SOLID COMPOSITIONS

The present application claims the benefit from and incorporates by reference the entire contents of U.S Provisional Application Serial No. 61/353,553, filed June 10, 2010, and U.S. Patent Application Serial No. 12/813,301, filed June 10, 2010

FIELD OF THE INVENTION

The present invention relates to solid compositions comprising anti-HCV compounds and methods of using the same to treat HCV infection.

BACKGROUND

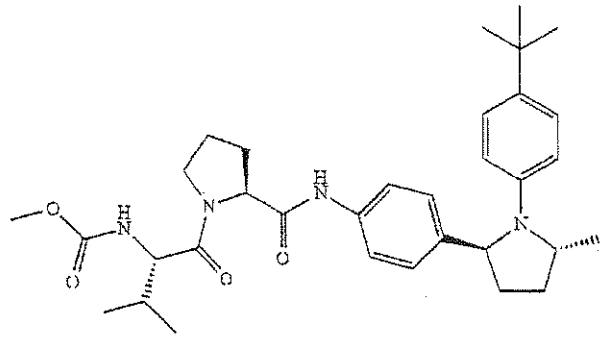
The hepatitis C virus (HCV) is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 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.

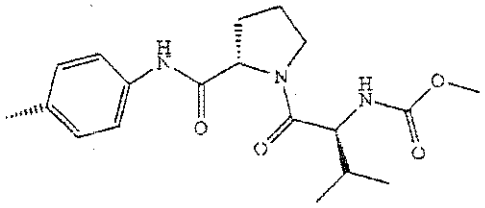
HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects,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

SUMMARY

In one aspect, there is provided a solid composition comprising

(1) dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate





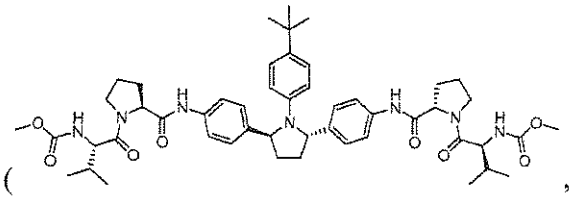
or a pharmaceutically acceptable salt thereof, in an amorphous form;

(2) a pharmaceutically acceptable hydrophilic polymer; and

(3) a pharmaceutically acceptable surfactant.

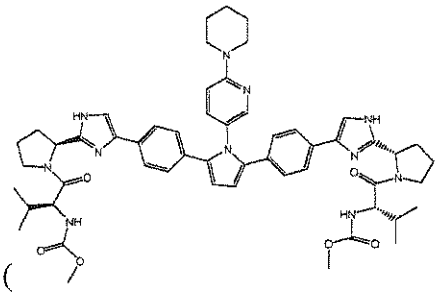
The present disclosure features solid compositions comprising a HCV inhibiting compound or a pharmaceutically acceptable salt thereof, wherein said HCV inhibiting compound is selected from the group consisting of:

dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-*tert*-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-

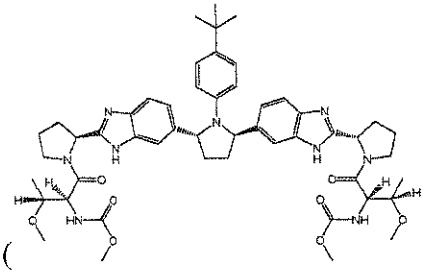
methyl-1-oxobutane-2,1-diyl)dicarbamate ( ,

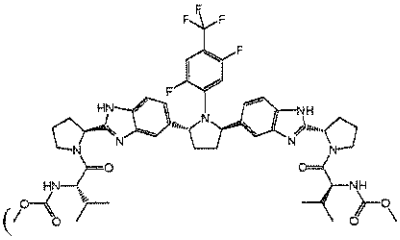
hereinafter Compound I_A),

methyl [(2S)-1-{(2S)-2-[4-(4-{5-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-[6-(piperidin-1-yl)pyridin-3-yl]-1H-pyrrol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

( , hereinafter Compound I_B),

methyl {(2*S*,3*R*)-1-[(2*S*)-2-{6-[(2*R*,5*R*)-1-(4-*tert*-butylphenyl)-5-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-6-yl)pyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate

( , hereinafter Compound I_C), and

methyl {(2S)-1-[(2S)-2-{5-[(2R,5R)-1-[2,5-difluoro-4-(trifluoromethyl)phenyl]-5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}pyrrolidin-2-yl]-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate ( , hereinafter Compound I_D).

