystic fibrosis. Ivacaftor made from the procedure exemplified therein was purified by HPLC and no characteristic details of the compound obtained were disclosed.

US 8410274 B2 describes both crystalline (polymorph A and B) and amorphous forms of Ivacaftor. Amorphous Ivacaftor and its amorphous phase with a polymer were described to have superior over their crystalline counterparts.

US 8471029 B2 discloses crystalline Form C of Ivacaftor, while US 8163772 B2 discloses various other the solid forms / co-forms of Ivacaftor, for example, salts, solvates, co-crystals and hydrates of Ivacaftor and exemplified specifically compounds selected from crystalline Ivacaftor.2-methylbutyric acid, Ivacaftor.propylene glycol, Ivacaftor.PEG 400.KOAc, Ivacaftor.lactic acid, Ivacaftor.isobutyric acid, Ivacaftor.propionic acid, Ivacaftor.H₂O, Ivacaftor.EtOH, Ivacaftor.2-propanol, Ivacaftor.besylate and Ivacaftor.besylate.H₂O and designated them as Form I to XVI

US 8674108 B2 discloses various crystalline solvates of Ivacaftor, wherein the crystalline solvates are designated as a solid form selected from the group consisting of Form D, to Form T, Form W, and Hydrate B and their preparative processes.

There remains a need for alternate solid forms of Lumacaftor and preparative processes thereof. Particularly, an amorphous form of a drug may exhibit a higher bioavailability than its crystalline counterparts, which leads to the selection of the amorphous form as the final drug substance for pharmaceutical dosage form development. Additionally, the solubility of crystalline form is lower than its amorphous form in some instances, particularly aqueous solubility, which may result in the difference in their in-vivo bioavailability. Therefore, it is desirable to have an amorphous form of a drug to meet the needs of drug development and also a reproducible process for their preparation. Hence, it is desirable to provide an amorphous Lumacaftor or its solid dispersion.

Prior art processes does not disclose a amenable process for the preparation of crystalline Form I of Lumacaftor and there remains a need for alternate process for the preparation of crystalline Form I of Lumacaftor in a cost effective and industrially viable manner.

There remains a need for alternate solid forms of Lumacaftor and / or Ivacaftor, preparative processes thereof. Specifically, there is a need for a solid form of Lumacaftor and / or Ivacaftor with a higher bioavailability and process ability, which leads to its selection as the final drug substance for pharmaceutical dosage form development. Therefore, it is desirable to have alternate solid forms of Lumacaftor and / or Ivacaftor to meet the needs of drug development and also a reproducible process for their preparation.

SUMMARY

In an aspect, the present application provides an amorphous form of Lumacaftor.

In another aspect, the present application provides a process for the preparation of an amorphous form of Lumacaftor, comprising the steps of:

- a) providing a solution of Lumacaftor in a suitable solvent or a mixture thereof;
- b) removing the solvent from the solution obtained in step a); and
- c) isolating the amorphous form of Lumacaftor.
- d) optionally combining amorphous form of step c) with at least one pharmaceutically acceptable excipient.

In another aspect, the present application provides a process for the preparation of amorphous form of Lumacaftor, comprising the steps of;

- a) providing a solution of Lumacaftor in a suitable solvent or a mixture thereof;
- b) contacting the solution obtained in step a) with an anti-solvent;
- c) isolating amorphous form of Lumacaftor.

In another aspect, the present application provides amorphous solid dispersion of Lumacaftor together with at least one pharmaceutically acceptable excipient.

In another aspect, the present application provides a process for the preparation of an amorphous solid dispersion of Lumacaftor, comprising the steps of:

- a) providing a solution of Lumacaftor and at least one pharmaceutically acceptable excipient in a suitable solvent or a mixture thereof;
- b) removing the solvent from the solution obtained in step a), and
- c) isolating the amorphous solid dispersion of Lumacaftor.
- d) optionally combining amorphous solid dispersion of step c) with at least one additional pharmaceutically acceptable excipient.

In another aspect, the present application provides a pharmaceutical composition comprising amorphous form of Lumacaftor or the amorphous solid dispersion of Lumacaftor together with at least one pharmaceutically acceptable excipient.

In another aspect, the present application provides a process for the preparation of crystalline Form I of Lumacaftor, comprising the steps of:

- a) providing a solution of Lumacaftor in a suitable solvent or a mixture thereof;
- b) optionally contacting the solution obtained in step a) with an anti-solvent;
- c) isolating crystalline Form I of Lumacaftor.

In another aspect, the present application provides a process for the preparation of crystalline form of Lumacaftor or a solvate thereof, comprising the step of converting

amorphous Lumacaftor to crystalline form of Lumacaftor or a solvate thereof.

In another aspect, the present application provides a process for the preparation of crystalline Form I of Lumacaftor, comprising the step of converting amorphous Lumacaftor to crystalline Form I of Lumacaftor.

In another aspect, the present application provides a pharmaceutical composition comprising crystalline Form I of Lumacaftor obtained by any of the processes as per the present application with at least one pharmaceutically acceptable excipient.

In an aspect, the present application provides a complex of Lumacaftor and Ivacaftor.

In specific aspects, the present application provides crystalline complex of Lumacaftor and Ivacaftor.

In another aspect, the present application provides Form LI-1 of crystalline complex of Lumacaftor and Ivacaftor, characterized by a PXRD pattern comprising peaks at about 6.13, 10.36, 10.69, 11.21, 13.55, 14.25 and $20.88 \pm 0.2^\circ 2\theta$. In an embodiment, the application provides Form LI-1, further characterized by a PXRD pattern having peaks at about 12.33, 15.12, 17.75, 22.64 and $23.92 \pm 0.2^\circ 2\theta$.

In another aspect, the present application provides Form LI-2 of crystalline complex of Lumacaftor and Ivacaftor, characterized by a PXRD pattern comprising peaks at about 7.44, 8.77, 12.09, 16.45, 17.74 and $20.37 \pm 0.2^\circ 2\theta$. In an embodiment, the application provides Form LI-2, further characterized by a PXRD pattern having peaks at about 14.77, 21.44, 21.99 and $22.65 \pm 0.2^\circ 2\theta$.

In another aspect, the present application provides a process for preparing a complex of Lumacaftor and Ivacaftor, which comprises:

- a) combining Lumacaftor and Ivacaftor in the presence of a solvent
- b) removing the solvent from the mixture of step a);
- c) isolating complex of Lumacaftor and Ivacaftor.

In another aspect, the present application provides a process for preparing a complex of Lumacaftor and Ivacaftor, which comprises:

- a) combining Lumacaftor and Ivacaftor in the presence of a solvent
- b) contacting an anti-solvent with the mixture of step a);
- c) isolating complex of Lumacaftor and Ivacaftor.

In another aspect, the present application provides a process for preparing a complex of Lumacaftor and Ivacaftor, which comprises:

- a) combining Lumacaftor and Ivacaftor optionally in the presence of a solvent

b) isolating complex of Lumacaftor and Ivacaftor.

In another aspect, the present application provides a process for the preparation of Form LI-1 of crystalline complex of Lumacaftor and Ivacaftor, comprising the steps

- a) providing a solution of Lumacaftor and Ivacaftor in ethanol or a mixture of ethanol and another solvent;
- b) removing the solvent of step a);
- c) isolating Form LI-1 of crystalline complex of Lumacaftor and Ivacaftor.

In another aspect, the present application provides a process for the preparation of Form LI-2 of crystalline complex of Lumacaftor and Ivacaftor, comprising the step of drying Form LI-1 of crystalline complex of Lumacaftor and Ivacaftor.

In another aspect, the present application provides an amorphous phase of Lumacaftor and Ivacaftor.

In another aspect, the present application provides a process for the preparation of amorphous phase of Lumacaftor and Ivacaftor, comprising the steps of:

- a) providing a solution of Lumacaftor and Ivacaftor in a suitable solvent or a mixture thereof;
- b) removing the solvent from the solution obtained in step a), and
- c) isolating the amorphous phase of Lumacaftor and Ivacaftor.
- d) optionally combining amorphous phase of Lumacaftor and Ivacaftor of step c) with at least one additional pharmaceutically acceptable excipient.

In an aspect, the present application provides a process for the preparation of amorphous phase of Lumacaftor and Ivacaftor, comprising the step of blending amorphous Lumacaftor and amorphous Ivacaftor, optionally in the presence of pharmaceutically acceptable excipient.

In another aspect, the present application provides pharmaceutical composition comprising complex of Lumacaftor and Ivacaftor together with at least one pharmaceutically acceptable excipient.

In another aspect, the present application provides a pharmaceutical composition comprising crystalline complex of Lumacaftor and Ivacaftor together with at least one pharmaceutically acceptable excipient.

In another aspect, the present application provides a pharmaceutical composition comprising amorphous phase of Lumacaftor and Ivacaftor together with at least one pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is an illustrative X-ray powder diffraction pattern of amorphous form of Lumacaftor prepared by the method of Example No 1.

Figure 2 is an illustrative X-ray powder diffraction pattern of amorphous form of Lumacaftor prepared by the method of Example No 3.

Figure 3 is an illustrative X-ray powder diffraction pattern of amorphous form of Lumacaftor prepared by the method of Example No 4.

Figure 4 is an illustrative X-ray powder diffraction pattern of amorphous solid dispersion of Lumacaftor with povidone K-30 prepared by the method of Example No 5.

Figure 5 is an illustrative X-ray powder diffraction pattern of amorphous solid dispersion of Lumacaftor with co-povidone NF prepared by the method of Example No 6.

Figure 6 is an illustrative X-ray powder diffraction pattern of amorphous solid dispersion of Lumacaftor with povidone K-30 and Syloid-244 FP NF prepared by the method of Example No 5.

Figure 7 is an illustrative X-ray powder diffraction pattern of amorphous solid dispersion of Lumacaftor with co-povidone NF and Syloid-244 FP NF prepared by the method of Example No 6.

Figure 8 is an illustrative X-ray powder diffraction pattern of amorphous solid dispersion of Lumacaftor with HPMC and Syloid-244 FP NF prepared by the method of Example No 7.

Figure 9 is an illustrative X-ray powder diffraction pattern of amorphous solid dispersion of Lumacaftor with HPMC prepared by the method of Example No 8.

Figure 10 is an illustrative X-ray powder diffraction pattern of crystalline Form I of Lumacaftor prepared by the method of Example No 10.

Figure 11 is an illustrative X-ray powder diffraction pattern of amorphous form of Lumacaftor prepared by the method of Example No 13.

Figure 12 is an illustrative X-ray powder diffraction pattern of Form LI-1 of crystalline complex of Lumacaftor and Ivacaftor prepared by the method of Example No 15.

Figure 13 is an illustrative X-ray powder diffraction pattern of Form LI-2 of crystalline complex of Lumacaftor and Ivacaftor prepared by the method of Example No 16.

Figure 14 is an illustrative X-ray powder diffraction pattern of amorphous phase of Lumacaftor and Ivacaftor prepared by the method of Example No 17.

DETAILED DESCRIPTION

In an aspect, the present application provides an amorphous form of Lumacaftor.

In an embodiment, the present application provides an amorphous form of Lumacaftor characterized by a powder X-ray diffraction (PXRD) pattern, substantially as illustrated by Figures 1, 2 or 3.

The present application provides a stable amorphous form of Lumacaftor suitable for powder handling and downstream processes.

In an embodiment, the amorphous form of Lumacaftor is stable for at least 2 months when packed in amber colored bottle and stored at ambient conditions.

In an embodiment, the amorphous form of Lumacaftor is stable for at least 1 month in all ICH storage conditions including (i) $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $65\%\text{RH} \pm 5\text{RH}$ (ii) $35^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $75\%\text{RH} \pm 5\text{RH}$ (iii) $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $75\%\text{RH} \pm 5\text{RH}$ and (iv) $2^{\circ}\text{C} - 8^{\circ}\text{C}$.

Amorphous form of Lumacaftor of the present application is surprisingly found to be also stable under mechanical stress such as grinding and milling. Further, the amorphous form of Lumacaftor is stable even under accelerated ICH conditions with relative humidity of more than 60% RH. In embodiments, the amorphous Lumacaftor is stable for more than 1 month when stored in any of the ICH packing conditions. In an embodiment, the present application provides a stable amorphous form of Lumacaftor with less than 5% of crystallinity, preferably with less than 1% crystallinity and more preferably devoid of crystallinity as per X-ray diffraction analysis.

In another aspect, the present application provides a process for the preparation of an amorphous form of Lumacaftor, comprising the steps of:

- a) providing a solution of Lumacaftor in a suitable solvent or a mixture thereof;
- b) removing the solvent from the solution obtained in step a); and
- c) isolating the amorphous form of Lumacaftor.
- d) optionally combining amorphous form of step c) with at least one pharmaceutically acceptable excipient

In an embodiment, suitable solvent at step a) of this aspect may be selected from C1-C6 alcohols, C3-C6 ketones, C5-C8 aliphatic or aromatic hydrocarbons, C3-C6 esters, C2-C6 aliphatic or cyclic ethers, C2-C6 nitriles, halogenated hydrocarbons, water or mixtures thereof.

In preferred embodiment, the suitable solvent may be selected from the group comprising of alcohol solvents such as methanol, ethanol, 2-propanol, 1-butanol, 2-

butanol, 1-pentanol, 2-pentanol, 3-pentanol; ketone solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone; esters solvents such as methyl acetate, ethyl acetate, isopropyl acetate; water and mixtures thereof.

In an embodiment, providing a solution at step a) may be carried out by dissolving Lumacaftor in a suitable solvent or by taking the reaction mixture containing Lumacaftor directly. In an embodiment, a solution of Lumacaftor can 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 an embodiment, a solution of Lumacaftor may be filtered to make it clear, free of unwanted particles. In embodiments, 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 an embodiment, removal of solvent at step b) may be carried out by methods known in the art or any procedure disclosed in the present application. In preferred embodiments, 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, thin film drying, agitated thin film drying and the like.

In preferred embodiment, the solvent may be removed under reduced pressures and at temperatures of less than about 100°C, less than about 60°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, depending upon the technique, solvent and equipment employed for the removal of the solvent.

In an embodiment, the isolation of an amorphous form of Lumacaftor at step c) involves recovering the solid obtained in step b). The solid obtained from step b) may be recovered using techniques such as by scraping, or by shaking the container, or adding solvent to make slurry followed by filtration, or other techniques specific to the equipment used. In an embodiment, the amorphous form of Lumacaftor obtained from step b) may be optionally dried before or after isolating it at step c).

Amorphous form of Lumacaftor obtained at step c) may be optionally combined with at least one pharmaceutically acceptable excipient at step d).

