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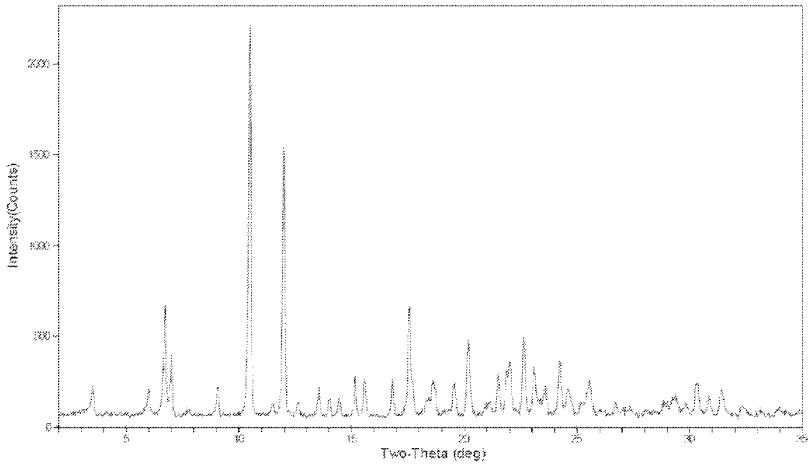


Figure 1

(57) **Abstract**: The present invention features crystalline forms of Compound I. In one embodiment, a crystalline form of Compound I has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 6.0, 6.7, 10.4, 11.9, 17.5, 17.7, 21.5, 22.0, 22.7, and 24.2.

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CRYSTAL FORMS

[0001] This application claims benefit of U.S. Provisional Patent Application No. 61/911,775, filed December 4, 2013, the entire content of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to crystalline polymorphs of Compound I, pharmaceutical compositions comprising the same, and methods of using the same to prepare pharmaceutical compositions.

BACKGROUND

[0003] The hepatitis C virus (HCV) is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides and encodes a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

[0004] HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often inadequate. Therefore, there is a need for new drugs to treat HCV infection.

BRIEF DESCRIPTION OF THE DRAWINGS

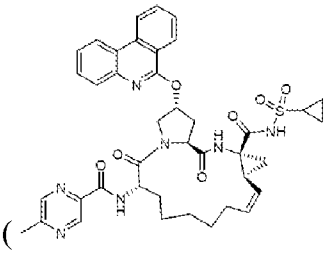
[0005] The drawings are provided for illustration, not limitation.

[0006] Figure 1 shows the powder X-ray diffraction (PXRD) pattern of Form A of Compound I

[0007] Figure 2 depicts the PXRD pattern of Form B of Compound I.

DETAILED DESCRIPTION

[0008] The present invention features crystalline polymorphs of (2R,6S,13aS,14aR,16aS,Z)-N-(cyclopropylsulfonyl)-6-(5-methylpyrazine-2-carboxamido)-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,5,6,7,8,9,10,11,13a,14,14a,15,16,16a-hexadecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a-carboxamide



; herein "Compound I"). Compound I is a potent HCV protease inhibitor. The synthesis and formulation of Compound I are described in U.S. Patent Application Publication Nos. 2010/0144608 and 2011/0312973, both of which are incorporated herein by reference in their entireties.

[0009] Crystal structures of large molecules such as Compound I are generally not predictable. The crystalline polymorphs of the invention were unexpectedly isolated, and prior to their preparation and isolation, the existence of these particular polymorphs had not been expected.

[0010] In one aspect, the invention features a crystalline form of Compound I (hereinafter Form A), which has characteristic peaks in the powder X-ray diffraction (PXRD) pattern at values of two theta (° 2θ) of 6.7, 7.0, 10.5, 12.0, 17.6, 20.2, 21.9, 22.0, 22.6, and 23.1. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 28%, 16%, 100%, 69%, 28%, 20%, 11%, 13%, 20%, and 12%, respectively.

[0011] In one embodiment of this aspect of the invention, Form A has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 6.73, 7.01, 10.49, 11.99, 17.57, 20.17, 21.88, 22.01, 22.64, and 23.10. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 28%, 16%, 100%, 69%, 28%, 20%, 11%, 13%, 20%, and 12%, respectively.

[0012] In another embodiment of this aspect of the invention, Form A has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 3.5, 6.7, 7.0, 9.1, 10.5, 12.0, 13.5, 15.2, 15.6, 16.8, 17.6, 18.6, 19.5, 20.2, 21.5, 21.9, 22.0, 22.6, 23.1, and 23.6. Preferably, these

peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 9%, 28%, 16%, 7%, 100%, 69%, 7%, 10%, 9%, 9%, 28%, 8%, 8%, 20%, 10%, 11%, 13%, 20%, 12%, and 8%, respectively.

[0013] In yet another embodiment of this aspect of the invention, Form A has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 3.52, 6.73, 7.01, 9.06, 10.49, 11.99, 13.55, 15.16, 15.58, 16.80, 17.57, 18.61, 19.55, 20.17, 21.51, 21.88, 22.01, 22.64, 23.10, and 23.60. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 9%, 28%, 16%, 7%, 100%, 69%, 7%, 10%, 9%, 9%, 28%, 8%, 8%, 20%, 10%, 11%, 13%, 20%, 12%, and 8%, respectively.

[0014] In another embodiment of this aspect of the invention, Form A has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 3.5, 6.0, 6.7, 7.0, 9.1, 10.5, 12.0, 13.5, 14.4, 15.2, 15.6, 16.8, 17.6, 18.6, 19.5, 20.2, 21.5, 21.9, 22.0, 22.6, 23.1, and 23.6. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 9%, 6%, 28%, 16%, 7%, 100%, 69%, 7%, 5%, 10%, 9%, 9%, 28%, 8%, 8%, 20%, 10%, 11%, 13%, 20%, 12%, and 8%, respectively.

[0015] In yet another embodiment of this aspect of the invention, Form A has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 3.52, 6.01, 6.73, 7.01, 9.06, 10.49, 11.99, 13.55, 14.45, 15.16, 15.58, 16.80, 17.57, 18.61, 19.55, 20.17, 21.51, 21.88, 22.01, 22.64, 23.10, and 23.60. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 9%, 6%, 28%, 16%, 7%, 100%, 69%, 7%, 5%, 10%, 9%, 9%, 28%, 8%, 8%, 20%, 10%, 11%, 13%, 20%, 12%, and 8%, respectively.

[0016] In still another embodiment of this aspect of the invention, Form A has characteristic PXRD peaks as shown in Figure 1.

[0017] Without limiting this aspect of the invention to any particular theory or calculation, Form A typically contains about 0 molecule of water per molecule of Compound I. Form A may also contain 0 to 3 molecules of water per molecule of Compound I, and/or contain other solvents (such as isopropyl alcohol) within the crystal lattice.