Compound I_A, I_B, I_C and I_D are potent HCV inhibitors. The solid compositions of the invention comprise (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, in an amorphous form, (2) a pharmaceutically acceptable hydrophilic polymer, and optionally (3) a pharmaceutically acceptable surfactant.

In one aspect, the present disclosure features a solid composition comprising a solid dispersion, wherein the solid dispersion comprises (1) a compound selected from Compound I_A, I_B, I_C or I_D (or a pharmaceutically acceptable salt thereof) in an amorphous form, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant. The surfactant can be, without limitation, either formulated in the solid dispersion or separately combined or mixed with the solid dispersion. Preferably, the hydrophilic polymer has a T_g of at least 50 °C. More preferably, the hydrophilic polymer has a T_g of at least 80 °C. Highly preferably, the hydrophilic polymer has a T_g of at least 100 °C. Also preferably, the surfactant has a HLB value of at least 10. Hydrophilic polymers with T_gs of below 50 °C, such as a polymer having a T_g of at least 25 °C, and/or surfactants having HLB values of below 10, can also be used.

In one embodiment of this aspect of the invention, the hydrophilic polymer is selected from 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, or polysaccharide. Non-limiting examples of suitable hydrophilic polymers include 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, graft copolymer of polyethylene glycol/polyvinyl caprolactam/polyvinyl acetate (e.g., Soluplus), 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, or xanthan gum, or a combination thereof. In some cases, sugar alcohols can be used in addition to, or in lieu of, hydrophilic polymers.

In another embodiment of this aspect of the disclosure, the surfactant is selected from polyoxyethylene castor oil derivates, 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, or sorbitan fatty acid mono ester. Non-limiting examples of suitable surfactants include 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), mono fatty acid ester of polyoxyethylene sorbitan, such as 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 (e.g., lauroglycol FCC), D-alpha-tocopheryl polyethylene glycol 1000 succinate, sucrose monostearate, sucrose distearate, sucrose monolaurate, sucrose dilaurate, sorbitan mono laurate, sorbitan monooleate, sorbitan monopalnitate, or sorbitan stearate, or a combination thereof. Other suitable ionic or non-ionic surfactants may also be used.

In yet another embodiment of this aspect of the disclosure, the solid dispersion is an amorphous solid dispersion. In still another embodiment, the solid dispersion is an amorphous solid dispersion which comprises (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, (2) the hydrophilic polymer, and (3) the surfactant. In a further embodiment, the solid dispersion is a solid solution comprising (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, and (2) the hydrophilic polymer. In yet another embodiment, the solid dispersion is a solid solution

comprising (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, (2) the hydrophilic polymer, and (3) the surfactant.

In yet another embodiment of this aspect of the disclosure, the hydrophilic polymer is a homopolymer or copolymer of N-vinyl pyrrolidone. Preferably, the hydrophilic polymer is copovidone.

In still another embodiment, the surfactant is D-alpha-tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS). In a further embodiment, the surfactant is lauroglycol FCC. In yet another embodiment, the surfactant is a combination of vitamin E TPGS and lauroglycol FCC. In still another embodiment, the surfactant is a sorbitan fatty acid ester, such as sorbitan mono laurate (Span 20). In another embodiment, the surfactant is selected from Tween 20, Tween 80, vitamin E TPGS, or lauroglycol FCC, or a combination thereof.

In yet another embodiment, a solid composition of the disclosure comprises an amorphous solid dispersion or a solid solution which comprises (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, (2) copovidone, and (3) a surfactant selected from vitamin E TPGS, Span 20, or a combination thereof.

In another embodiment, a solid composition of the disclosure comprises an amorphous solid dispersion or a solid solution which comprises (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, (2) copovidone, and (3) a combination of vitamin E TPGS and lauroglycol FCC.

In still another embodiment, a solid composition of the disclosure comprises an amorphous solid dispersion or a solid solution which comprises (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, (2) copovidone, and (3) a surfactant selected from Tween 20 or Tween 80.

In another aspect, the present disclosure features processes of making a solid composition of the present invention. In one embodiment, the process comprises drying a solvent in a liquid solution, wherein said solution comprises: (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof; (2) a pharmaceutically acceptable hydrophilic polymer; and optionally (3) a pharmaceutically acceptable surfactant. The drying process can be carried out using any suitable solvent evaporation techniques including but not limited to spray-drying techniques.