In an embodiment, amorphous form of Lumacaftor may be combined with

excipient using a technique known in the art or by the procedures disclosed in the present application.

In preferred embodiment, amorphous form of Lumacaftor may be combined with excipient either by physical blending of both the solid components or by suspending both the components in a suitable solvent and conditions, such that both the components remain unaffected. Blending may be carried out using techniques known in the art such as rotatory cone dryer, fluidized bed dryer or the like optionally under reduced pressure / vacuum or inert atmosphere such nitrogen at suitable temperature and sufficient time to obtain uniform composition of amorphous form of Lumacaftor and at least one pharmaceutically acceptable excipient.

In an embodiment, amorphous form of Lumacaftor may be combined with the excipient by evaporating the suspension or solution of amorphous form of Lumacaftor and at least one pharmaceutically acceptable excipient.

In an embodiment, pharmaceutically acceptable excipient may include, but not limited to an inorganic oxide such as SiO₂, TiO₂, ZnO₂, ZnO, Al₂O₃ and zeolite; a water insoluble polymer is selected from the group consisting of cross-linked polyvinyl pyrrolidinone, cross-linked cellulose acetate phthalate, cross-linked hydroxypropyl methyl cellulose acetate succinate, microcrystalline cellulose, polyethylene/polyvinyl alcohol copolymer, polyethylene/polyvinyl pyrrolidinone copolymer, cross-linked carboxymethyl cellulose, sodium starch glycolat, and cross-linked styrene divinyl benzene or any other excipient at any aspect of present application.

In preferred embodiment, pharmaceutically acceptable excipient may be selected from the group consisting of silicon dioxide, e.g. colloidal or fumed silicon dioxide or porous silica; copolymers, such as polyethylene/polyvinyl alcohol copolymer, polyethylene/polyvinyl pyrrolidinone copolymer; and cellulose, preferably microcrystalline cellulose.

Amorphous form of Lumacaftor isolated at step c) or d) may be dried in suitable drying equipment such as vacuum oven, rotatory cone dryer, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying may be carried out at atmospheric pressure or under reduced pressures at temperatures of less than about 100°C, less than about 60°C, less than about 40°C, or any other suitable temperatures. The drying may be carried out for any time period required for obtaining a desired quality, such as from about 15 minutes to 10 hours or longer.

In another aspect, the present application provides a process for the preparation of

amorphous Lumacaftor, comprising the steps of;

- a) providing a solution of Lumacaftor in a suitable solvent or a mixture thereof;
- b) contacting the solution obtained in step a) with an anti-solvent;
- c) isolating amorphous form of Lumacaftor.

In an embodiment, step a) of this aspect may be carried out by providing a solution of Lumacaftor in a suitable solvent or a mixture thereof.

Suitable solvent may be selected from the group comprising of alcohol solvents such as alcohol such methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 2-pentanol, 3-pentanol; ketone solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone; ester solvents such as methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, n-butyl acetate, iso-butyl acetate; halogenated hydrocarbon such as dichloromethane, chloroform, tetrachloro methane; aromatic hydrocarbon such as toluene, xylene, cumene; ether solvents such as di ethyl ether, di isopropyl ether, tetrahydrofuran, dioxane, anisole; nitrile solvents such as acetonitrile, propionitrile; aprotic solvents such as dimethyl sulphoxide, formamide, dimethyl formamide, dimethyl acetamide, water and mixtures thereof.

In an embodiment, providing a solution at step a) may be carried out by dissolving Lumacaftor in a suitable solvent or by taking the reaction mixture containing Lumacaftor directly. Lumacaftor used in providing the solution of step a) may be in any solid form such as crystalline, amorphous or a mixture thereof. In an embodiment, a solution of Lumacaftor can 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 an embodiment, a solution of Lumacaftor may be filtered to make it clear, free of unwanted particles. In embodiments, the obtained solution may be optionally treated with an adsorbent material, such as carbon and/or hydrosorbent, to remove colored components, etc., before filtration.

Step b) of this aspect may be carried out optionally by contacting the solution of step a) with an anti-solvent. The anti-solvent may be a solvent in which Lumacaftor has low solubility and which include, but not limited to water; hydrocarbons like n-pentane, n-hexane, n-heptane, cyclohexane, methyl cyclohexane; ethers like diethyl ether, di isopropyl ether or mixtures thereof.

In an embodiment, the anti-solvent of step (b) may be contacted either by adding anti-solvent to the solution of step (a) or by adding the solution of step (a) to the anti-

solvent.

In an embodiment, the anti-solvent of step (b) may be contacted with solution of step (a) for sufficient time for the precipitation of amorphous Lumacaftor. In embodiments, the anti-solvent of step (b) may be contacted with solution of step (a) either in one portion or multiple small portions or by drop wise addition.

In an embodiment, anti-solvent of step (b) may be contacted with solution of step a) at suitable temperature of about 0°C and reflux temperature of the solvent used. In preferred embodiment, anti-solvent of step (b) may be contacted with solution of step a) at temperature of about 50°C and above.

In an embodiment, anti-solvent may be contacted in sufficient quantity to precipitate amorphous Lumacaftor from the reaction mixture.

In an embodiment, the mixture of a) or step b) may be cooled to relatively lower temperatures to complete the formation of amorphous form Lumacaftor.

In an embodiment, the mixture of step a) or step b) may be cooled to suitable temperature at which amorphous Lumacaftor is stable and / or does not crystallize. Mixture of step a) or step b) may be cooled either drastically or gradually, at a constant or step wise cooling rate based on the required quality of the product such as chemical purity, particle size or shape.

The mixture of step a) or step b) may be stirred under suitable conditions at which amorphous Lumacaftor is stable and / or does not crystallize. In an embodiment, the mixture of step a) or step b) may be stirred at suitable temperature and for sufficient time to complete precipitation of amorphous Lumacaftor.

Step c) of this aspect may be carried out by isolating amorphous form of Lumacaftor by employing any of the techniques known to a person skilled in art. Techniques for the isolation of amorphous of Lumacaftor include, but not limited to: decantation, filtration by gravity or suction,

Amorphous form of Lumacaftor isolated at step c) may be dried in suitable drying equipment such as vacuum oven, rotatory cone dryer, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying may be carried out at atmospheric pressure or under reduced pressures at temperatures of less than about 100°C, less than about 60°C, less than about 40°C, or any other suitable temperatures. The drying may be carried out for any time period required for obtaining a desired quality, such as from about 15 minutes to 10 hours or longer.

In an aspect, the present application provides pharmaceutical composition comprising amorphous form of Lumacaftor and atleast one pharmaceutically acceptable excipient.

In an aspect, the present application provides amorphous solid dispersion of Lumacaftor together with atleast one pharmaceutically acceptable excipient.

In an embodiment, the present application provides amorphous solid dispersion of Lumacaftor together with atleast one pharmaceutically acceptable excipient characterized by a powder X-ray diffraction (PXRD) pattern, substantially as illustrated by Figures 4, 5, 6 or 7.

In another aspect, the present application provides a process for the preparation of an amorphous solid dispersion of Lumacaftor, comprising the steps of:

- e) providing a solution of Lumacaftor and atleast one pharmaceutically acceptable excipient in a suitable solvent or a mixture thereof;
- f) removing the solvent from the solution obtained in step a), and
- g) isolating the amorphous solid dispersion of Lumacaftor.
- h) optionally combining amorphous solid dispersion of step c) with atleast one additional pharmaceutically acceptable excipient.

In an embodiment, suitable solvent at step a) of this aspect may be selected from C1-C6 alcohols, C3-C6 ketones, C5-C8 aliphatic or aromatic hydrocarbons, C3-C6 esters, C2-C6 aliphatic or cyclic ethers, C2-C6 nitriles, halogenated hydrocarbons, water or mixtures thereof.

In preferred embodiment, the suitable solvent may be selected from the group consisting of alcohol solvents such as methanol, ethanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 2-pentanol, 3-pentanol; ketone solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone; esters solvents such as methyl acetate, ethyl acetate, isopropyl acetate; water and mixtures thereof.

In an embodiment, atleast one pharmaceutically acceptable excipient of this aspect 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, polyethylene glycol monomethyl ether, polyethylene glycol, poloxamer 188, pluronic F-68, methylcellulose, methacrylic acid copolymer (Eudragit), hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose, hydroxypropyl cellulose SL, hydroxyethyl

cellulose, gelucire 44/14, ethyl cellulose, D-alpha-tocopheryl polyethylene glycol 1000 succinate, cellulose acetate phthalate, carboxymethylethylcellulose and 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, dextrans, 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.

In an embodiment, providing a solution at step a) may be carried out by dissolving Lumacaftor and at least one pharmaceutically acceptable excipient in a suitable solvent simultaneously or by dissolving components in a suitable solvent separately to form individual solutions and combining those solutions later.

In an embodiment, a solution of Lumacaftor 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 an embodiment, a solution of Lumacaftor and the excipient may be filtered to make it clear, free of unwanted particles. In embodiments, 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 an embodiment, removal of solvent at step b) may be carried out by methods known in the art or any procedure disclosed in the present application. In preferred embodiments, 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 preferred embodiment, the solvent may be removed under reduced pressures, at temperatures of less than about 100°C, less than about 60°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, depending upon the technique, solvent and equipment employed for the removal of the solvent.

In an embodiment, the isolation of an amorphous solid dispersion of Lumacaftor and excipient at step c) involves recovering the solid obtained in step b). The solid obtained from step b) may be recovered using techniques such as by scraping, or by shaking the container, or adding solvent to make slurry followed by filtration, or other techniques specific to the equipment used.

In an embodiment, the amorphous solid dispersion of Lumacaftor and excipient obtained from step b) may be optionally dried before or after isolating at step c).

Amorphous solid dispersion of Lumacaftor obtained at step c) may be optionally combined with at least one additional pharmaceutically acceptable excipient at step d).

In an embodiment, amorphous solid dispersion of Lumacaftor may be combined with additional excipient using a technique known in the art or by the procedures disclosed in the present application.

In preferred embodiment, amorphous solid dispersion of the present application may be combined with additional excipient either by physical blending of both the solid components or by suspending both the components in a suitable solvent and conditions, such that both the components remain unaffected. Blending may be carried out using techniques known in the art such as rotatory cone dryer, fluidized bed dryer or the like optionally under reduced pressure / vacuum or inert atmosphere such as nitrogen at suitable temperature and sufficient time to obtain uniform composition of amorphous solid dispersion of Lumacaftor with pharmaceutically acceptable excipient and at least one additional pharmaceutically acceptable excipient.

In an embodiment, amorphous solid dispersion of the present application may be combined with additional excipient by evaporating the suspension or solution of amorphous solid dispersion of Lumacaftor and additional excipient.

In an embodiment, pharmaceutically acceptable additional excipient may be same or different from the excipient used in the preparation of amorphous solid dispersion of Lumacaftor. Additional excipient may include, but not limited to an inorganic oxide such as SiO₂, TiO₂, ZnO₂, ZnO, Al₂O₃ and zeolite; a water insoluble polymer is selected from the group consisting of cross-linked polyvinyl pyrrolidinone, cross-linked cellulose acetate phthalate, cross-linked hydroxypropyl methyl cellulose acetate succinate, microcrystalline cellulose, polyethylene/polyvinyl alcohol copolymer, polyethylene/polyvinyl pyrrolidinone copolymer, cross-linked carboxymethyl cellulose,

sodium starch glycolat, and cross-linked styrene divinyl benzene or any other excipient at any aspect of present application.

In preferred embodiment, pharmaceutically acceptable additional excipient may be selected from the group consisting of silicon dioxide, e.g. colloidal or fumed silicon dioxide or porous silica; copolymers, such as polyethylene/polyvinyl alcohol copolymer, polyethylene/polyvinyl pyrrolidinone copolymer; and cellulose, preferably microcrystalline cellulose.

Amorphous solid dispersion of Lumacaftor isolated at step c) or d) may be dried in a suitable drying equipment such as tray dryer, vacuum oven, rotatory cone dryer, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying may be carried out at atmospheric pressure or under reduced pressures at temperatures of less than about 100°C, less than about 60°C, less than about 40°C, or any other suitable temperatures. The drying may be carried out for any time period required for obtaining a desired quality, such as from about 15 minutes to 10 hours or longer.

In an aspect, the present application provides pharmaceutical composition comprising amorphous solid dispersion of Lumacaftor with atleast one pharmaceutically acceptable excipient and atleast one additional pharmaceutically acceptable excipient.

In an aspect, the present application provides pharmaceutical compositions comprising amorphous Lumacaftor and atleast one pharmaceutically acceptable excipient, in particular in the form of solid dispersions and adsorbates, and a process for preparing the same. In embodiments, the pharmaceutically acceptable excipient is selected from the excipients at any aspect of present application.

In embodiments, the present application provides adsorbates, wherein Lumacaftor is associated with a suitable substrate. Suitable substrate may be a particulate and/or porous substrate, wherein this substrate has an outer and/or inner surface onto which the API may be adsorbed. This means that if the substrate has pores, these pores are filled by the Lumacaftor and the substrate remains unaffected, it does not, at least not essentially, change during and / or after the adsorption. In embodiments, the suitable substrate is selected from the excipients at any aspect of present application.

Amorphous form of Lumacaftor or its solid dispersion may be obtained alternatively either by employing a melt-extrusion technique. In embodiment, amorphous product may be obtained by employing suitable melt-extrusion conditions or any of the procedures known in the art for obtaining amorphous product by melt-extrusion technique.

In another aspect, the present application provides amorphous Lumacaftor, its solid dispersion or pharmaceutical composition comprising Lumacaftor having a chemical purity of at least 99% by HPLC or at least 99.5% by HPLC or at least 99.9% by HPLC.

In another aspect, the present application provides a process for the preparation of crystalline Form I of Lumacaftor, comprising the steps of:

- a) providing a solution of Lumacaftor in a suitable solvent or a mixture thereof;
- b) optionally contacting the solution obtained in step a) with an anti-solvent;
- c) isolating crystalline Form I of Lumacaftor.

In an embodiment, step a) of this aspect may be carried out by providing a solution of Lumacaftor in a suitable solvent or a mixture thereof.

Suitable solvent may be selected from the group comprising of alcohol solvents such as alcohol such methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 2-pentanol, 3-pentanol; ketone solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone; ester solvents such as methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, n-butyl acetate, iso-butyl acetate; halogenated hydrocarbon such as dichloromethane, chloroform, tetrachloro methane; aromatic hydrocarbon such as toluene, xylene, cumene; nitrile solvents such as acetonitrile, propionitrile; aprotic solvents such as dimethyl sulphoxide, formamide, dimethyl formamide, dimethyl acetamide, water and mixtures thereof.