[0018] In another aspect, the invention features another crystalline form of Compound I (hereinafter Form B), which has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 6.0, 6.7, 10.4, 11.9, 17.5, 17.7, 21.5, 22.0, 22.7, and 24.2. Preferably, these peaks have

higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 15%, 23%, 100%, 64%, 19%, 20%, 14%, 19%, 25%, and 16%, respectively.

[0019] In one embodiment of this aspect of the invention, Form B has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 5.95, 6.67, 10.43, 11.95, 17.51, 17.67, 21.51, 22.04, 22.66, and 24.23. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 15%, 23%, 100%, 64%, 19%, 20%, 14%, 19%, 25%, and 16%, respectively.

[0020] In another embodiment of this aspect of the invention, Form B has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 3.4, 6.0, 6.7, 6.9, 9.0, 10.4, 11.9, 15.6, 17.5, 17.7, 18.4, 18.7, 20.1, 21.5, 21.8, 22.0, 22.7, 23.1, 24.2, and 24.7. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 9%, 15%, 23%, 8%, 10%, 100%, 64%, 9%, 19%, 20%, 10%, 13%, 12%, 14%, 8%, 19%, 25%, 10%, 16%, and 9%, respectively.

[0021] In another embodiment of this aspect of the invention, Form B has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 3.43, 5.95, 6.67, 6.94, 9.00, 10.43, 11.95, 15.55, 17.51, 17.67, 18.36, 18.65, 20.13, 21.51, 21.82, 22.04, 22.66, 23.12, 24.23, and 24.66. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 9%, 15%, 23%, 8%, 10%, 100%, 64%, 9%, 19%, 20%, 10%, 13%, 12%, 14%, 8%, 19%, 25%, 10%, 16%, and 9%, respectively.

[0022] In another embodiment of this aspect of the invention, Form B has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 3.4, 6.0, 6.7, 6.9, 9.0, 10.4, 11.5, 11.9, 12.6, 14.4, 15.1, 15.6, 16.8, 17.5, 17.7, 18.4, 18.7, 19.5, 20.1, 20.9, 21.5, 21.8, 22.0, 22.7, 23.1, 23.6, 24.2, 24.7. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 9%, 15%, 23%, 8%, 10%, 100%, 6%, 64%, 6%, 6%, 7%, 9%, 7%, 19%, 20%, 10%, 13%, 6%, 12%, 5%, 14%, 8%, 19%, 25%, 10%, 6%, 16%, and 9%, respectively.

[0023] In another embodiment of this aspect of the invention, Form B has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 3.43, 5.95, 6.67, 6.94, 9.00, 10.43, 11.46, 11.95, 12.59, 14.42, 15.11, 15.55, 16.75, 17.51, 17.67, 18.36, 18.65, 19.51, 20.13, 20.94, 21.51, 21.82, 22.04, 22.66, 23.12, 23.55, 24.23, and 24.66. Preferably, these peaks have higher

intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 9%, 15%, 23%, 8%, 10%, 100%, 6%, 64%, 6%, 6%, 7%, 9%, 7%, 19%, 20%, 10%, 13%, 6%, 12%, 5%, 14%, 8%, 19%, 25%, 10%, 6%, 16%, and 9%, respectively.

[0024] In still another embodiment of this aspect of the invention, Form B has characteristic PXRD peaks as shown in Figure 2.

[0025] Without limiting this aspect of the invention to any particular theory or calculation, Form B typically contains about 1 molecule of water per molecule of Compound I. Form B may also contain 0 to 3 molecules of water per molecule of Compound I.

[0026] In still another aspect, the present invention features a crystalline form of Compound I (hereinafter Class 1), wherein when the crystalline form is equilibrated at 70% relative humidity, it has characteristic peaks in the PXRD pattern as Form B. For example, a Class 1 crystal, upon being equilibrated at 70% relative humidity, can have characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 6.7, 7.0, 10.5, 12.0, 15.6, 16.8, 17.6, 17.7, 18.4, 18.7, and 20.2. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 20%, 6%, 100%, 92%, 13%, 11%, 73%, 73%, 36%, 45%, and 33%, respectively. As non-limiting examples, Forms A and B are Class 1 of the crystalline form of Compound I.

[0027] In one embodiment of this aspect of the invention, a crystalline form of Class 1, upon equilibrated at 40% relative humidity, has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 6.7, 10.5, 12.0, 15.6, 17.6, 17.7, 18.3, 18.7, 20.2, 21.0, 21.5, and 22.0. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 15%, 100%, 88%, 14%, 67%, 67%, 38%, 45%, 32%, 17%, 35%, and 58%, respectively.

[0028] In another embodiment of this aspect of the invention, a crystalline form of Class 1, upon equilibrated at 20% relative humidity, has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 6.7, 10.5, 12.0, 17.5, 17.7, 18.4, 18.7, 19.5, 20.1, 21.0, 21.5, and 22.0. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 13%, 100%, 82%, 50%, 75%, 33%, 39%, 11%, 28%, 10%, 28%, and 48%, respectively.

[0029] In another embodiment of this aspect of the invention, a crystalline form of Class 1, upon equilibrated at 5% relative humidity, has characteristic peaks in the PXRD pattern at

values of two theta (° 2θ) of 6.0, 6.7, 10.4, 11.9, 17.4, 17.7, 18.4, 18.6, 20.0, 20.9, 21.5, and 22.0. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 10%, 5%, 100%, 70%, 45%, 57%, 48%, 41%, 23%, 18%, 35%, and 34%, respectively.

[0030] In another embodiment of this aspect of the invention, a crystalline form of Class 1, upon equilibrated under dry nitrogen, has characteristic peaks in the PXRD pattern at values of two theta (° 2θ) of 6.0, 6.7, 10.4, 11.9, 17.4, 17.7, 18.4, 18.6, 20.0, 20.9, 21.5, and 22.0. Preferably, these peaks have higher intensities than other peaks in the PXRD pattern. Also preferably, these peaks have relative intensities of 10%, 5%, 100%, 70%, 45%, 57%, 48%, 41%, 23%, 18%, 35%, and 34%, respectively.

[0031] As used herein, PXRD data can be collected using a G3000 diffractometer (Inel Corp., Artenay, France) equipped with a curved position-sensitive detector and parallel-beam optics. The diffractometer is operated with a copper anode tube (1.5 kW fine focus) at 40 kV and 30 mA. An incident-beam germanium monochromator provides monochromatic Cu–K_α radiation, which has a wavelength of 1.54178 Å. The diffractometer is calibrated using the attenuated direct beam at one-degree intervals. Calibration is checked using a silicon powder line position reference standard (NIST 640c). The instrument is computer-controlled using Symphonix software (Inel Corp., Artenay, France) and the data are analyzed using Jade software (version 6.5, Materials Data, Inc., Livermore, CA). The sample can be loaded onto an aluminum sample holder and leveled with a glass slide. PXRD peak position measurements are typically ± 0.2 degrees two-theta (° 2θ).