In another embodiment, the process comprises solidifying a melt which comprises: (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof; (2) a pharmaceutically acceptable hydrophilic polymer; and optionally (3) a pharmaceutically acceptable surfactant.

A solid composition of the disclosure may also contain other additives or ingredients, such as coloring agents, flavoring agents, lubricants or preservatives. A solid composition of the invention can be prepared into any suitable dosage forms, such as capsule, dragee, granule, powder, or tablet.

A solid composition of the disclosure may further comprise another anti-HCV agent, for example, an agent selected from HCV helicase inhibitors, HCV polymerase inhibitors, HCV protease inhibitors, HCV NS5A inhibitors, CD81 inhibitors, cyclophilin inhibitors, or internal ribosome entry site (IRES) inhibitors.

The present disclosure further features methods of using a solid composition of the present disclosure to treat HCV infection. The methods comprise administering a solid composition of the present disclosure to a patient in need thereof, thereby reducing the blood or tissue level of HCV virus in the patient.

Other features, objects, and advantages of the present disclosure are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the disclosure, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the disclosure will become apparent to those skilled in the art from the detailed description.

DETAILED DESCRIPTION

The present invention features solid compositions comprising (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, in an amorphous form, (2) a pharmaceutically acceptable hydrophilic polymer, and optionally (3) a pharmaceutically acceptable surfactant. Formulating Compound I_A, I_B, I_C and I_D in an amorphous form can increase the inherent drug solubility and dissolution rate, thereby enhancing the bioavailability of the compound.

A non-limiting way to form an amorphous form of Compound I_A, I_B, I_C or I_D (or a pharmaceutically acceptable salt thereof) is through the formation of solid dispersions with a

polymeric carrier. The presence of hydrophilic polymer(s) and optional surfactant(s), as well as the dispersion of Compound I_A, I_B, I_C or I_D (or a pharmaceutically acceptable salt thereof) in an amorphous form in a matrix containing the polymer(s), can significantly enhance the dissolution rate of the compound. In some cases, a solid dispersion formulation can also effectively maintain Compound I_A, I_B, I_C or I_D (or a pharmaceutically acceptable salt thereof) in its supersaturation state to allow for better absorption.

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. These particles are often of less than 400 μm in size, such as less than 100, 10, or 1 μm in size. 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.

The term AUC_∞ or $AUC_{0\text{-inf}}$ refers to the area under the plasma concentration time curve (AUC) extrapolated to infinity.

The terms "weight percent" or "percent by weight" or "% by weight" or "wt %" denote the weight of an individual component in a composition or mixture as a percentage of the weight of the composition or mixture.

In one aspect, the present invention features a solid composition comprising (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, in an amorphous form, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant. The compound (or the salt thereof) and the polymer are formulated in a solid dispersion. The surfactant may be formulated in the same solid dispersion; or the surfactant can be separately combined or mixed with the solid dispersion.

In one embodiment, a solid composition of the invention comprises an amorphous solid dispersion which comprises (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, (2) a pharmaceutically acceptable hydrophilic polymer,

and (3) a pharmaceutically acceptable surfactant. In another embodiment, a solid composition of the invention comprises a solid solution which comprises (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, and (2) a pharmaceutically acceptable hydrophilic polymer. In still another embodiment, a solid composition of the invention comprises a solid solution which comprises (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant. In yet another embodiment, a solid composition of the invention comprises a glassy solution which includes (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, and (2) a pharmaceutically acceptable hydrophilic polymer. In a further embodiment, a solid composition of the invention comprises a glassy solution which includes (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, (2) a pharmaceutically acceptable hydrophilic polymer, and (3) a pharmaceutically acceptable surfactant.

A solid composition (or a solid dispersion) of the invention can contain, for example, at least 1% by weight of Compound I_A, I_B, I_C or I_D (or a pharmaceutically acceptable salt thereof), preferably at least 5%, including, e.g., at least 10%. For instance, a solid composition (or a solid dispersion) of the invention can contain from 1 to 50% by weight of the compound (or the salt thereof). For another instance, a solid composition (or a solid dispersion) of the invention can contain from 5 to 30% by weight of the compound (or the salt thereof). Preferably, a solid composition (or a solid dispersion) of the invention contains from 5 to 15% by weight of the compound (or the salt thereof).