In an embodiment, providing a solution at step a) may be carried out by dissolving Lumacaftor in a suitable solvent or by taking the reaction mixture containing Lumacaftor directly. Lumacaftor used in providing the solution of step a) may be in any solid form such as crystalline, amorphous or a mixture thereof. In an embodiment, a solution of Lumacaftor can 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 an embodiment, a solution of Lumacaftor may be filtered to make it clear, free of unwanted particles. In embodiments, the obtained solution may be optionally treated with an adsorbent material, such as carbon and/or hydrosorbent, to remove colored components, etc., before filtration.

Step b) of this aspect may be carried out optionally by contacting the solution of step a) with an anti-solvent. The anti-solvent may be a solvent in which Lumacaftor has low solubility and which include, but not limited to water; hydrocarbons like n-pentane, n-hexane, n-heptane, cyclohexane, methyl cyclohexane; ethers like diethyl ether, di

isopropyl ether or mixtures thereof.

In an embodiment, the anti-solvent of step (b) may be contacted either by adding anti-solvent to the solution of step (a) or by adding the solution of step (a) to the anti-solvent.

In an embodiment, the anti-solvent of step (b) may be contacted with solution of step (a) for sufficient time for the crystallization of Form I of Lumacaftor. In embodiments, the anti-solvent of step (b) may be contacted with solution of step (a) either in one portion or multiple small portions or by drop wise addition.

In an embodiment, anti-solvent of step (b) may be contacted with solution of step a) at suitable temperature of about 0°C and reflux temperature of the solvent used.

In an embodiment, anti-solvent may be contacted in sufficient quantity to crystallize Form I of Lumacaftor from the reaction mixture.

In an embodiment, the mixture of step a) or step b) may be cooled to relatively lower temperatures to crystallize or complete the formation of crystalline Form I of Lumacaftor.

In an embodiment, the solution of Lumacaftor of step a) may be cooled to suitable temperature at which crystalline Form I is stable and / or readily crystallizes out from the solution. Solution of Lumacaftor of step a) may be cooled either drastically or gradually, at a constant or step wise cooling rate based on the required quality of the product such as chemical purity, particle size or shape.

In another embodiment, the mixture of step b) may be cooled to suitable temperature at which crystalline Form I is stable and / or completely crystallizes out.

The mixture of step a) or step b) may be stirred under suitable conditions in which crystalline Form I. In an embodiment, the mixture of step a) or step b) may be stirred at suitable temperature and for sufficient time to completely crystallize Form I of Lumacaftor. In an embodiment, the mixture may be stirred at a suitable temperature of about 0°C and above for atleast 0.5 hour or more.

Step c) of this aspect may be carried out by isolating crystalline Form I of Lumacaftor by employing any of the techniques known to a person skilled in art. Techniques for the isolation of crystalline Form I of Lumacaftor include, but not limited to: decantation, filtration by gravity or suction,

Crystalline Form I of Lumacaftor isolated at step c) may be dried in suitable drying equipment such as vacuum oven, rotatory cone dryer, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying may be carried out at atmospheric

pressure or under reduced pressures at temperatures of less than about 100°C, less than about 60°C, less than about 40°C, or any other suitable temperatures. The drying may be carried out for any time period required for obtaining a desired quality, such as from about 15 minutes to 10 hours or longer.

In another aspect, the present application provides a process for the preparation of crystalline Form I of Lumacaftor, comprising the step of converting amorphous Lumacaftor to crystalline Form I of Lumacaftor.

In an embodiment, the step of converting amorphous Lumacaftor to crystalline Form I may be carried out by suspending or re-crystallizing amorphous Lumacaftor in a suitable solvent or mixture of solvents.

Re-crystallizing amorphous Lumacaftor may be carried out by according previous aspect or any of the methods or procedures described or exemplified in the present application.

In an embodiment, amorphous Lumacaftor may be suspended in a suitable solvent or mixture of solvents under suitable conditions in which crystalline Form I is stable.

In an embodiment, suitable solvent may be selected from the group consisting of alcohol solvents such as water; aprotic solvents such as dimethyl sulphoxide, formamide, dimethyl formamide, dimethyl acetamide; alcohol such methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 1-pentanol, 2-pentanol, 3-pentanol; ketone solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone; ester solvents such as methyl acetate, ethyl acetate, isopropyl acetate, n-propyl acetate, n-butyl acetate, iso-butyl acetate; halogenated hydrocarbon such as dichloromethane, chloroform, tetrachloro methane; aromatic hydrocarbon such as toluene, xylene, cumene; ether solvents such as di ethyl ether, di isopropyl ether, tetrahydrofuran, dioxane, anisole; nitrile solvents such as acetonitrile, propionitrile; and mixtures thereof.

In an embodiment, amorphous Lumacaftor may be suspended in water or aqueous organic solvent mixture under suitable conditions in which crystalline Form I is stable.

In an embodiment, amorphous Lumacaftor may be suspended in the solvent at suitable temperature between 0°C and reflux temperature of the solvent used. In an embodiment, amorphous Lumacaftor may be suspended in the solvent for sufficient time to complete the conversion of amorphous form to crystalline Form I of Lumacaftor for atleast 0.5 hours or more.

In an embodiment, the isolation of crystalline Form I of Lumacaftor may be carried out by employing any of the techniques known to a person skilled in art.

Techniques for the isolation of Lumacaftor include, but not limited to: decantation, filtration by gravity or suction, centrifugation, and the like, and optionally washing with a solvent.

Crystalline Form I of Lumacaftor may be dried in suitable drying equipment such as vacuum oven, rotatory cone dryer, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying may be carried out at atmospheric pressure or under reduced pressures at temperatures of less than about 100°C, less than about 60°C, less than about 40°C, or any other suitable temperatures. The drying may be carried out for any time period required for obtaining a desired quality, such as from about 15 minutes to 10 hours or longer.

In another aspect, the present application provides crystalline Form I of Lumacaftor obtained according any of the previous aspects. The present application provides a crystalline Form I of Lumacaftor having x-ray diffraction pattern as depicted in figure – 1.

In another aspect, the present application provides a process for the preparation of crystalline form of Lumacaftor or a solvate thereof, comprising the step of converting amorphous Lumacaftor to crystalline form of Lumacaftor. In embodiments, the crystalline form may be selected from crystalline Form I or solvate Form A or any other crystalline form of Lumacaftor or a solvate thereof

In another aspect, the present application provides a pharmaceutical composition comprising crystalline Form I of Lumacaftor obtained according any of the previous aspects and atleast one additional pharmaceutically acceptable excipient.

The prior art exemplified the processes involving either the conversion of a salt of Lumacaftor such as HCl salt or the hydrolysis of an ester of Lumacaftor such as t. Bu ester to obtain crystalline Form I of Lumacaftor which are different from the processes of the present application. Further, the processes of present application are simple and industrially viable procedures to obtain crystalline Form I of Lumacaftor.

Amorphous form, its preparation methods or the process of converting amorphous form to crystalline form of Lumacaftor are not reported in the literature.

The processes of the aspects of the present application may be useful to enhance the chemical purity and stability of the product obtained.

In another aspect, the present application provides crystalline Form I of Lumacaftor or its pharmaceutical composition, wherein the chemical purity of

Lumacaftor may be more than 99% by HPLC or more than 99.5% by HPLC or more than 99.9% by HPLC.

In the aspects of the present application, Lumacaftor that is used as starting material may be purified employing any of the purification techniques known in the art or procedures described or exemplified in the instant application, before using.

In an aspect, the present application provides a complex of Lumacaftor and Ivacaftor. In specific aspects, the present application provides crystalline complex or amorphous phase of Lumacaftor and Ivacaftor.

In another aspect, the present application provides Form LI-1 of crystalline complex of Lumacaftor and Ivacaftor, characterized by a PXRD pattern comprising peaks at about 6.13, 10.36, 10.69, 11.21, 13.55, 14.25 and $20.88 \pm 0.2^\circ 2\theta$. In an embodiment, the application provides Form LI-1, further characterized by a PXRD pattern having peaks at about 12.33, 15.12, 17.75, 22.64 and $23.92 \pm 0.2^\circ 2\theta$.

In an embodiment, the present application provides Form LI-1 of crystalline complex of Lumacaftor and Ivacaftor, characterized by a PXRD pattern substantially as shown in figure 12.

In another aspect, the present application provides Form LI-2 of crystalline complex of Lumacaftor and Ivacaftor, characterized by a PXRD pattern comprising peaks at about 7.44, 8.77, 12.09, 16.45, 17.74 and $20.37 \pm 0.2^\circ 2\theta$. In an embodiment, the application provides Form LI-2, further characterized by a PXRD pattern having peaks at about 14.77, 21.44, 21.99 and $22.65 \pm 0.2^\circ 2\theta$.

In an embodiment, the present application provides Form LI-2 of crystalline complex of Lumacaftor and Ivacaftor, characterized by a PXRD pattern substantially as shown in figure 13.

Lumacaftor and Ivacaftor present in the complex of Lumacaftor and Ivacaftor according to instant application may contain in any desired ratio, for example the ratio of Lumacaftor to Ivacaftor may be 1: 1.25 or 2:1.25 or any other ratio suitable to impart desired activity or based on the regulatory requirement by any agency.

In another aspect, the present application provides a process for preparing a complex of Lumacaftor and Ivacaftor, which comprises:

- a) combining Lumacaftor and Ivacaftor with a suitable solvent;

- b) removing the solvent from the mixture of step a);
- c) isolating complex of Lumacaftor and Ivacaftor.

Step a) of this aspect may be carried out by combining Lumacaftor and Ivacaftor in the presence of a solvent or a mixture thereof.

In an embodiment, the mixture of Lumacaftor and Ivacaftor may be combined with solvent at any suitable temperatures, such as at about 0°C to about the reflux temperature of the solvent or mixture thereof.

In an embodiment the mixture of Lumacaftor and Ivacaftor in the solvent may be either a heterogeneous or homogeneous phase.

In an embodiment, the mixture of Lumacaftor and Ivacaftor in solvent may be optionally filtered to make particle free solution when it is a homogeneous clear solution and treated with a decolorizing agent, such as carbon, before filtration.

Step b) of this aspect may be carried out by removal of solvent employing any method known in the art or any procedure disclosed in the present application. In preferred embodiments, removal of solvent may include, but not limited to: slow solvent evaporation, fast solvent evaporation under atmospheric pressure or reduced pressure / vacuum using suitable equipment such as Büchi® Rotavapor®, spray drier, thin film drier, sublimation of the components using freeze drier and the like.

In an embodiment, solvent may be removed partially or completely from the mixture of step a). In an embodiment, additional solvent may be added to the mixture of step b) when the solvent is removed completely.

In an embodiment, the mixture of step a) or step b) may be stirred for sufficient time and suitable temperature to complete the formation of complex of Lumacaftor and Ivacaftor.

Step c) of this aspect may be carried out by isolation of complex of Lumacaftor and Ivacaftor by any methods known in the art or procedures described in the present application. In an embodiment, complex of Lumacaftor and Ivacaftor may be isolated by employing any of the techniques, but not limited to: decantation, filtration by gravity or suction, centrifugation, adding solvent to make slurry followed by filtration, or other techniques specific to the equipment used and the like, and optionally washing with a solvent.

In an embodiment, isolated complex of Lumacaftor and Ivacaftor may be dried in a suitable drying equipment such as tray dryer, vacuum oven, rotatory cone dryer, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying may be carried out at atmospheric pressure or under reduced pressures at temperatures of less than about 150°C, less than about 120°C, less than about 100°C, or any other suitable temperatures. Drying can

be carried out at temperatures and times sufficient to achieve desired quality of product. Drying may be carried out for any time period required for obtaining a desired quality, such as from about 15 minutes to 10 hours or longer.

In another aspect, the present application provides a process for preparing a complex of Lumacaftor and Ivacaftor, which comprises:

- a) combining Lumacaftor and Ivacaftor in the presence of a solvent;
- b) contacting an anti-solvent with the mixture of step a);
- c) isolating complex of Lumacaftor and Ivacaftor.

Step a) of this aspect may be carried out by combining Lumacaftor and Ivacaftor in the presence of a solvent or a mixture thereof.

In an embodiment, the mixture of Lumacaftor and Ivacaftor may be combined with solvent at any suitable temperatures, such as at about 0°C to about the reflux temperature of the solvent or mixture thereof.

In an embodiment the mixture of Lumacaftor and Ivacaftor in the solvent may be either a heterogeneous or homogeneous phase.

In an embodiment, the mixture of Lumacaftor and Ivacaftor in solvent may be optionally filtered to make particle free solution when it is a homogeneous clear solution and treated with a decolorizing agent, such as carbon, before filtration.

In an embodiment, the mixture of Lumacaftor and Ivacaftor in solvent may be cooled to suitable temperature for the precipitation of complex of Lumacaftor and Ivacaftor from the mixture. In an embodiment, the mixture of Lumacaftor and Ivacaftor in solvent may be cooled drastically or gradually with either constant rate of cooling or by step-wise cooling periodically to achieve desired complex of Lumacaftor and Ivacaftor.

In an embodiment, the mixture of Lumacaftor and Ivacaftor in solvent may be stirred for sufficient time to complete formation of complex of Lumacaftor and Ivacaftor. In an embodiment, the mixture of Lumacaftor and Ivacaftor in solvent may be stirred for at least 1 hour or more, preferably for at least 24 hours or more and more preferably at least 48 hours or more.

In an embodiment, the mixture of Lumacaftor and Ivacaftor in solvent may be stirred at suitable temperature for the formation of complex of Lumacaftor and Ivacaftor. In an embodiment, the mixture of Lumacaftor and Ivacaftor in solvent may be stirred at 0°C and above, preferably between 0°C to reflux temperature of the solvent used, more preferably between 0°C and 50°C.

Step b) of this aspect may be carried out by contacting an anti-solvent with the mixture of step a). In an embodiment, an anti-solvent may be contacted for sufficient time and at suitable temperature to complete the formation of complex of Lumacaftor and Ivacaftor. Anti-solvent is a solvent in which the complex of Lumacaftor and Ivacaftor has minimum solubility and it may include but not limited to water; aliphatic hydrocarbons, such as hexane, heptane, cyclohexane; aromatic hydrocarbons, such as toluene, xylene and chlorobenzene; ethers, such as diethyl ether, di-isopropyl ether, tetrahydrofuran, dioxane; or the like.

In an embodiment, anti-solvent may be added to the mixture of step a) or the mixture of step a) may be added to the anti-solvent. The addition may be carried out either by drastically by one pot addition or in multiple pots or gradually with controlled rate of addition.