[0032] In another aspect, the present invention features a crystalline form described above which is substantially pure. As used herein, the term "substantially pure", when used in reference to a given crystalline form, refers to the crystalline form which is at least about 90% pure. This means that the crystalline form does not contain more than about 10% of any other form of Compound I. More preferably, the term "substantially pure" refers to a crystalline form of Compound I which is at least about 95% pure. This means that the crystalline form of Compound I does not contain more than about 5% of any other form of Compound I. Even more preferably, the term "substantially pure" refers to a crystalline form of Compound I which is at least about 97% pure. This means that the crystalline form of Compound I does not contain more than about 3% of any other form of Compound I.

[0033] In one embodiment, the present invention feature Form A of Compound I which is substantially pure. Any Form A described above can be substantially pure, such as at least 90% pure, preferably at least 95% pure, or more preferably at least 97%.

[0034] In another embodiment, the present invention feature Form B of Compound I which is substantially pure. Any Form B described above can be substantially pure, such as at least 90% pure, preferably at least 95% pure, or more preferably at least 97%.

[0100] In another embodiment, the present invention feature Class 1 of Compound I which is substantially pure. Any Class 1 described herein can be substantially pure, such as at least 90% pure, preferably at least 95% pure, or more preferably at least 97%.

[0101] In yet another aspect, the present invention features processes of using a crystalline form of the invention (e.g., Form A, B, or Class 1 of the crystalline form of Compound I) to make a composition comprising Compound I. The processes comprise dissolving a crystalline form of the invention in a solvent. Any crystalline form described hereinabove (e.g., Class 1, or Form A or B) can be used in a process of the invention.

[0102] In one embodiment, the solvent is a volatile solvent such as ethanol or methanol. A suitable excipient, such as a hydrophilic polymer described below or a sugar alcohol, can also be dissolved in the solvent. The solution thus produced can then be dried to remove the solvent, such as via spray drying, freeze drying or other solvent evaporization techniques, thereby creating a solid dispersion that comprises Compound I and the excipient. Preferably, Compound I is in an amorphous form in the solid dispersion. More preferably, the solid dispersion is a solid solution or a glassy solution. In many cases, a pharmaceutically acceptable surfactant described below can also be added to the solution prior to solvent removal; and as a result, the solid dispersion/solid solution/glass solution produced according to this embodiment also comprises the surfactant.

[0103] In another embodiment, the solvent is an excipient, such as a hydrophilic polymer described below or a sugar alcohol, in a molten or rubbery state. The crystalline form of Compound I dissolves in the molten or rubbery excipient. Heating may be used to facilitate the dissolving and mixing of the crystalline form of Compound I in the molten or rubbery excipient. Preferably, melt extrusion is used to dissolve and mix the crystalline form of Compound I in the excipient. A solution or melt thus produced can be cooled and solidified to form a solid dispersion that comprises Compound I and the excipient. Preferably, Compound I is in an

amorphous form in the solid dispersion. More preferably, the solid dispersion is a solid solution or a glassy solution. The solid dispersion, solid solution or glassy solution can be milled, ground or granulated, and then compressed into a tablet or another suitable solid dosage form with or without other additives. The solid dispersion, solid solution or glassy solution can also be directly shaped or configured into a tablet or another suitable solid dosage form. In many cases, a pharmaceutically acceptable surfactant described below can be added to the solution or melt prior to solidification; and as a result, the solid dispersion/solid solution/glassy solution produced according to this embodiment also comprises the surfactant.

[0104] In yet another embodiment, both heating and a volatile solvent are used to dissolve a crystalline form of Compound I in a solution comprising a suitable excipient.

[0105] As used herein, the term "solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed throughout the other component or components. For example, an active ingredient or a combination of active ingredients can be dispersed in a matrix comprised of a pharmaceutically acceptable hydrophilic polymer(s) and a pharmaceutically acceptable surfactant(s). The term "solid dispersion" encompasses systems having small particles of one phase dispersed in another phase. When a solid dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase (as defined in thermodynamics), such a solid dispersion is called a "solid solution." A glassy solution is a solid solution in which a solute is dissolved in a glassy solvent.

[0106] Non-limiting examples of excipients suitable for use in a process of the invention include numerous hydrophilic polymers. Preferably, a hydrophilic polymer employed in a process of the invention has a T_g of at least 50 °C, more preferably at least 60 °C, and highly preferably at least 80 °C including, but not limited to from, 80 °C to 180 °C, or from 100 °C to 150 °C. Methods for determining T_g values of organic polymers are described in INTRODUCTION TO PHYSICAL POLYMER SCIENCE (2nd Edition by L.H. Sperling, published by John Wiley & Sons, Inc., 1992). The T_g value can be calculated as the weighted sum of the T_g values for homopolymers derived from each of the individual monomers, i.e., the polymer $T_g = \Sigma W_i \bullet X_i$ where W_i is the weight percent of monomer i in the organic polymer, and X_i is the T_g value for the homopolymer derived from monomer i. T_g values for the homopolymers may be taken from POLYMER HANDBOOK (2nd Edition by J. Brandrup and E.H. Immergut, Editors, published by

John Wiley & Sons, Inc., 1975). Hydrophilic polymers with a T_g as described above may allow for the preparation of solid dispersions that are mechanically stable and, within ordinary temperature ranges, sufficiently temperature stable so that the solid dispersions may be used as dosage forms without further processing or be compacted to tablets with only a small amount of tabletting aids. Hydrophilic polymers having a T_g of below 50°C may also be used.

[0107] Preferably, a hydrophilic polymer employed in the present invention is water-soluble. A solid composition of the present invention can also comprise poorly water-soluble or water-insoluble polymer or polymers, such as cross-linked polymers. A hydrophilic polymer comprised in a solid composition of the present invention preferably has an apparent viscosity, when dissolved at 20 °C in an aqueous solution at 2 % (w/v), of 1 to 5000 mPa·s., and more preferably of 1 to 700 mPa·s, and most preferably of 5 to 100 mPa·s.

[0108] Hydrophilic polymers suitable for use in a process of the invention include, but are not limited to, homopolymers or copolymers of N-vinyl lactams, such as homopolymers or copolymers of N-vinyl pyrrolidone (e.g., polyvinylpyrrolidone (PVP), or copolymers of N-vinyl pyrrolidone and vinyl acetate or vinyl propionate); cellulose esters or cellulose ethers, such as alkylcelluloses (e.g., methylcellulose or ethylcellulose), hydroxyalkylcelluloses (e.g., hydroxypropylcellulose), hydroxyalkylalkylcelluloses (e.g., hydroxypropylmethylcellulose), and cellulose phthalates or succinates (e.g., cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, or hydroxypropylmethylcellulose acetate succinate); high molecular polyalkylene oxides, such as polyethylene oxide, polypropylene oxide, and copolymers of ethylene oxide and propylene oxide; polyacrylates or polymethacrylates, such as methacrylic acid/ethyl acrylate copolymers, methacrylic acid/methyl methacrylate copolymers, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymers, poly(hydroxyalkyl acrylates), and poly(hydroxyalkyl methacrylates); polyacrylamides; vinyl acetate polymers, such as copolymers of vinyl acetate and crotonic acid, and partially hydrolyzed polyvinyl acetate (also referred to as partially saponified "polyvinyl alcohol"); polyvinyl alcohol; oligo- or polysaccharides, such as carrageenans, galactomannans, and xanthan gum; polyhydroxyalkylacrylates; polyhydroxyalkyl-methacrylates; copolymers of methyl methacrylate and acrylic acid; polyethylene glycols (PEGs); or any mixture thereof.

[0109] Non-limiting examples of preferred hydrophilic polymers for use in a process of the invention include polyvinylpyrrolidone (PVP) K17, PVP K25, PVP K30, PVP K90,

hydroxypropyl methylcellulose (HPMC) E3, HPMC E5, HPMC E6, HPMC E15, HPMC K3, HPMC A4, HPMC A15, HPMC acetate succinate (AS) LF, HPMC AS MF, HPMC AS HF, HPMC AS LG, HPMC AS MG, HPMC AS HG, HPMC phthalate (P) 50, HPMC P 55, Ethocel 4, Ethocel 7, Ethocel 10, Ethocel 14, Ethocel 20, copovidone (vinylpyrrolidone-vinyl acetate copolymer 60/40), polyvinyl acetate, methacrylate/methacrylic acid copolymer (Eudragit) L100-55, Eudragit L100, Eudragit S100, polyethylene glycol (PEG) 400, PEG 600, PEG 1450, PEG 3350, PEG 4000, PEG 6000, PEG 8000, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, and poloxamer 407.

[0110] Of these, homopolymers or copolymers of N-vinyl pyrrolidone, such as copolymers of N-vinyl pyrrolidone and vinyl acetate, are preferred. A non-limiting example of a preferred polymer is a copolymer of 60 % by weight of N-vinyl pyrrolidone and 40 % by weight of vinyl acetate. Other preferred polymers include, without limitation, hydroxypropyl methylcellulose (HPMC, also known as hypromellose in USP), such as hydroxypropyl methylcellulose grade E5 (HPMC-E5); and hydroxypropyl methylcellulose acetate succinate (HPMC-AS).

[0111] A pharmaceutically acceptable surfactant employed in a process of the invention is preferably a non-ionic surfactant. More preferably, the non-ionic surfactant has an HLB value of from 2-20. The HLB system (Fiedler, H.B., ENCYLOPEDIA OF EXCIPIENTS, 5th ed., Aulendorf: ECV-Editio-Cantor-Verlag (2002)) attributes numeric values to surfactants, with lipophilic substances receiving lower HLB values and hydrophilic substances receiving higher HLB values.

[0112] Non-limiting examples of pharmaceutically acceptable surfactants that are suitable for use in a process of the invention include polyoxyethylene castor oil derivates, e.g. polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor® EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate such as polyethylenglycol 40 hydrogenated castor oil (Cremophor® RH 40, also known as polyoxyl 40 hydrogenated castor oil or macrogolglycerol hydroxystearate) or polyethylenglycol 60 hydrogenated castor oil (Cremophor® RH 60); or a mono fatty acid ester of polyoxyethylene sorbitan, such as a mono fatty acid ester of polyoxyethylene (20) sorbitan, e.g. polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene (20) sorbitan monopalmitate (Tween® 40), or polyoxyethylene (20) sorbitan monolaurate (Tween® 20). Other non-limiting examples of suitable surfactants include polyoxyethylene alkyl ethers, e.g.

polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether; polyoxyethylene alkylaryl ethers, e.g. polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether; polyethylene glycol fatty acid esters, e.g. PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate; alkylene glycol fatty acid mono esters, e.g. propylene glycol monolaurate (Lauroglycol®); sucrose fatty acid esters, e.g. sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate; sorbitan fatty acid mono esters such as sorbitan mono laurate (Span® 20), sorbitan monooleate, sorbitan monopalnitate (Span® 40), or sorbitan stearate. Other suitable surfactants include, but are not limited to, block copolymers of ethylene oxide and propylene oxide, also known as polyoxyethylene polyoxypropylene block copolymers or polyoxyethylene polypropyleneglycol, such as Poloxamer® 124, Poloxamer® 188, Poloxamer® 237, Poloxamer® 388, or Poloxamer® 407 (BASF Wyandotte Corp.).

[0113] Non-limiting examples of preferred surfactants for use in a process of the invention include polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, Cremophor RH 40, Cremophor EL, Gelucire 44/14, Gelucire 50/13, D-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), propylene glycol laurate, sodium lauryl sulfate, and sorbitan monolaurate.

[0114] A pharmaceutically acceptable surfactant as used herein can be a mixture of pharmaceutically acceptable surfactants, such as a combination of a surfactant having an HLB value of below 10 and another surfactant having an HLB value of no lees than 10.

[0115] In one embodiment, a surfactant having an HLB value of at least 10 is used in a process of the invention. In another embodiment, a surfactant having an HLB value of below 10 is used in a process of the invention. In yet another embodiment, a mixture of two or more surfactants (e.g., a combination of one surfactant having an HLB value of at least 10 and another surfactant having an HLB value of below 10) is used in a process of the invention.

[0116] In one embodiment, a process of the invention comprises dissolving a crystalline form of the invention (e.g., Class 1 of the crystalline form of Compound I, or Form A or B), a hydrophilic polymer described above, and a surfactant described above to form a solution (e.g., a melt). The hydrophilic polymer can be selected, for example, from the group consisting of homopolymer of N-vinyl lactam, copolymer of N-vinyl lactam, cellulose ester, cellulose ether,