In an embodiment, isolation of complex of Lumacaftor and Ivacaftor may be carried out by any methods known in the art or procedures described in the present application. In an embodiment, complex of Lumacaftor and Ivacaftor may be isolated by employing any of the techniques, but not limited to: decantation, filtration by gravity or suction, centrifugation, adding solvent to make slurry followed by filtration, or other techniques specific to the equipment used and the like, and optionally washing with a solvent.

In an embodiment, isolated complex of Lumacaftor and Ivacaftor may be dried in a suitable drying equipment such as tray dryer, vacuum oven, rotatory cone dryer, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying may be carried out at atmospheric pressure or under reduced pressures at temperatures of less than about 150°C, less than about 120°C, less than about 100°C, or any other suitable temperatures. Drying can be carried out at temperatures and times sufficient to achieve desired quality of product. Drying may be carried out for any time period required for obtaining a desired quality, such as from about 15 minutes to 10 hours or longer.

In another aspect, the present application provides a process for preparing a complex of Lumacaftor and Ivacaftor, which comprises:

- a) combining Lumacaftor and Ivacaftor optionally in the presence of a solvent;
- b) isolating complex of Lumacaftor and Ivacaftor.

Step a) of this aspect may be carried out by combining Lumacaftor and Ivacaftor optionally in the presence of a solvent or a mixture thereof.

In an embodiment, Lumacaftor and Ivacaftor may be combined either on the presence

or absence of a solvent according to any of the suitable techniques known in the art. Suitable techniques may include, but not limited to blending, grinding or milling the mixture of Lumacaftor and Ivacaftor, optionally in the presence of a solvent such as solvent-drop grinding method or a melt-crystallization of the mixture of Lumacaftor and Ivacaftor.

In an embodiment, the mixture of Lumacaftor and Ivacaftor optionally in the presence of a solvent may be ground in suitable equipment known in the art such as mortar-pestle, ball mill, wet mill or the like.

In an embodiment, the mixture of Lumacaftor and Ivacaftor may be subjected to melt-crystallization i.e., heating the mixture of Lumacaftor and Ivacaftor to obtain molten mass at suitable temperature and cooling it back to crystalize.

In an embodiment, the mixture of Lumacaftor and Ivacaftor may be suspended in a solvent or mixture of solvents for sufficient time and at suitable temperature to afford a complex of Lumacaftor and Ivacaftor.

The complex of Lumacaftor and Ivacaftor obtained by the process of any aspects of the present application is Form LI-1, characterized by a PXRD pattern comprising peaks at about 6.13, 10.36, 10.69, 11.21, 13.55, 14.25 and $20.88 \pm 0.2^\circ 2\theta$. In an embodiment, Form LI-1 is further characterized by a PXRD pattern having peaks at about 12.33, 15.12, 17.75, 22.64 and $23.92 \pm 0.2^\circ 2\theta$. In another embodiment, Form LI-1 is characterized by a PXRD pattern substantially as shown in figure 12.

The complex of Lumacaftor and Ivacaftor obtained by the process of any aspects of the present application is Form LI-2, characterized by a PXRD pattern comprising peaks at about 7.44, 8.77, 12.09, 16.45, 17.74 and $20.37 \pm 0.2^\circ 2\theta$. In an embodiment, Form LI-2 is further characterized by a PXRD pattern having peaks at about 14.77, 21.44, 21.99 and $22.65 \pm 0.2^\circ 2\theta$. In another embodiment, Form LI-2 is characterized by a PXRD pattern substantially as shown in figure 13.

In another aspect, the present application provides a process for the preparation of Form LI-1 of crystalline complex of Lumacaftor and Ivacaftor, comprising the steps

- a) providing a solution of Lumacaftor and Ivacaftor in ethanol or a mixture of ethanol and another solvent;
- b) removing the solvent of step a);
- c) isolating Form LI-1 of crystalline complex of Lumacaftor and Ivacaftor.

Step a) of this aspect may be carried out by dissolving Lumacaftor and Ivacaftor in

ethanol or a mixture of ethanol and another solvent or by dissolving Lumacaftor and Ivacaftor separately in ethanol or a mixture of ethanol and another solvent and combining the two solutions.

Dissolution may be carried out by heating the mixture of Lumacaftor and / or Ivacaftor in ethanol or a mixture thereof from about 25°C to reflux temperature of ethanol or mixture thereof. The solution may be made particle free by filtering the solution, optionally the solution may be treated with carbon, hydrosorb or any decolorizing agent before filtration.

Step b) may be carried out by removing the solvent from the solution of step a). Solvent removal may be carried out by evaporating the solvent either under reduced pressure or atmospheric pressure using suitable equipment such as Buchi rotavapour, rotatory cone vacuum drier, spray drier, thin film drier or the like. In an embodiment, the solvent removal may be carried out by sublimation using suitable equipment such as freeze drier or the like.

In an embodiment, the solvent may be partially or completely evaporated from the solution of step a). In embodiments, where the solvent of step a) is completely evaporated, additional amount solvent may be added.

In an embodiment, the mixture of Lumacaftor and Ivacaftor may be suspended in ethanol or a mixture of ethanol and other solvent for sufficient time and at suitable temperature to afford Form LI-1 of the complex of Lumacaftor and Ivacaftor.

In an embodiment, the contents of step b) may be stirred for sufficient time to completely precipitate the complex for atleast one hour or more. In an embodiment, the contents may be stirred at a suitable temperature at about 0°C and above.

Isolation of Form LI-1 of crystalline complex of Lumacaftor and Ivacaftor may be carried out by any methods known in the art or procedures described in the present application. In an embodiment, Form LI-1 of complex may be isolated by employing any of the techniques, but not limited to: decantation, filtration by gravity or suction, centrifugation, adding solvent to make slurry followed by filtration, or other techniques specific to the equipment used and the like, and optionally washing with a solvent.

In another aspect, the present application provides a process for the preparation of Form LI-2 of crystalline complex of Lumacaftor and Ivacaftor, comprising the step of drying Form LI-1 of crystalline complex of Lumacaftor and Ivacaftor.

In an embodiment, drying Form LI-1 of crystalline complex may be carried out in suitable drying equipment such as air drier like tray drier; vacuum driers like tray driers, Buchi rotavapour, rotatory cone vacuum driers; controlled humidifiers or the like.

In an embodiment, drying Form LI-1 of crystalline complex may be carried out at suitable temperatures of about 25°C to 150°C. In an embodiment, drying Form LI-1 may be carried out at about 80°C to 120°C.

In an embodiment, drying Form LI-1 of crystalline complex may be carried out for sufficient time for complete conversion of Form LI-1 to Form LI-2. In an embodiment, drying Form LI-1 may be carried out for at least 15 minutes or more.

In another aspect, the present application provides an amorphous phase of Lumacaftor and Ivacaftor.

In an embodiment, the amorphous phase of Lumacaftor and Ivacaftor may optionally comprise at least one pharmaceutically acceptable excipient and / or anti-oxidant.

In an embodiment, the present application provides an amorphous phase of Lumacaftor and Ivacaftor, characterized by a PXRD pattern substantially as shown in figure 14.

In an embodiment, amorphous phase of Lumacaftor and Ivacaftor may be obtained by combining desired ratios of Lumacaftor and Ivacaftor to obtain a stable and suitable product for development.

In an aspect, the present application provides a process for the preparation of amorphous phase of Lumacaftor and Ivacaftor, comprising the step of blending amorphous Lumacaftor and amorphous Ivacaftor, optionally in the presence of a pharmaceutically acceptable excipient.

In an embodiment, starting materials such as amorphous form of Lumacaftor may be obtained by methods or procedures described in the previous aspects of instant application, while the amorphous form of Ivacaftor may be obtained according to any methods known in the art.

In an embodiment, amorphous phase of Lumacaftor and Ivacaftor may be obtained by combining amorphous Lumacaftor with amorphous Ivacaftor in desired ratio.

Lumacaftor and Ivacaftor present in the amorphous phase of Lumacaftor and Ivacaftor according to instant application may contain in any desired ratio, for example the ratio of Lumacaftor to Ivacaftor may be 1: 1.25 or 2:1.25 or any other ratio suitable to impart desired activity or based on the regulatory requirement by any agency.

In an embodiment, amorphous phase of Lumacaftor and Ivacaftor may be obtained either by blending of Lumacaftor and Ivacaftor or by combining both these components in the presence of a solvent and suitable conditions. Lumacaftor and Ivacaftor may be combined

according to methods known in the art or by the procedures described or exemplified in any aspect of instant application.

In an embodiment, amorphous phase of Lumacaftor and Ivacaftor may be obtained by physical blending of Lumacaftor and Ivacaftor in suitable blending equipment known in the art such as rotatory cone dryer, fluidized bed dryer or the like optionally under reduced pressure or inert atmosphere such as nitrogen at suitable temperature and sufficient time to obtain uniform amorphous phase of Lumacaftor and Ivacaftor.

In an embodiment, amorphous phase of Lumacaftor and Ivacaftor may be obtained by combining amorphous Lumacaftor with amorphous Ivacaftor in desired mole ratio, for example 1:1.25 or 2:1.25 according to suitable methods such as physical blending. In an embodiment, amorphous phase of Lumacaftor and Ivacaftor may be obtained by blending amorphous Lumacaftor with amorphous Ivacaftor physically in a desired mole ratio suitable to impart desired activity or based on the regulatory requirement by any agency.

In an alternative embodiment, amorphous phase of Lumacaftor and Ivacaftor may be obtained by the suspending or dissolving Lumacaftor and Ivacaftor in a solvent and isolating amorphous phase of Lumacaftor and Ivacaftor.

In another aspect, the present application provides a process for the preparation of amorphous phase of Lumacaftor and Ivacaftor, comprising the steps of:

- a) providing a solution of Lumacaftor and Ivacaftor in a suitable solvent or a mixture thereof;
- b) removing the solvent from the solution obtained in step a), and
- c) isolating the amorphous phase of Lumacaftor and Ivacaftor.
- d) optionally combining amorphous phase of Lumacaftor and Ivacaftor of step c) with atleast one additional pharmaceutically acceptable excipient.

In an embodiment, providing a solution at step a) may be carried out by dissolving Lumacaftor and Ivacaftor in a suitable solvent simultaneously or by dissolving components in a suitable solvent separately to form individual solutions and combining those solutions later. In an embodiment, a solution of step a) may be prepared optionally in the presence of a pharmaceutically acceptable excipient.

In an embodiment, a solution of Lumacaftor and Ivacaftor 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 an embodiment, a solution of Lumacaftor and Ivacaftor may be filtered to make it

clear, free of unwanted particles. In embodiments, 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 an embodiment, removal of solvent at step b) may be carried out by methods known in the art or any procedure disclosed in the present application. In preferred embodiments, 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 preferred embodiment, the solvent may be removed under reduced pressures, at temperatures of less than about 100°C, less than about 60°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 depending upon the technique, solvent and equipment employed for the removal of the solvent.

In an embodiment, the isolation of amorphous phase of Lumacaftor and Ivacaftor at step c) involves recovering the solid obtained in step b). The solid obtained from step b) may be recovered using techniques such as by scraping, or by shaking the container, or adding solvent to make slurry followed by filtration, or other techniques specific to the equipment used.

In an embodiment, the amorphous phase of Lumacaftor and Ivacaftor obtained from step b) may be optionally dried before or after isolating at step c).

Amorphous phase of Lumacaftor and Ivacaftor obtained at step c) may be optionally combined with at least one additional pharmaceutically acceptable excipient at step d).

In an embodiment, amorphous phase of Lumacaftor and Ivacaftor may be combined with additional excipient using a technique known in the art or by the procedures disclosed in the present application.

In an embodiment, amorphous phase of Lumacaftor and Ivacaftor of the present application may be combined with the excipient either by physical blending of both the solid components or by suspending both the components in a suitable solvent and conditions, such that both the components remain unaffected. Blending may be carried out using techniques known in the art such as physical blending in rotatory cone dryer, fluidized bed dryer or the like optionally under reduced pressure / vacuum or inert atmosphere such nitrogen at suitable temperature and sufficient time to obtain uniform composition of amorphous phase of Lumacaftor and Ivacaftor.

Pharmaceutically acceptable excipient of this aspect 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, polyethylene glycol monomethyl ether, polyethylene glycol, poloxamer 188, pluronic F-68, methylcellulose, methacrylic acid copolymer (Eudragit), hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, hydroxypropylmethyl cellulose, hydroxypropyl cellulose SL, hydroxyethyl cellulose, gelucire 44/14, ethyl cellulose, D-alpha-tocopheryl polyethylene glycol 1000 succinate, cellulose acetate phthalate, carboxymethylethylcellulose and 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, dextrans, 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 inorganic oxide such as Syloid, SiO₂, TiO₂, ZnO₂, ZnO, Al₂O₃ and zeolite; a water insoluble polymer is selected from the group consisting of cross-linked polyvinyl pyrrolidinone, cross-linked cellulose acetate phthalate, cross-linked hydroxypropyl methyl cellulose acetate succinate, microcrystalline cellulose, polyethylene/polyvinyl alcohol copolymer, polyethylene/polyvinyl pyrrolidinone copolymer, cross-linked carboxymethyl cellulose, sodium starch glycolat, and cross-linked styrene divinyl benzene 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.

Solvent that may be used in any aspect of the present application may include, but not limited to water; ketones, such as acetone, methyl ethyl ketone, methyl isobutyl ketone, and diethyl ketone; esters, such as ethyl acetate, propyl acetate, isopropyl acetate, and butyl acetate; alcohols, such as methanol, ethanol, ethylene glycol, 1-propanol, 2-propanol (isopropyl alcohol), 1-butanol, 2-butanol, iso-butyl alcohol, t-butyl alcohol, 2-ethoxyethanol;

nitriles, such as acetonitrile and propionitrile; halogenated hydrocarbons, such as dichloromethane, chloroform and carbontetrachloride; and dimethoxyethane; aprotic non-polar solvents such as dimethylsulfoxide; formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone; any mixtures of two or more thereof.

The ratio of Lumacaftor to Ivacaftor that may be used in the preparation of the complex or amorphous phase of Lumacaftor and Ivacaftor according to any aspect of the instant application may contain any desired ratio, for example the ratio of Lumacaftor to Ivacaftor may be 1: 1.25 or 2:1.25 or any other ratio suitable to impart desired activity or based on the regulatory requirement by any agency.

Lumacaftor and / or Ivacaftor that may be used as starting material for the preparation of complex or amorphous phase of Lumacaftor and Ivacaftor in any of the aspects of the present application may be either in a crystalline or amorphous form or in any other solid form reported in the literature.

Lumacaftor and / or Ivacaftor that may be used in any aspect of the present application may be purified by any methods known in the art such as column chromatography, fractional distillation, acid-base treatment, slurring or re-crystallization, before using.