polyalkylene oxide, polyacrylate, polymethacrylate, polyacrylamide, polyvinyl alcohol, vinyl acetate polymer, oligosaccharide, and polysaccharide. As a non-limiting example, the hydrophilic polymer is selected from the group consisting of homopolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone and vinyl acetate, copolymer of N-vinyl pyrrolidone and vinyl propionate, polyvinylpyrrolidone, methylcellulose, ethylcellulose, hydroxyalkylcelluloses, hydroxypropylcellulose, hydroxyalkylalkylcellulose, hydroxypropylmethylcellulose, cellulose phthalate, cellulose succinate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, hydroxypropylmethylcellulose acetate succinate, polyethylene oxide, polypropylene oxide, copolymer of ethylene oxide and propylene oxide, methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymer, poly(hydroxyalkyl acrylate), poly(hydroxyalkyl methacrylate), copolymer of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate, carrageenan, galactomannan, and xanthan gum. Preferably, the hydrophilic polymer is selected from polyvinylpyrrolidone (PVP) K17, PVP K25, PVP K30, PVP K90, hydroxypropyl methylcellulose (HPMC) E3, HPMC E5, HPMC E6, HPMC E15, HPMC K3, HPMC A4, HPMC A15, HPMC acetate succinate (AS) LF, HPMC AS MF, HPMC AS HF, HPMC AS LG, HPMC AS MG, HPMC AS HG, HPMC phthalate (P) 50, HPMC P 55, Ethocel 4, Ethocel 7, Ethocel 10, Ethocel 14, Ethocel 20, copovidone (vinylpyrrolidone-vinyl acetate copolymer 60/40), polyvinyl acetate, methacrylate/methacrylic acid copolymer (Eudragit) L100-55, Eudragit L100, Eudragit S100, polyethylene glycol (PEG) 400, PEG 600, PEG 1450, PEG 3350, PEG 4000, PEG 6000, PEG 8000, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, or poloxamer 407. More preferably, the hydrophilic polymer is selected from homopolymers of vinylpyrrolidone (e.g., PVP with Fikentscher K values of from 12 to 100, or PVP with Fikentscher K values of from 17 to 30), or copolymers of 30 to 70% by weight of N-vinylpyrrolidone (VP) and 70 to 30% by weight of vinyl acetate (VA) (e.g., a copolymer of 60% by weight VP and 40% by weight VA). The surfactant can be selected, for example, from the group consisting of polyoxyethyleneglycerol triricinoleate or polyoxyl 35 castor oil (Cremophor® EL; BASF Corp.) or polyoxyethyleneglycerol oxystearate, mono fatty acid ester of polyoxyethylene sorbitan, polyoxyethylene alkyl ether, polyoxyethylene alkylaryl ether, polyethylene glycol fatty acid ester, alkylene glycol fatty acid mono ester, sucrose fatty acid

ester, and sorbitan fatty acid mono ester. As a non-limited example, the surfactant is selected from the group consisting of polyethylenglycol 40 hydrogenated castor oil (Cremophor® RH 40, also known as polyoxyl 40 hydrogenated castor oil or macrogolglycerol hydroxystearate), polyethylenglycol 60 hydrogenated castor oil (Cremophor® RH 60), a mono fatty acid ester of polyoxyethylene (20) sorbitan (e.g. polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene (20) sorbitan monopalmitate (Tween® 40), or polyoxyethylene (20) sorbitan monolaurate (Tween® 20)), polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether, polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether, PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate, propylene glycol monolaurate, sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalnitate, and sorbitan stearate. Preferably, the surfactant is selected from polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, Cremophor RH 40, Cremophor EL, Gelucire 44/14, Gelucire 50/13, D-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS), propylene glycol laurate, sodium lauryl sulfate, or sorbitan monolaurate. More preferably, the surfactant is selected from sorbitan monolaurate or D-alpha-tocopheryl polyethylene glycol 1000 succinate.

[0117] In another embodiment, a process of the invention comprises dissolving a crystalline form of the invention (e.g., Class 1 of the crystalline form of Compound I, or Form A or B), a hydrophilic polymer described above, and a surfactant described above to form a solution (e.g., a melt). The hydrophilic polymer is a homopolymer or copolymer of N-vinyl pyrrolidone (e.g., copovidone). The pharmaceutically acceptable surfactant can be, e.g., vitamin E TPGS, or sorbitan monolaurate.

[0118] A melt-extrusion process of the invention typically comprises preparing a melt from (1) a crystalline form of the invention (e.g., Class 1, or Form A or B, of Compound I), (2) a hydrophilic polymer described above (or another suitable binder), and (3) preferably a surfactant described above. The melt can then be cooled until it solidifies. The crystalline form of Compound I initially used will disappear upon the formation of the melt. The melt may also include other additives. "Melting" means a transition into a liquid or rubbery state in which it is

possible for one component to get embedded, preferably homogeneously embedded, in the other component or components. In many cases, the polymer component will melt and the other components including the crystalline form of Compound I and the surfactant will dissolve in the melt thereby forming a solution. Melting usually involves heating above the softening point of the polymer. The preparation of the melt can take place in a variety of ways. The mixing of the components can take place before, during or after the formation of the melt. For example, the components can be mixed first and then melted or be simultaneously mixed and melted. The melt can also be homogenized in order to disperse Compound I efficiently. In addition, it may be convenient first to melt the polymer and then to mix in and homogenize Compound I. In one example, all materials except the surfactant are blended and fed into an extruder, while the surfactant is molten externally and pumped in during extrusion.

[0119] In another example, the melt comprises Compound I and a hydrophilic polymer described above, and the melt temperature is in the range of from 100 to 170 °C, preferably from 120 to 150 °C, and highly preferably from 135 to 140 °C. The melt can also include a pharmaceutically acceptable surfactant described above.

[0120] In still another example, the melt comprises Compound I, at least another anti-HCV agent (e.g., a HCV polymerase inhibitor, or a NS5A inhibitor, or a combination of a HCV polymerase inhibitor and a NS5A inhibitor), and a hydrophilic polymer described above. The melt can also include a pharmaceutically acceptable surfactant described above.

[0121] In many cases, the melt also comprises ritonavir.

[0122] To start a melt-extrusion process, Compound I is employed in a crystalline form of the invention, e.g., Class 1, or Form A or B. A crystalline form of the invention may also be first dissolved in a suitable liquid solvent such as alcohols, aliphatic hydrocarbons, esters or, in some cases, liquid carbon dioxide; the solvent can be removed, e.g. evaporated, upon preparation of the melt.

[0123] Various additives can also be included in the melt, for example, flow regulators (e.g., colloidal silica), lubricants, fillers, disintegrants, plasticizers, colorants, or stabilizers (e.g., antioxidants, light stabilizers, radical scavengers, and stabilizers against microbial attack).

[0124] The melting and/or mixing can take place in an apparatus customary for this purpose. Particularly suitable ones are extruders or kneaders. Suitable extruders include single screw extruders, intermeshing screw extruders or multiscrew extruders, preferably twin screw

extruders, which can be corotating or counterrotating and, optionally, be equipped with kneading disks. It will be appreciated that the working temperatures will be determined by the kind of extruder or the kind of configuration within the extruder that is used. Part of the energy needed to melt, mix and dissolve the components in the extruder can be provided by heating elements. However, the friction and shearing of the material in the extruder may also provide a substantial amount of energy to the mixture and aid in the formation of a homogeneous melt of the components.

[0125] The melt can range from thin to pasty to viscous. Shaping of the extrudate can be conveniently carried out by a calender with two counter-rotating rollers with mutually matching depressions on their surface. The extrudate can be cooled and allow to solidify. The extrudate can also be cut into pieces, either before (hot-cut) or after solidification (cold-cut).

[0126] The solidified extrusion product can be further milled, ground or otherwise reduced to granules. The solidified extrudate, as well as each granule produced, comprises a solid dispersion, preferably a solid solution, of Compound I in a matrix comprised of the hydrophilic polymer and optionally the pharmaceutically acceptable surfactant. Where the granules do not contain any surfactant, a pharmaceutically acceptable surfactant described above can be added to and blended with the granules. The extrusion product can also be blended with other active ingredient(s) (e.g., ritonavir) and/or additive(s) before being milled or ground to granules. The granules can be further processed into suitable solid oral dosage forms.

[0127] In one example, copovidone and a surfactant described above are mixed and granulated, followed by the addition of aerosil and a crystalline form of Compound I of the invention (e.g., Class 1, or Form A or B). The mixture can also contain ritonavir. The mixture, which may contain for example 5% by weight of Compound I, is then milled. The mixture is then subject to extrusion, and the extrudate thus produced can be milled and sieved for further processing to make capsules or tablets. The surfactant employed in this example can also be added through liquid dosing during extrusion.

[0128] The approach of solvent evaporation, e.g., via spray-drying, provides the advantage of allowing for processability at lower temperatures, if needed, and allows for other modifications to the process in order to further improve powder properties. The spray-dried powder can then be formulated further, if needed, and final drug product is flexible with regards to whether capsule, tablet or any other solid dosage form is desired.

[0129] Exemplary spray-drying processes and spray-drying equipment are described in K. Masters, SPRAY DRYING HANDBOOK (Halstead Press, New York, 4th ed., 1985). Non-limiting examples of spray-drying devices that are suitable for the present invention include spray dryers manufactured by Niro Inc. or GEA Process Engineering Inc., Buchi Labortechnik AG, and Spray Drying Systems, Inc. A spray-drying process generally involves breaking up a liquid mixture into small droplets and rapidly removing solvent from the droplets in a container (spray drying apparatus) where there is a strong driving force for evaporation of solvent from the droplets. Atomization techniques include, for example, two-fluid or pressure nozzles, or rotary atomizers. The strong driving force for solvent evaporation can be provided, for example, by maintaining the partial pressure of solvent in the spray drying apparatus well below the vapor pressure of the solvent at the temperatures of the drying droplets. This may be accomplished by either (1) maintaining the pressure in the spray drying apparatus at a partial vacuum; (2) mixing the liquid droplets with a warm drying gas (e.g., heated nitrogen); or (3) both.

[0130] The temperature and flow rate of the drying gas, as well as the spray dryer design, can be selected so that the droplets are dry enough by the time they reach the wall of the apparatus. This help to ensure that the dried droplets are essentially solid and can form a fine powder and do not stick to the apparatus wall. The spray-dried product can be collected by removing the material manually, pneumatically, mechanically or by other suitable means. The actual length of time to achieve the preferred level of dryness depends on the size of the droplets, the formulation, and spray dryer operation. Following the solidification, the solid powder may stay in the spray drying chamber for additional time (e.g., 5-60 seconds) to further evaporate solvent from the solid powder. The final solvent content in the solid dispersion as it exits the dryer is preferably at a sufficiently low level so as to improve the stability of the final product. For instance, the residual solvent content of the spray-dried powder can be less than 2% by weight. Highly preferably, the residual solvent content is within the limits set forth in the International Conference on Harmonization (ICH) Guidelines. In addition, it may be useful to subject the spray-dried composition to further drying to lower the residual solvent to even lower levels. Methods to further lower solvent levels include, but are not limited to, fluid bed drying, infra-red drying, tumble drying, vacuum drying, and combinations of these and other processes.

[0131] Like the solid extrudate described above, the spray dried product contains a solid dispersion, preferably a solid solution, of Compound I in a matrix comprised of a hydrophilic

polymer described above and optionally a pharmaceutically acceptable surfactant described above. Where the spray dried product does not contain any surfactant, a pharmaceutically acceptable surfactant described above can be added to and blended with the spray-dried product before further processing.

[0132] Before feeding into a spray dryer, a crystalline form of Compound I of the invention (e.g., Class 1, or Form A or B), a hydrophilic polymer described above, as well as other optional active ingredients or excipients such as a pharmaceutically acceptable surfactant described above, can be dissolved in a solvent. Suitable solvents include, but are not limited to, alkanols (e.g., methanol, ethanol, 1-propanol, 2-propanol or mixtures thereof), acetone, acetone/water, alkanol/water mixtures (e.g., ethanol/water mixtures), or combinations thereof. The solution can also be preheated before being fed into the spray dryer. In many cases, ritonavir is dissolved together with the crystalline form of Compound I.

[0133] The solid dispersion produced by melt-extrusion, spray-drying or other techniques can be prepared into any suitable solid oral dosage forms. In one embodiment, the solid dispersion prepared by melt-extrusion, spray-drying or other techniques (e.g., the extrudate or the spray-dried powder) can be compressed into tablets. The solid dispersion can be either directly compressed, or milled or ground to granules or powders before compression. Compression can be done in a tablet press, such as in a steel die between two moving punches. When a solid composition comprises Compound I and another anti-HCV agent, it is possible to separately prepare solid dispersions of each individual active ingredient and then blend the optionally milled or ground solid dispersions before compacting. Compound I and another anti-HCV agent can also be prepared in the same solid dispersion, optionally milled and/or blended with other additives, and then compressed into tablets. Likewise, when a solid composition comprises Compound I and ritonavir, it is possible to separately prepare solid dispersions of each individual active ingredient and then blend the optionally milled or ground solid dispersions before compacting. Compound I and ritonavir can also be prepared in the same solid dispersion, optionally milled and/or blended with other additives, and then compressed into tablets.

[0134] At least one additive, such as one selected from flow regulators, lubricants, fillers, disintegrants or plasticizers, may be used in compressing the solid dispersion. These additives can be mixed with ground or milled solid dispersion before compacting. Disintegrants promote a rapid disintegration of the compact in the stomach and keeps the liberated granules separate from

one another. Non-limiting examples of suitable disintegrants are cross-linked polymers such as cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethylcellulose or sodium croscarmellose. Non-limiting examples of suitable fillers (also referred to as bulking agents) are lactose monohydrate, calcium hydrogenphosphate, microcrystalline cellulose (e.g., Avicell), silicates, in particular silicium dioxide, magnesium oxide, talc, potato or corn starch, isomalt, or polyvinyl alcohol. Non-limiting examples of suitable flow regulators include highly dispersed silica (e.g., colloidal silica such as Aerosil), and animal or vegetable fats or waxes. Non-limiting examples of suitable lubricants include polyethylene glycol (e.g., having a molecular weight of from 1000 to 6000), magnesium and calcium stearates, sodium stearyl fumarate, and the like.