In another aspect, the present application provides pharmaceutical composition comprising complex or amorphous phase of Lumacaftor and Ivacaftor together with at least one pharmaceutically acceptable excipient. In an embodiment, the present application provides a pharmaceutical composition comprising crystalline forms of complex of Lumacaftor and Ivacaftor together with at least one pharmaceutically acceptable excipient.

In another aspect, the present application provides pharmaceutical composition comprising complex of Lumacaftor and Ivacaftor and at least one pharmaceutically acceptable excipient, wherein complex of Lumacaftor and Ivacaftor may be selected from group comprising of Form LI-1, Form LI-2 and amorphous form of complex of Lumacaftor and Ivacaftor or mixtures thereof.

In another aspect, the present application provides complex or amorphous phase of Lumacaftor and Ivacaftor or its pharmaceutical composition comprising Lumacaftor and / or Ivacaftor having a chemical purity of at least 99% by HPLC or at least 99.5% by HPLC or at least 99.9% by HPLC.

In another aspect, the present application provides crystalline or amorphous forms of Lumacaftor or its pharmaceutical composition, wherein particle size (D90) of Lumacaftor may be less than 100 microns or less than 50 microns or less than 20 microns.

In embodiment, the particle size of Lumacaftor obtained according to any of the aspects of instant application may be reduced using any of the suitable techniques known in the art such as wet or dry milling. In embodiment, the particle size obtained before or after particle size reduction may be less than 100 microns or less than 50 microns or less than 20 microns.

X-ray powder diffraction patterns described herein were generated using a Bruker AXS D8 Advance powder X-ray diffractometer with a copper K-alpha radiation source. Generally, a diffraction angle (2θ) in powder X-ray diffractometry may have an error in the range of $\pm 0.2^\circ$. Therefore, the aforementioned diffraction angle values should be understood as including values in the range of about $\pm 0.2^\circ$. Accordingly, the present invention includes not only crystals whose peak diffraction angles in powder X-ray diffractometry completely coincide with each other, but also crystals whose peak diffraction angles coincide with each other with an error of about $\pm 0.2^\circ$. Therefore, in the present specification, the phrase "having a diffraction peak at a diffraction angle (2θ) $\pm 0.2^\circ$ of 6.3° " means "having a diffraction peak at a diffraction angle (2θ) of 6.1° to 6.5° ". Although the intensities of peaks in the x-ray powder diffraction patterns of different batches of a compound may vary slightly, the peak relationships and the peak locations are characteristic for a specific polymorphic form. The relative intensities of the PXRD peaks may vary somewhat, depending on factors such as the sample preparation technique, crystal size distribution, various filters used, the sample mounting procedure, and the particular instrument employed. Moreover, instrumental variation and other factors may slightly affect the 2-theta values. Therefore, the term "substantially" in the context of PXRD is meant to encompass that peak assignments may vary by plus or minus about 0.2° . Moreover, new peaks may be observed or existing peaks may disappear, depending on the type of the machine or the settings (for example, whether a filter is used or not).

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 $\pm 10\%$, preferably within a range of $\pm 5\%$, more preferably within a range of $\pm 2\%$, still more preferably within a range of $\pm 1\%$ of its value. For example "about 10" should be construed as meaning within the range of 9 to 11, preferably within the range of 9.5 to 10.5, more preferably within the range of 9.8 to 10.2, and still more preferably within the range of 9.9 to 10.1.

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.

The terms "amorphous form of Lumacaftor" and "amorphous Lumacaftor" indicate that the Lumacaftor is present in substantially amorphous state in the composition (e.g. solid dispersion, adsorbate or pharmaceutical composition). "Substantially" amorphous denotes that 90 %, preferably 95 % or 99 %, more preferably all of the Lumacaftor being present in the solid dispersion, on the adsorbate or in the pharmaceutical composition is amorphous. In other words, an "amorphous" Lumacaftor composition denotes a Lumacaftor-containing composition, which does not contain substantial amounts, preferably does not contain noticeable amounts, of crystalline portions of Lumacaftor 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 Lumacaftor, preferably 90%, 95% or all of the Lumacaftor 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.

The term "adsorbate" when used in the present application, specifies that the Lumacaftor is, preferably evenly, and preferably homogeneously, distributed on the inner and/or outer surface of the particulate substrate.

The terms "crystalline Form I of Lumacaftor" indicates that the Lumacaftor is present in substantially crystalline Form I. "Substantially" crystalline denotes that at least 80 %, preferably 90 % or 95 %, more preferably all of the Lumacaftor is crystalline Form I. In other words, "crystalline Form I" of Lumacaftor denotes Lumacaftor, which does not contain substantial amounts, preferably does not contain noticeable amounts, of any other crystalline portions of Lumacaftor e.g. measurable upon X-ray powder diffraction analysis.

The terms "complex of Lumacaftor and Ivacaftor" or "complex" includes a molecular entity formed by association of two or more component molecular entities (ionic or uncharged), or by association of two or more chemical species. The bonding between the components may be non-covalent and is normally weaker than covalent bonding. Accordingly, the complex of Lumacaftor and Ivacaftor described herein is a molecular entity formed by the association between Lumacaftor and Ivacaftor. The Lumacaftor-Ivacaftor complex may in some embodiments exist as a solid state form that is referred to herein as a salt or an inclusion complex or supra-molecular complex or co-crystal form of Lumacaftor-Ivacaftor complex or as an Lumacaftor-Ivacaftor co-crystal or as a crystalline Lumacaftor-Ivacaftor complex.

The terms "crystalline complex of Lumacaftor and Ivacaftor" or "crystalline complex" includes solvates, hydrates, and anhydrides of complex of Lumacaftor and Lumacaftor. The percent crystallinity of any of the crystalline forms of complex described herein can vary with respect to the total amount of complex. In particular, certain embodiments provide for the percent crystallinity of a crystalline form of complex being at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 99%. In some embodiments, the percent crystallinity can be substantially 100%, where substantially 100% indicates that the entire amount of complex appears to be crystalline as best can be determined using methods known in the art.

The term "amorphous phase of Lumacaftor and Ivacaftor" when used in the present application, denotes a state where most of the Lumacaftor and Ivacaftor, preferably 90%, 95% or all of the Lumacaftor and / or Ivacaftor of the amorphous phase, is homogeneously molecularly dispersed. Preferably amorphous phase, relates to a molecular dispersion where the component molecules are uniformly but irregularly dispersed in a non-ordered way. In other words, in an amorphous phase, the two components form a homogeneous one-phase

system. In a preferred embodiment, in the amorphous phase of Lumacaftor and Ivacaftor according to the present invention no chemical bonds can be detected between the components. The amorphous phase of Lumacaftor and Ivacaftor may in some embodiments exist as a solid state form that is referred to herein as a solid dispersion or a premix of Lumacaftor and Ivacaftor or as an amorphous solid dispersion of Lumacaftor and Ivacaftor.

An “alcohol” is an organic compound containing a carbon bound to a hydroxyl group. “C1-C6 alcohols” include, but are not limited to, methanol, ethanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, hexafluoroisopropyl alcohol, ethylene glycol, 1-propanol, 2-propanol (isopropyl alcohol), 2-methoxyethanol, 1-butanol, 2-butanol, i-butyl alcohol, t-butyl alcohol, 2-ethoxyethanol, diethylene glycol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, cyclohexanol, phenol, glycerol, or the like.

An “aliphatic hydrocarbon” is a liquid hydrocarbon compound, which may be linear, branched, or cyclic and may be saturated or have as many as two double bonds. A liquid hydrocarbon compound that contains a six-carbon group having three double bonds in a ring is called “aromatic.” Examples of “C5-C8 aliphatic or aromatic hydrocarbons” include, but are not limited to, n-pentane, isopentane, neopentane, n-hexane, isohexane, 3-methylpentane, 2,3-dimethylbutane, neohexane, n-heptane, isohexane, 3-methylhexane, neoheptane, 2,3-dimethylpentane, 2,4-dimethylpentane, 3,3-dimethylpentane, 3-ethylpentane, 2,2,3-trimethylbutane, n-octane, isooctane, 3-methylheptane, neooctane, cyclohexane, methylcyclohexane, cycloheptane, benzene, toluene, ethylbenzene, m-xylene, o-xylene, p-xylene, trimethylbenzene, chlorobenzene, fluorobenzene, trifluorotoluene, anisole, or any mixtures thereof.

An “ester” is an organic compound containing a carboxyl group $-(C=O)-O-$ bonded to two other carbon atoms. “C3-C6 esters” include, but are not limited to, ethyl acetate, n-propyl acetate, n-butyl acetate, isobutyl acetate, t-butyl acetate, ethyl formate, methyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like.

An “ether” is an organic compound containing an oxygen atom $-O-$ bonded to two other carbon atoms. “C2-C6 ethers” include, but are not limited to, diethyl ether, diisopropyl ether, methyl t-butyl ether, glyme, diglyme, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, dibutyl ether, dimethylfuran, 2-methoxyethanol, 2-ethoxyethanol, anisole, or the like.

A “halogenated hydrocarbon” is an organic compound containing a carbon bound to a halogen. Halogenated hydrocarbons include, but are not limited to, dichloromethane, 1,2-dichloroethane, trichloroethylene, perchloroethylene, 1,1,1-trichloroethane, 1,1,2-

trichloroethane, chloroform, carbon tetrachloride, or the like.

A “ketone” is an organic compound containing a carbonyl group $-(C=O)-$ bonded to two other carbon atoms. “C3-C6 ketones” include, but are not limited to, acetone, ethyl methyl ketone, diethyl ketone, methyl isobutyl ketone, ketones, or the like.

A “nitrile” is an organic compound containing a cyano $-(C\equiv N)$ bonded to another carbon atom. “C2-C6Nitriles” include, but are not limited to, acetonitrile, propionitrile, butanenitrile, or the like.

EXAMPLES

Example-1: Preparation of Amorphous form of Lumacaftor

Lumacaftor (0.5 g) was dissolved in methanol (30 mL) at 45°C and filtered the solution to make it particle free. The clear solution was taken into a Buchi flask and evaporated the solvent completely using rotavapour under vacuum at 55°C to obtain the title compound. XRPD: Amorphous.

Example-2: Preparation of Amorphous form of Lumacaftor.

Lumacaftor (0.5 g) was dissolved in acetone (20 mL) at 50°C and filtered the solution to make it particle free. The clear solution was taken into a Buchi flask and evaporated the solvent completely using rotavapour under vacuum at 55°C to obtain the title compound. XRPD: Amorphous.

Example-3: Preparation of Amorphous form of Lumacaftor

Lumacaftor (0.5 g) was dissolved in methanol (30 mL) at 50°C and filtered the solution to make it particle free. The clear solution was taken into a Buchi flask and evaporated the solvent completely using rotavapour under vacuum at 55°C. Syloid-244 FP NF (0.5 g) was added to it and blended at 25°C for 25 minutes to obtain title compound. XRPD: Amorphous

Example-4: Preparation of Amorphous form of Lumacaftor

Lumacaftor (2 g) was dissolved in methanol (100 mL) at 50°C and filtered the solution to make it particle free. The clear solution was spray dried with 70% aspirator, flow rate of 9 mL/ minute and inlet temperature of 80°C and out let temperature of 46°C to obtain the title compound. XRPD: Amorphous.

Example-5: Preparation of Amorphous solid dispersion of Lumacaftor and Povidone

Lumacaftor (0.5 g) was dissolved in methanol (60 mL) at 50°C and filtered the solution to make it particle free. Povidone K-30 solution (0.5 g in 20 mL of methanol) was added to above Lumacaftor solution. The combined solution was taken into a Buchi flask and

evaporated the solvent completely using rotavapour under vacuum at 55°C to obtain amorphous solid dispersion. Syloid-244 FP NF (0.5 g) was added to it and blended at 25°C for 13 minutes to obtain title compound. XRPD: Amorphous.

Example-6: Preparation of Amorphous solid dispersion of Lumacaftor and Co-povidone.

Lumacaftor (0.5 g) was dissolved in methanol (60 mL) at 50°C and filtered the solution to make it particle free. Co-povidone NF solution (0.5 g in 20 mL of methanol) was added to above Lumacaftor solution. The combined solution was taken into a Buchi flask and evaporated the solvent completely using rotavapour under vacuum at 55°C to obtain amorphous solid dispersion. Syloid-244 FP NF (0.5 g) was added to it and blended at 25°C for 19 minutes to obtain title compound. XRPD: Amorphous.

Example-7: Preparation of Amorphous solid dispersion of Lumacaftor and hydroxypropylmethylcellulose (HPMC).

Lumacaftor (0.5 g) was dissolved in methanol (10 mL) at 50°C and filtered the solution to make it particle free. HPMC solution (0.5 g in 20 mL of methanol) was added to above Lumacaftor solution. The combined solution was taken into a Buchi flask and evaporated the solvent completely using rotavapour under vacuum at 55°C to obtain amorphous solid dispersion. Syloid-244 FP NF (0.5 g) was added to it and blended at 25°C for 10 minutes to obtain title compound. XRPD: Amorphous.

Example-8: Preparation of Amorphous solid dispersion of Lumacaftor and hydroxypropylmethylcellulose (HPMC) by spray drying.

Lumacaftor (2 g) was dissolved in methanol (30 mL) at 55°C and filtered the solution to make it particle free. HPMC solution (2 g in 30 mL of methanol) was added to above Lumacaftor solution. The clear solution was spray dried with 65% aspirator, flow rate of 6 mL/ minute and inlet temperature of 70°C and out let temperature of 42°C to obtain the title compound. XRPD: Amorphous

Example-9: Preparation of crystalline Form I of Lumacaftor.

Lumacaftor (0.5 g) was dissolved in ethyl acetate (10 mL) at 70°C and cooled the mixture to 27°C. This mixture was stirred at the same temperature for 1 hour and filtered the solid to obtain the title compound.

Example-10: Preparation of crystalline form I of Lumacaftor

Lumacaftor (0.5 g) was dissolved in 1-propanol (15 mL) at 65°C and cooled the mixture to 27°C. This mixture was stirred for 1 hour at the same temperature and filtered the solid to obtain title compound.

Example-11: Preparation of crystalline form I of Lumacaftor

Lumacaftor (0.5 g) was dissolved in methanol (20 mL) at 70°C and filtered the solution to make it particle free. This clear solution was added to water (30 mL) at 27°C and stirred for 4 hours at the same temperature. The solid was filtered to obtain the title compound.

Example-12: Preparation of crystalline form I of Lumacaftor

Amorphous Lumacaftor (0.2 g) was suspended in water (4 mL) at 27°C and stirred at the same temperature for 24 hours. The solid was filtered to obtain the title compound.

Example-13: Preparation of amorphous Lumacaftor.

Lumacaftor (0.2 g) was dissolved in dimethyl sulphoxide (1.2 mL) at 78°C and water (3 mL) was added at 80°C to this clear solution. This mixture was cooled to 25°C and stirred at the same temperature for 2.5 hours. Some of the reaction mass was filtered to obtain amorphous form of Lumacaftor.

Example-14: Preparation of crystalline form I of Lumacaftor

The remaining suspension of example-5 containing amorphous Lumacaftor in the mixture of dimethyl sulphoxide and water was stirred at 27°C for 5 hours and the solid was filtered to obtain the title compound.

Example-15: Preparation of Form LI-1 of crystalline complex of Lumacaftor and Ivacaftor

A mixture of Lumacaftor (1.0 g) and Ivacaftor (0.867 g) was dissolved in ethanol (100 mL) at 60°C for 24 minutes. The clear solution was evaporated under reduced pressure at 60°C to remove the solvent. Ethanol (50 mL) was added and stirred the suspension for 21 hours at 25°C. Solids were filtered to obtain the title compound.

Example-16: Preparation of Form LI-2 of crystalline complex of Lumacaftor and Ivacaftor

Form LI-1 obtained in example-1 was dried in air tray drier at 120°C for 2 hours to obtain the title compound.

Example-17: Preparation of amorphous phase of Lumacaftor and Ivacaftor

Lumacaftor (2.0 g) and Ivacaftor (1.25 g) were dissolved in methanol (200 mL) at 60°C and filtered the solution to make it particle free. Evaporated the solvent from the above solution using a spray drier at 30% feed pump flow, 70% aspirator at 70°C and 42°C of inlet and outlet temperatures respectively to obtain title compound.

CLAIMS

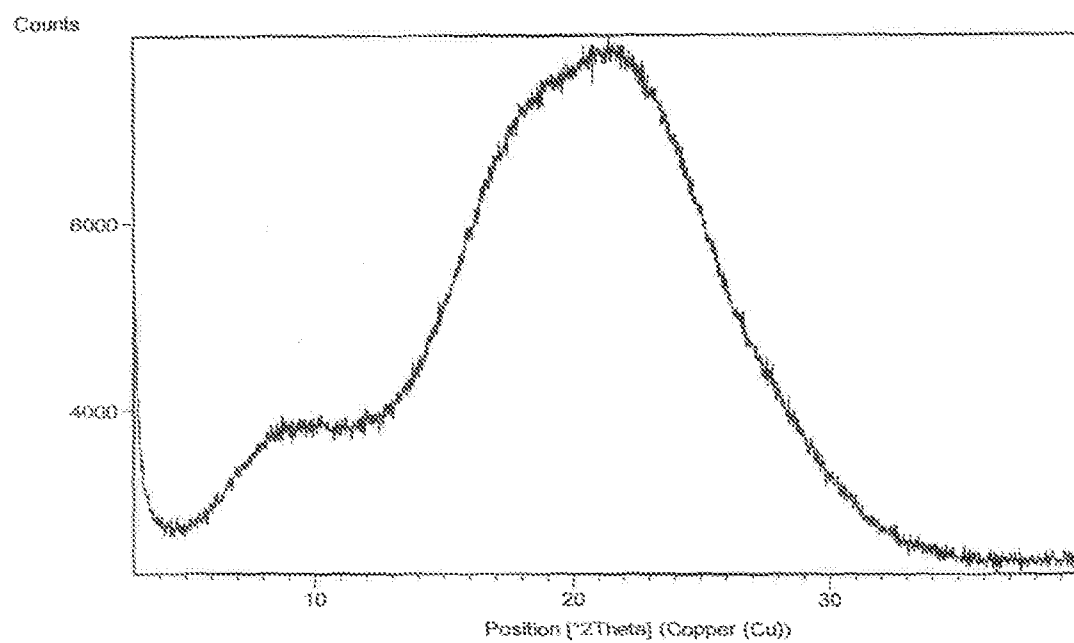
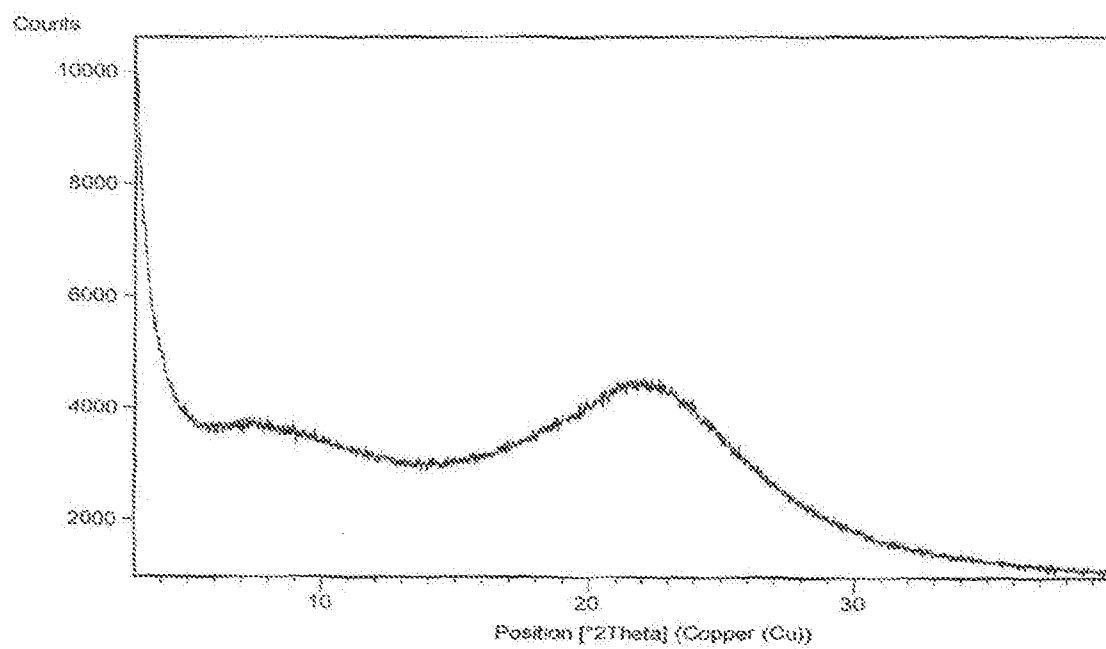
1. An amorphous form of Lumacaftor.
2. A process for the preparation of an amorphous form of Lumacaftor, comprising the steps of:
 - a) providing a solution of Lumacaftor in a suitable solvent or a mixture thereof;
 - b) removing the solvent from the solution obtained in step a); and
 - c) isolating the amorphous form of Lumacaftor.
 - d) optionally combining the amorphous form of step c) with at least one pharmaceutically acceptable excipient.
3. A process of claim 2, wherein suitable solvent at step a) may be selected from the group comprising of alcohol solvents such as methanol, ethanol, 2-propanol; ketone solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone; or mixtures thereof.
4. A process of claims 2, wherein the pharmaceutically acceptable excipient at step d) is selected from the group comprising of silicon dioxide such as colloidal or fumed silicon dioxide or porous silica; copolymers such as polyethylene/polyvinyl alcohol copolymer, polyethylene/polyvinyl pyrrolidinone copolymer; and cellulose such as microcrystalline cellulose.
5. An amorphous solid dispersion of Lumacaftor together with at least one pharmaceutically acceptable excipient.
6. An amorphous solid dispersion of Lumacaftor of claim 3, wherein the pharmaceutically acceptable excipient is selected from the group comprising of polyvinyl pyrrolidine, 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, polyethylene glycol monomethyl ether, polyethylene glycol, poloxamer 188, pluronic F-68, methylcellulose, methacrylic acid copolymer (Eudragit), hydroxypropylmethyl cellulose (HPMC), hydroxypropylmethyl cellulose phthalate (HPMC phthalate), hydroxypropylmethyl cellulose acetate succinate (HPMC AS), hydroxypropyl cellulose SL (HPC), hydroxy ethyl cellulose (HEC) and ethyl cellulose (EC).
7. A process for the preparation of an amorphous solid dispersion of Lumacaftor with at least one pharmaceutically acceptable excipient, comprising the steps of:

- a) providing a solution of Lumacaftor and at least one pharmaceutically acceptable excipient in a suitable solvent or a mixture thereof;
 - b) removing the solvent from the solution obtained in step a) and
 - c) isolating the amorphous solid dispersion of Lumacaftor.
 - d) optionally combining amorphous solid dispersion of step c) with at least one additional pharmaceutically acceptable excipient.
8. A process of claims 7, wherein suitable solvent at step a) may be selected from the group comprising of alcohol solvents such as methanol, ethanol, 2-propanol; ketone solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone; or mixtures thereof.
9. A process of claims 7, wherein the pharmaceutically acceptable excipient at step d) is selected from the group comprising of silicon dioxide such as colloidal or fumed silicon dioxide or porous silica; copolymers such as polyethylene/polyvinyl alcohol copolymer, polyethylene/polyvinyl pyrrolidinone copolymer; and cellulose such as microcrystalline cellulose.
10. A pharmaceutical composition comprising an amorphous form of Lumacaftor together and at least one pharmaceutically acceptable excipient.
11. A pharmaceutical composition comprising an amorphous solid dispersion of Lumacaftor with at least one pharmaceutically acceptable excipient and at least one additional pharmaceutically acceptable excipient.
12. A process for the preparation of crystalline Form I of Lumacaftor, comprising the steps of:
- a) providing a solution of Lumacaftor in a suitable solvent or a mixture thereof;
 - b) optionally contacting the solution obtained in step a) with an anti-solvent;
 - c) isolating crystalline Form I of Lumacaftor.
13. A process for the preparation of crystalline Form I of Lumacaftor, comprising the step of converting amorphous Lumacaftor to crystalline Form I of Lumacaftor.
14. A process for the preparation of crystalline form of Lumacaftor or a solvate thereof, comprising the step of converting amorphous Lumacaftor to crystalline form of Lumacaftor or a solvate thereof.
15. A process for the preparation of amorphous form of Lumacaftor, comprising the steps of:
- a) providing a solution of Lumacaftor in a suitable solvent or a mixture thereof;
 - b) contacting the solution obtained in step a) with an anti-solvent;

- c) isolating amorphous form of Lumacaftor.
- 16.** A complex of Lumacaftor and Ivacaftor.
- 17.** A crystalline complex of Lumacaftor and Ivacaftor.
- 18.** Crystalline Form LI-1 of complex of Lumacaftor and Ivacaftor, characterized by a PXRD pattern comprising peaks at 6.13, 10.36, 10.69, 11.21, 13.55, 14.25 and $20.88 \pm 0.2^\circ 2\theta$.
- 19.** Crystalline Form LI-1 of claim 18, further characterized by a PXRD pattern having peaks at 12.33, 15.12, 17.75, 22.64 and $23.92 \pm 0.2^\circ 2\theta$.
- 20.** Crystalline Form LI-2 of complex of Lumacaftor and Ivacaftor, characterized by a PXRD pattern comprising peaks at 7.44, 8.77, 12.09, 16.45, 17.74 and $20.37 \pm 0.2^\circ 2\theta$.
- 21.** Crystalline Form LI-2 of claim 20, further characterized by a PXRD pattern having peaks at 14.77, 21.44, 21.99 and $22.65 \pm 0.2^\circ 2\theta$.
- 22.** A complex of claim 16, wherein the complex is a co-crystal of Lumacaftor and Ivacaftor.
- 23.** A process for preparing a complex of Lumacaftor and Ivacaftor, which comprises:
 - a) combining Lumacaftor and Ivacaftor in the presence of a solvent
 - b) removing the solvent from the mixture of step a);
 - c) isolating complex of Lumacaftor and Ivacaftor.
- 24.** A process for preparing a complex of Lumacaftor and Ivacaftor, which comprises:
 - a) combining Lumacaftor and Ivacaftor in the presence of a solvent
 - b) contacting an anti-solvent with the mixture of step a);
 - c) isolating complex of Lumacaftor and Ivacaftor.
- 25.** A process for preparing a complex of Lumacaftor and Ivacaftor, which comprises:
 - a) combining Lumacaftor and Ivacaftor optionally in the presence of a solvent
 - b) isolating complex of Lumacaftor and Ivacaftor.
- 26.** A process for the preparation of crystalline Form LI-1 of complex of Lumacaftor and Ivacaftor, comprising the steps
 - a) providing a solution of Lumacaftor and Ivacaftor in ethanol or a mixture of ethanol and another solvent;
 - b) removing the solvent of step a);
 - c) isolating crystalline Form LI-1 of complex of Lumacaftor and Ivacaftor.
- 27.** A process for the preparation of crystalline Form LI-2 of complex of Lumacaftor and Ivacaftor, comprising the step of drying crystalline Form LI-1 of complex of

Lumacaftor and Ivacaftor.

28. An amorphous phase of Lumacaftor and Ivacaftor.
29. A process for the preparation of amorphous phase of Lumacaftor and Ivacaftor, comprising the steps of:
 - a) providing a solution of Lumacaftor and Ivacaftor in a suitable solvent or a mixture thereof;
 - b) removing the solvent from the solution obtained in step a), and
 - c) isolating the amorphous phase of Lumacaftor and Ivacaftor.
 - d) optionally combining amorphous phase of Lumacaftor and Ivacaftor of step c) with at least one additional pharmaceutically acceptable excipient.
30. A process for the preparation of amorphous phase of Lumacaftor and Ivacaftor, comprising the step of blending amorphous Lumacaftor and amorphous Ivacaftor.
31. A pharmaceutical composition comprising a complex of Lumacaftor and Ivacaftor together with at least one pharmaceutically acceptable excipient.
32. A pharmaceutical composition comprising crystalline complex of Lumacaftor and Ivacaftor together with at least one pharmaceutically acceptable excipient.
33. A pharmaceutical composition of claim 32, wherein crystalline complex of Lumacaftor and Ivacaftor is selected from the group comprising of Crystalline Form LI-1, Crystalline Form LI-2 and a mixture thereof.
34. A pharmaceutical composition comprising amorphous phase of Lumacaftor and Ivacaftor together with at least one pharmaceutically acceptable excipient.