[0135] Various other additives may also be used in preparing a solid composition prepared according to a process of the invention, for example dyes such as azo dyes, organic or inorganic pigments such as aluminium oxide or titanium dioxide, or dyes of natural origin; stabilizers such as antioxidants, light stabilizers, radical scavengers, stabilizers against microbial attack.

[0136] In one embodiment, a process of the invention described above uses Form A of Compound I which is substantially pure. Any Form A described above can be used in a process of the invention. For instance, the Form A crystal used can be at least 90% pure, preferably at least 95% pure, or more preferably at least 97%.

[0137] In another embodiment, a process of the invention described above uses Form B of Compound I which is substantially pure. Any Form B described above can be used in a process of the invention. For instance, the Form B crystal used can be at least 90% pure, preferably at least 95% pure, or more preferably at least 97%.

[0138] In another embodiment, a process of the invention described above uses Class 1 of Compound I which is substantially pure. Any Class 1 of Compound I described herein can be used in a process of the invention. For instance, the Class 1 crystal used can be at least 90% pure, preferably at least 95% pure, or more preferably at least 97%.

[0139] In yet another aspect, the present invention features compositions comprising a crystalline form of Compound I of the invention. Preferably, the crystalline form is substantially pure, such as at least 90% pure, preferably at least 95% pure, or more preferably at least 97% pure. In one embodiment, a composition of the invention comprises at least 5% by weight of a substantially pure crystalline form of the invention. In another embodiment, the composition of

the invention comprises at least 10% by weight of a substantially pure crystalline form of the invention. In still another embodiment, a composition of the invention comprises at least 5% by weight of one or more crystalline forms of the invention. In yet another embodiment, a composition of the invention comprises at least 10% by weight of one or more crystalline forms of the invention.

Example 1. Preparation of Crystalline Form B of Compound I

[0140] Dissolved 1.8 grams of ABT-450 in 35 mL of a solvent mixture of 1:2:0.5 v/v/v IPAc/EtOH/water by heating to 45 C. To the solution added 22 mL of DI water in four aliquots at 45 C. Cooled to 20 C and continued stirring overnight. Isolated solid via lab filtration and dried under ambient conditions. Solids were analyzed by PXRD and found to conform to Class 1 Form B pattern.

Example 2. Preparation of Crystalline Form A of Compound I

[0141] Exposed Class 1 Form B solids to 0% relative humidity for no less than 48 hrs and then transferred and collected PXRD pattern under 0% RH environment, to ensure conversion back to Form B pattern did not take place. PXRD pattern was found to conform to Class 1 Form A pattern.

[0142] The foregoing description of the present invention provides illustration and description, but is not intended to be exhaustive or to limit the invention to the precise one disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention. Thus, it is noted that the scope of the invention is defined by the claims and their equivalents.

What is claimed is:

1. A crystalline form of Compound I, wherein said crystalline form has characteristic peaks in PXRD pattern at values of two theta (° 2θ) of 6.7, 7.0, 10.5, 12.0, 17.6, 20.2, 21.9, 22.0, 22.6, and 23.1.

2. The crystalline form of claim 1, wherein said crystalline form has characteristic peaks in PXRD pattern at values of two theta (° 2θ) of 3.52, 6.73, 7.01, 9.06, 10.49, 11.99, 13.55, 15.16, 15.58, 16.80, 17.57, 18.61, 19.55, 20.17, 21.51, 21.88, 22.01, 22.64, 23.10, and 23.60.

3. A crystalline form of Compound I, wherein said crystalline form has characteristic peaks in PXRD pattern at values of two theta (° 2θ) of 6.0, 6.7, 10.4, 11.9, 17.5, 17.7, 21.5, 22.0, 22.7, and 24.2

4. The crystalline form of claim 3, wherein said crystalline form has characteristic peaks in PXRD pattern at values of two theta (° 2θ) of 3.43, 5.95, 6.67, 6.94, 9.00, 10.43, 11.95, 15.55, 17.51, 17.67, 18.36, 18.65, 20.13, 21.51, 21.82, 22.04, 22.66, 23.12, 24.23, and 24.66

5. A composition comprising the crystalline form of claim 1.

6. A process for making a composition comprising Compound I, comprising dissolving the crystalline form of claim 1 in a solvent.

7. A composition comprising the crystalline form of claim 3.

8. A process for making a composition comprising Compound I, comprising dissolving the crystalline form of claim 3 in a solvent.

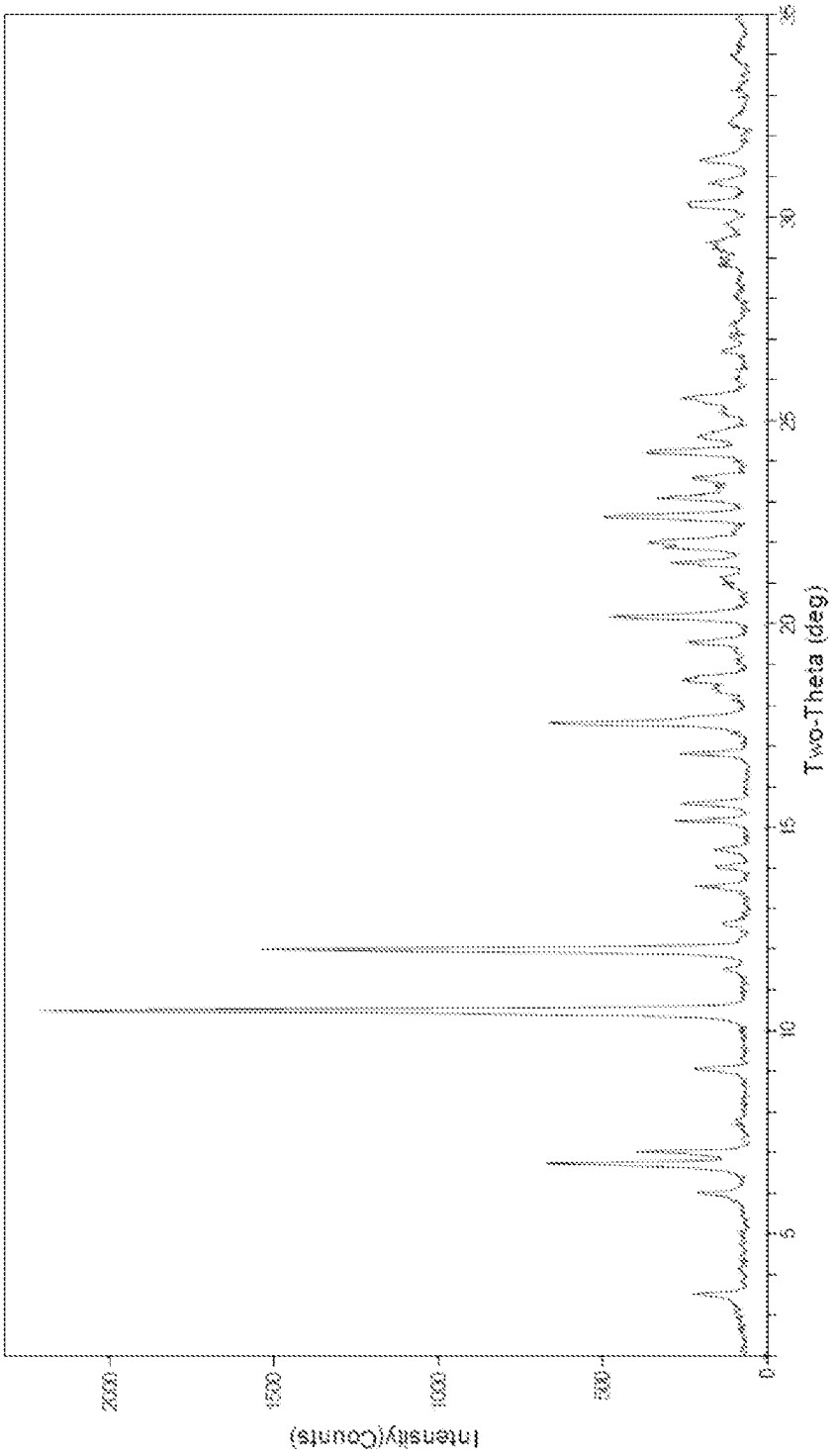

Intensity(Counts)
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0
5
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15
20
25
30
35
Two-Theta (deg)

Figure 1

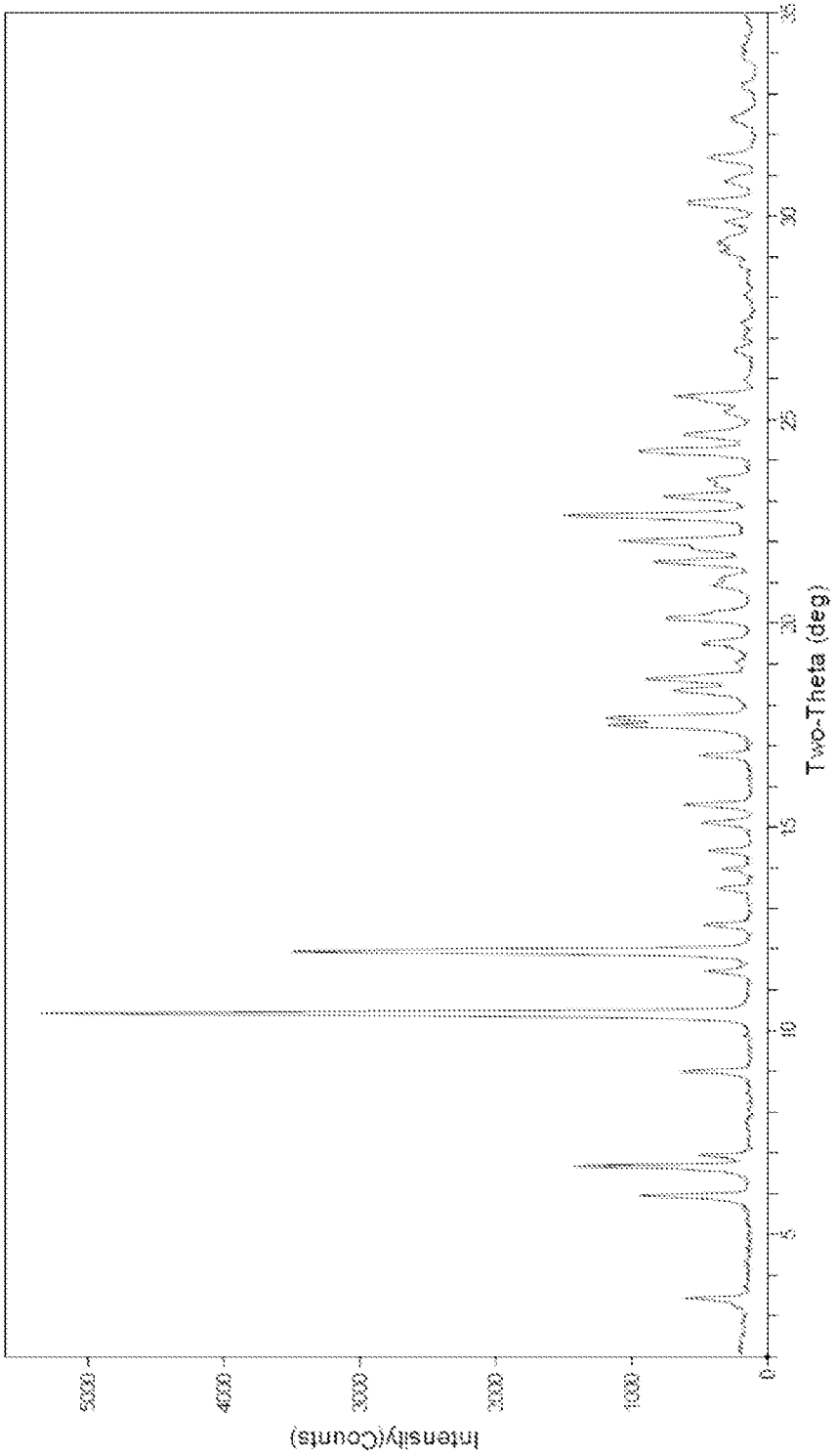

Intensity(Counts)
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2000
1000
0
5
10
15
20
25
30
35
Two-Theta (deg)

Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/068362

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/407
ADD.

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)
C07D A61K

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)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/030359 A2 (ENANTA PHARJMACEUTICALS INC [US]; ABBOTT LAB [US]; KU YIYIN [US]; MCDA) 18 March 2010 (2010-03-18) page 82; example 49d & US 2010/144608 A1 (KU YIYIN [US] ET AL) 10 June 2010 (2010-06-10) cited in the application	1-8
Y	WO 2011/112558 A2 (ABBOTT LAB [US]; ENANTA PHARM INC [US]; LIEPOLD BERND [DE]; ROSENBLATT) 15 September 2011 (2011-09-15) paragraphs [0052], [0059]; example 2 & US 2011/312973 A1 (LIEPOLD BERND [DE] ET AL) 22 December 2011 (2011-12-22) cited in the application	1-8
X,P	WO 2014/011840 A1 (ABBVIE INC [US]) 16 January 2014 (2014-01-16) the whole document	1-8

☐ 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	Date of mailing of the international search report
10 February 2015	18/02/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Frelon, Didier

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/068362

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

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

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

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

see additional sheet

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8

crystalline forms of Compound I

1.1. claims: 1, 2(completely); 5-8(partially)

crystalline form A

1.2. claims: 3, 4(completely); 5-8(partially)

crystalline form B

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