**Figure 1****Figure 2**

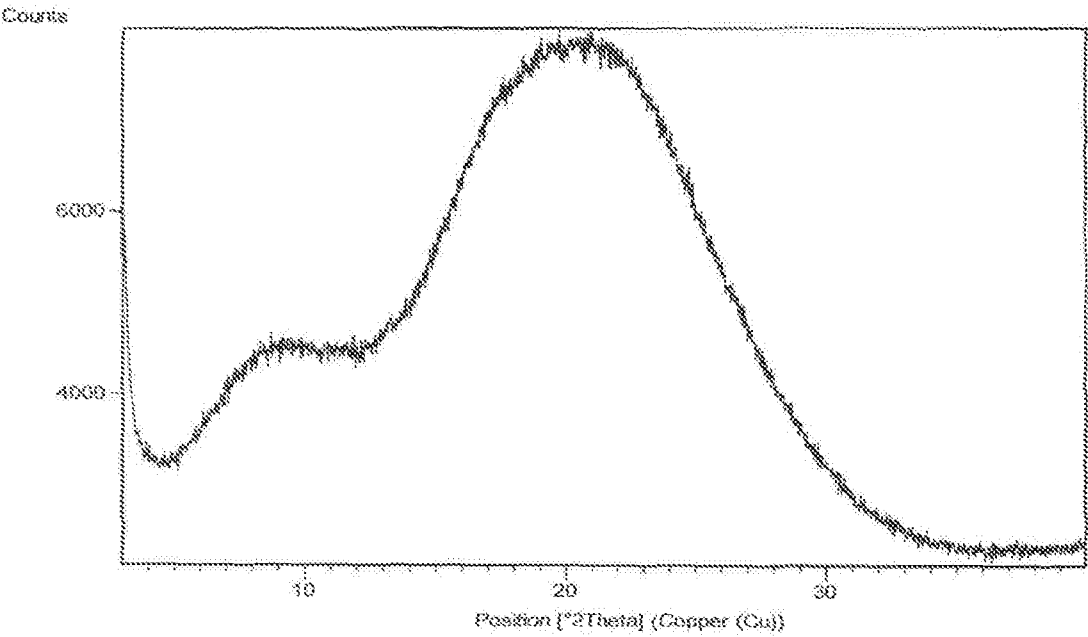


Figure 3

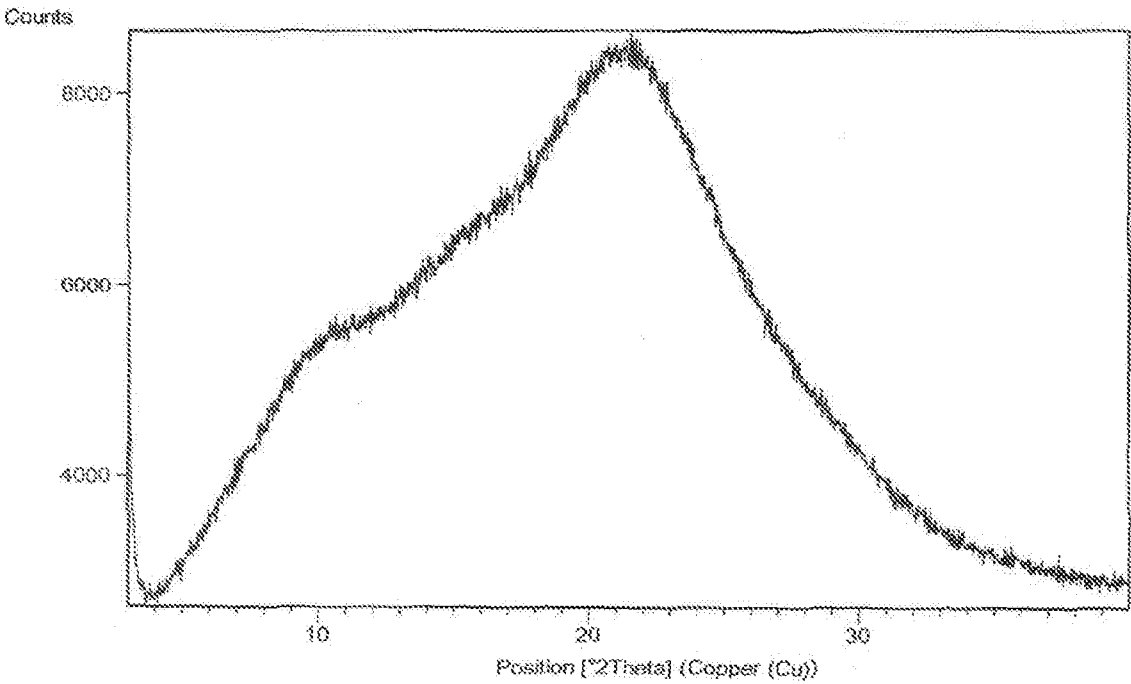


Figure 4

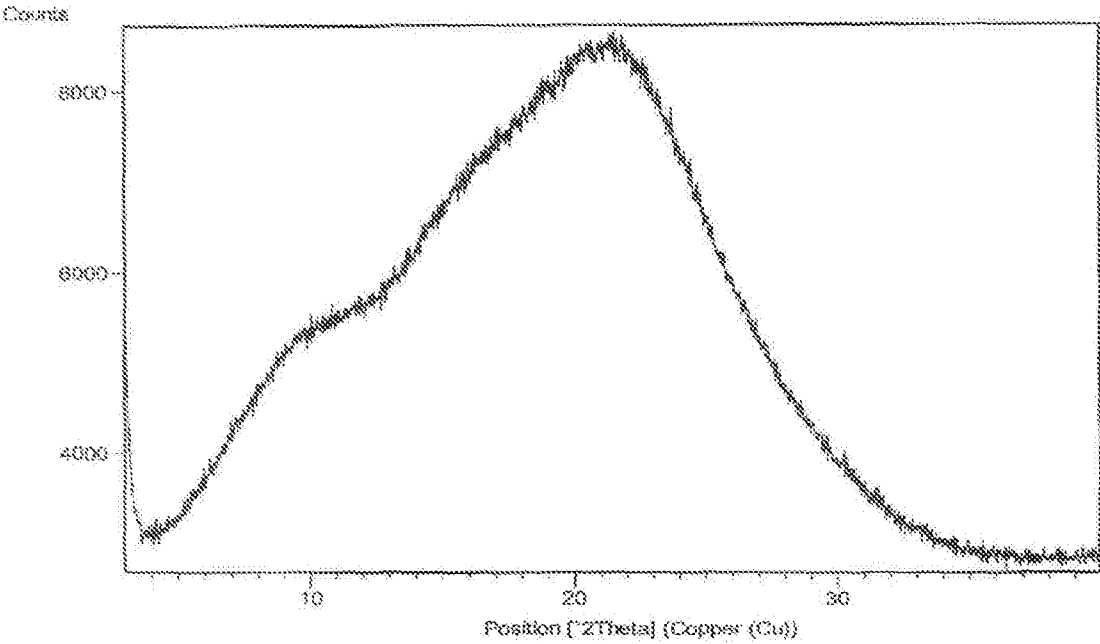


Figure 5

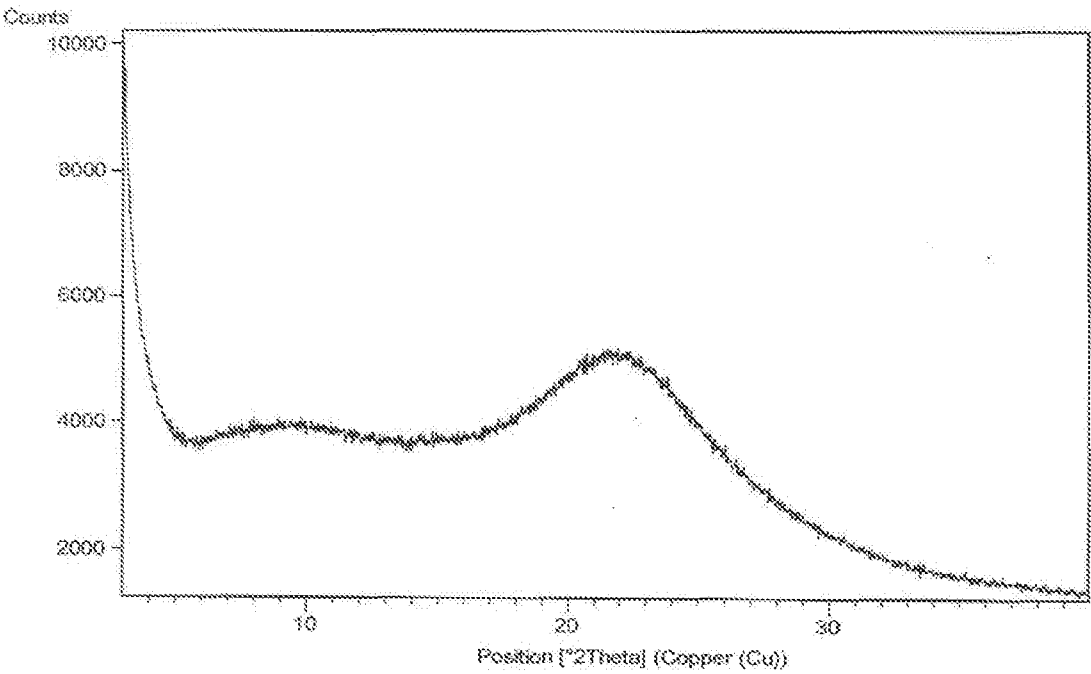


Figure 6

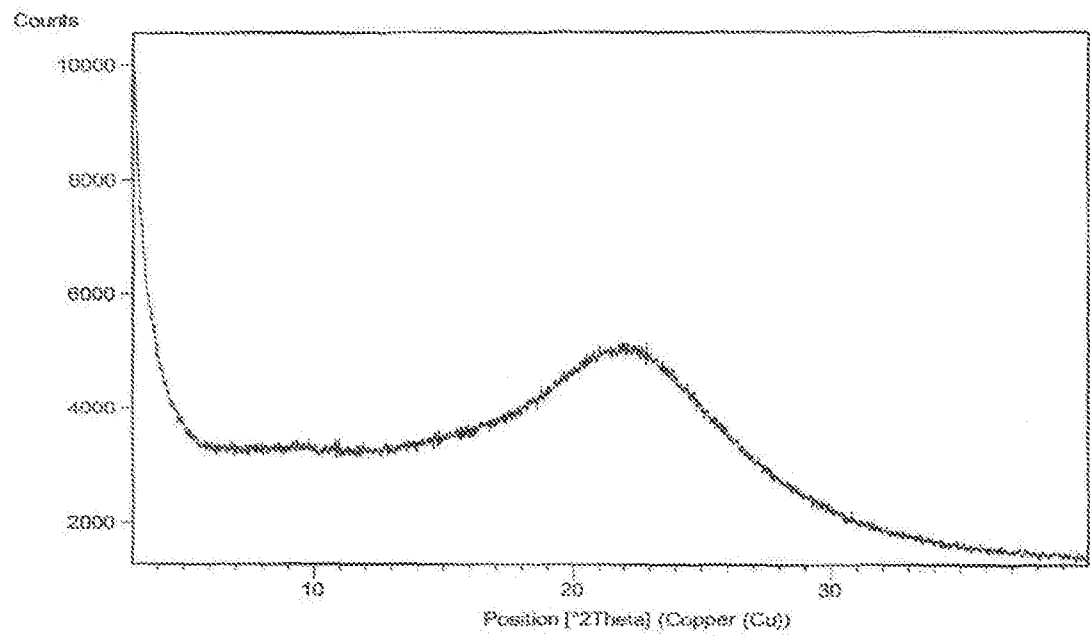


Figure 7

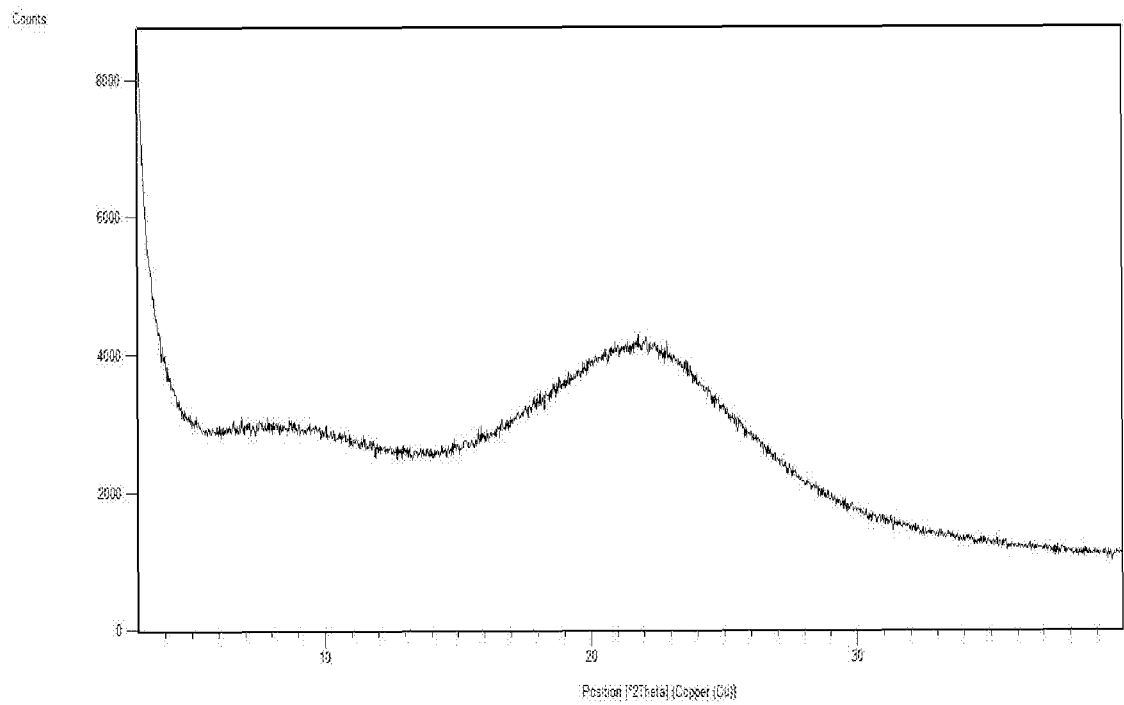
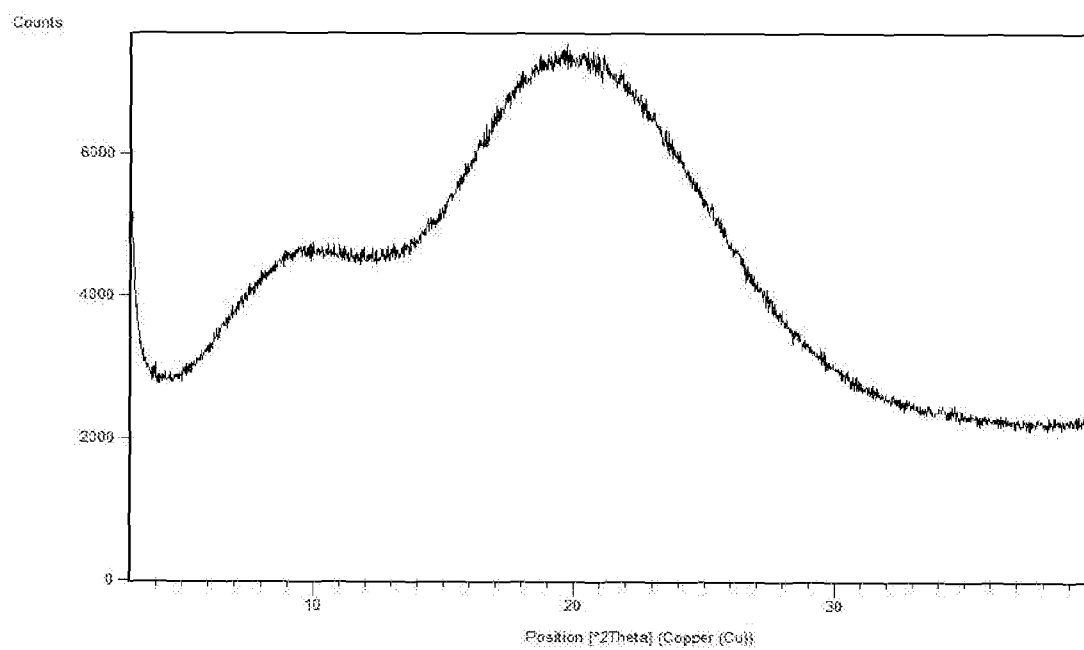
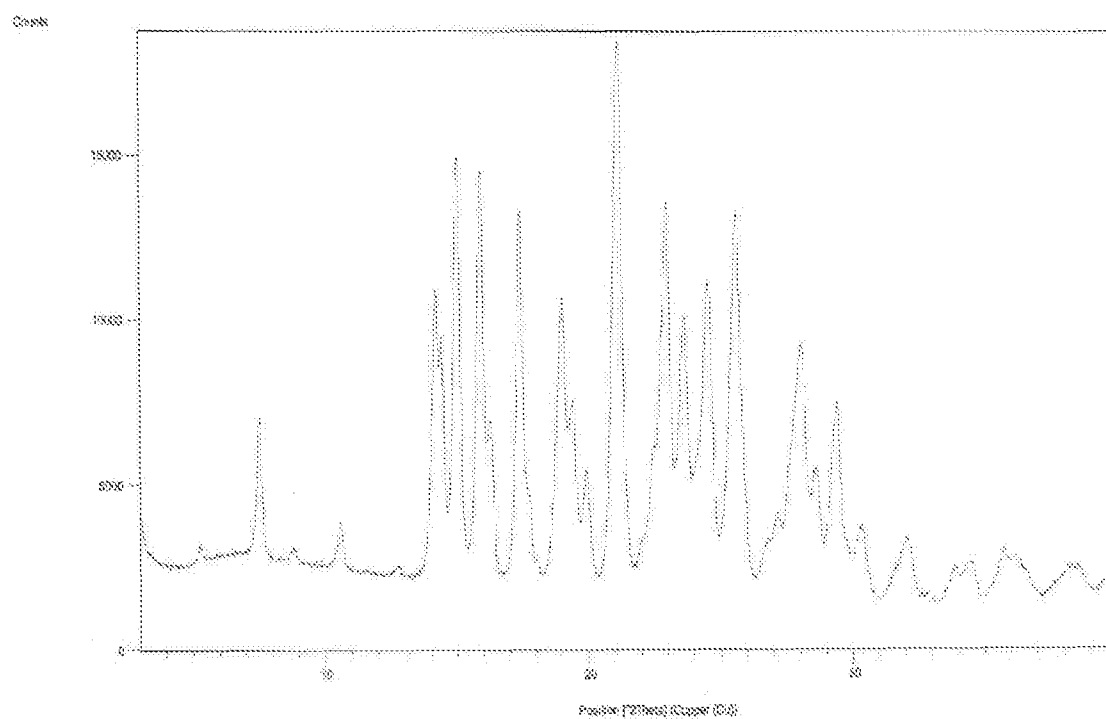


Figure 8

**Figure 9****Figure 10**

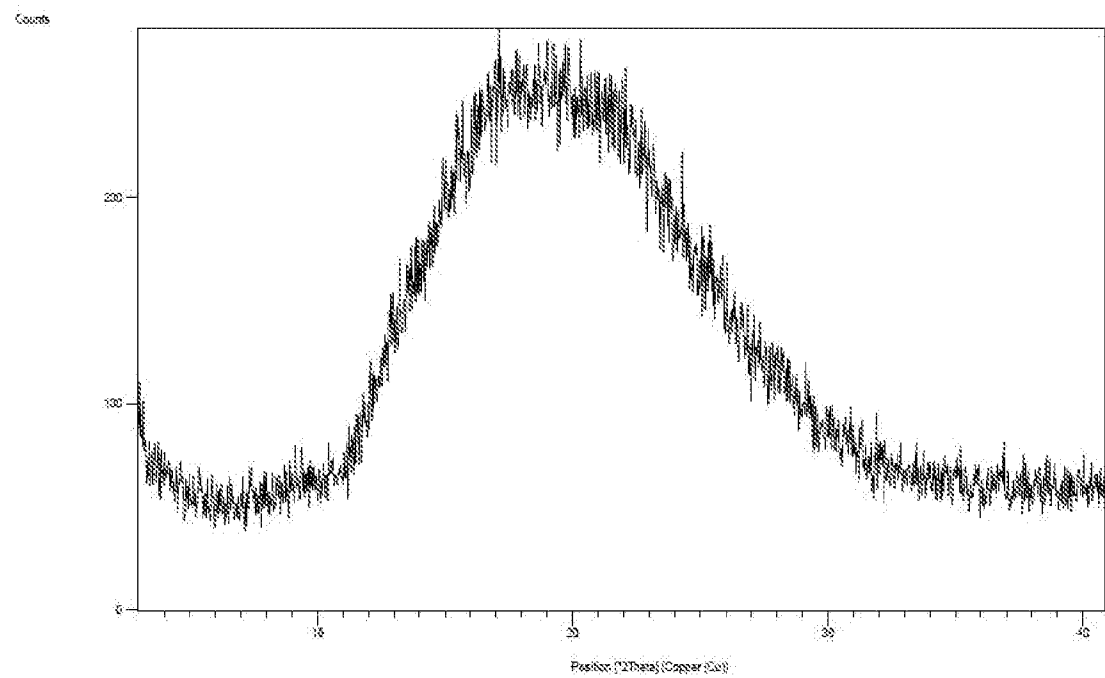


Figure 11

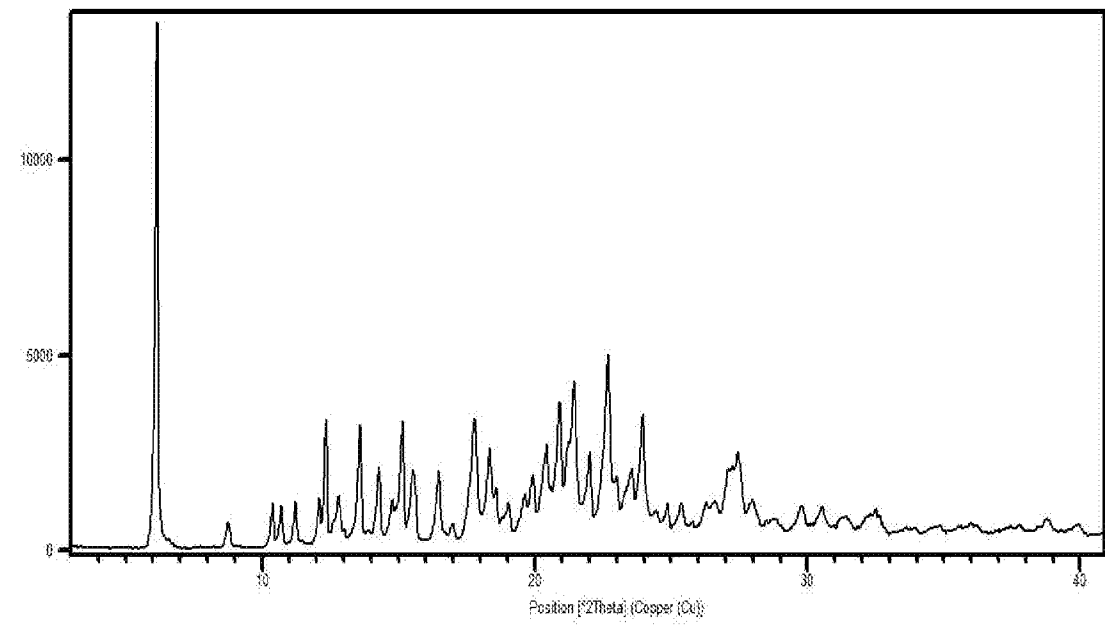


Figure 12

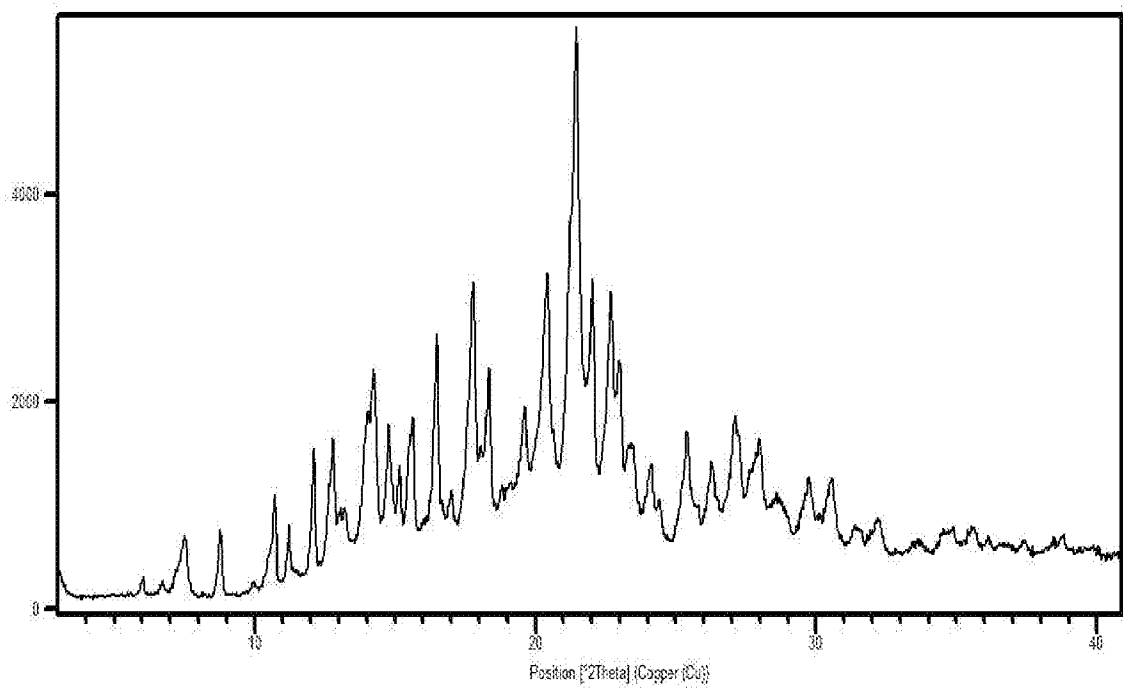


Figure 13

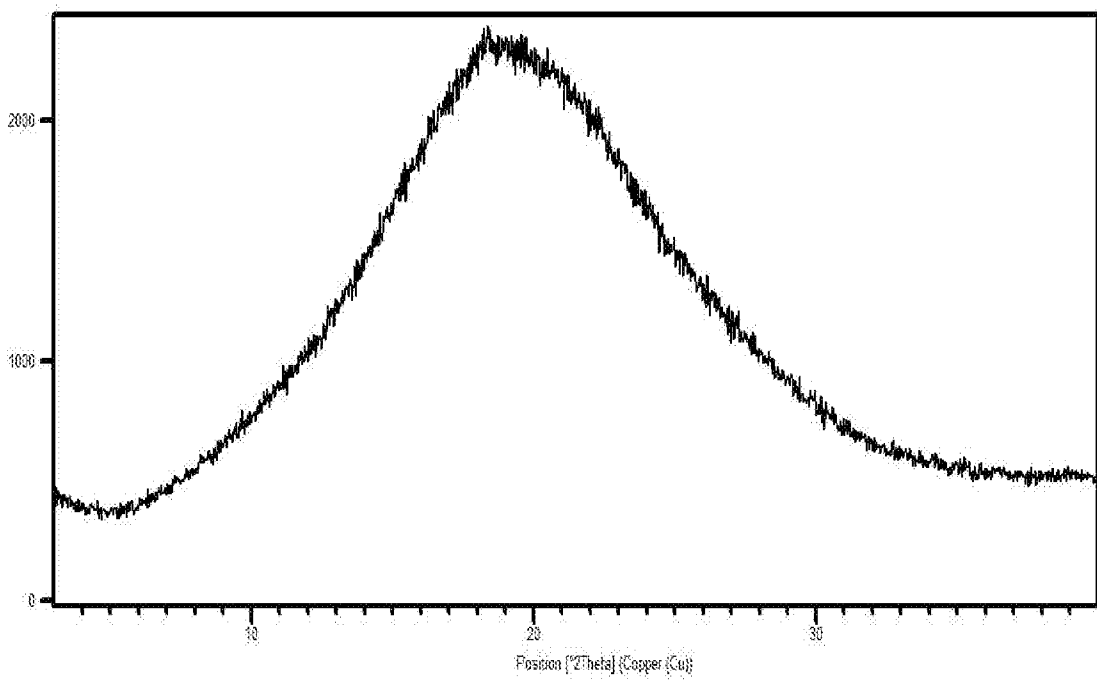


Figure 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2017/050003

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/00,C07D405/12 Version=2017.01

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K31/00,C07D

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

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

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008306062A1 (HADIDA Ruah Sara S et al.) 11 Dec 2008 The whole Document, specifically see paragraph 228 on page 34 and compound 396 on page 87)	1-34
X	US 8507534 B2 (VERTEX PHARMACEUTICALS INCORPORATED) 13 Aug 2013 The whole Document, specifically see paragraph 87	1-34

☐ 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

"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

30-05-2017

Date of mailing of the international search report

30-05-2017

Name and mailing address of the ISA/

Indian Patent Office
Plot No.32, Sector 14,Dwarka,New Delhi-110075
Facsimile No.

Authorized officer

Dr. Manmeet Kumar
Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2017/050003

Citation	Pub.Date	Family	Pub.Date
US 2008306062 A1	11-12-2008	WO 2007056341 A1	18-05-2007
		EP 1945632 A1	23-07-2008
US 8507534 B2	13-08-2013	US 20090170905 A1	02-07-2009
		EP 2225230 B1	16-11-2016