A solid dispersion of the invention may contain at least 30% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such hydrophilic polymers. Preferably, the solid dispersion contains at least 40% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such hydrophilic polymers. More preferably, the solid dispersion contains at least 50% (including, e.g., at least 60%, 70%, 80% or 90%) by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers. A solid dispersion (or a solid composition) of the invention may also contain at least 1% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. Preferably, the solid dispersion (or solid composition) contains at least 2% by weight of a

pharmaceutically acceptable surfactant or a combination of such surfactants. More preferably, the solid dispersion (or solid composition) contains from 4% to 20% by weight of the surfactant(s), such as from 5% to 10% by weight of the surfactant(s).

In one embodiment, a solid dispersion (or a solid composition) of the invention comprises at least 30% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and at least 1% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. In another embodiment, a solid dispersion (or a solid composition) of the invention comprises at least 50% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and from 2% to 20% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. In yet another embodiment, a solid dispersion (or a solid composition) of the invention comprises from 50% to 90% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and from 3% to 15% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants. In yet another embodiment, a solid dispersion (or a solid composition) of the invention comprises from 70% to 90% by weight of a pharmaceutically acceptable hydrophilic polymer or a combination of such polymers, and from 5% to 10% by weight of a pharmaceutically acceptable surfactant or a combination of such surfactants.

Preferably, a hydrophilic polymer employed in the present 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 $T_g = \Sigma W_i \cdot X_i$ 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.

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.

Hydrophilic polymers suitable for use in a solid composition 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); graft copolymers of polyethylene glycol/polyvinyl caprolactam/polyvinyl acetate, or any mixture or combination thereof. In some cases, sugar alcohols can be used in addition to, or in lieu of, hydrophilic polymers.

Non-limiting examples of preferred hydrophilic polymers for 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, Soluplus, poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, and poloxamer 407.

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).

A pharmaceutically acceptable surfactant employed in the present invention is preferably a non-ionic surfactant. Ionic surfactants may also be used. More preferably, a solid composition of the present invention comprises a pharmaceutically acceptable surfactant having an HLB value of from 2-20. A solid composition of the present invention can also include a mixture of pharmaceutically acceptable surfactants, with at least one surfactant having an HLB value of no less than 10 and at least another surfactant having an HLB value of below 10. In one example, each surfactant comprised in a solid composition of the invention has an HLB value of at least 10. In another example, each surfactant comprised in a solid composition of the invention has an HLB value of below 10. In yet another example, a solid composition of the present invention includes at least two pharmaceutically acceptable surfactants, one having an HLB value of at least 10 and the other having an HLB value of below 10. 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.

Non-limiting examples of pharmaceutically acceptable surfactants that are suitable for the present 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, such as lauroglycol FCC); 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; D-alpha-tocopheryl polyethylene glycol 1000 succinate; or a combination or mixture thereof. 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.). As described above, a mixture of surfactants can be used in a solid composition of the present invention.

Non-limiting examples of preferred surfactants for the invention include to 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.

In one embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, and (2) a pharmaceutically acceptable hydrophilic polymer. The solid composition also includes a

pharmaceutically acceptable surfactant which preferably is formulated in the amorphous solid dispersion or solid solution. 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, graft copolymer of polyethylene glycol/polyvinyl caprolactam/polyvinyl acetate, 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, Soluplus, 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, D-alpha-tocopheryl polyethylene glycol 1000 succinate, 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, D-alpha-tocopheryl polyethylene glycol 1000 succinate, propylene glycol monolaurate, or a combination thereof (e.g., a combination of D-alpha-tocopheryl polyethylene glycol 1000 succinate and lauroglycol FCC).

In another embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, and (2) a homopolymer or copolymer of N-vinyl pyrrolidone (e.g., copovidone). The solid composition also comprises a pharmaceutically acceptable surfactant (e.g., vitamin E TPGS, sorbitan monolaurate, or a

combination of vitamin E TPGS and lauroglycol FCC), wherein the surfactant preferably is formulated in the amorphous solid dispersion or solid solution.

In yet another embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) a compound selected from Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, (2) copovidone, and (3) a pharmaceutically acceptable surfactant (e.g., vitamin E TPGS, sorbitan monolaurate, or a combination of vitamin E TPGS and lauroglycol FCC). The amorphous solid dispersion or solid solution may also include another pharmaceutically acceptable surfactant.

In still another embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) 10% by weight Compound I_A, I_B, I_C or I_D (or a pharmaceutically acceptable salt thereof) (2) 82% by weight copovidone, and (3) 5% by weight vitamin E TPGS and 2% by weight lauroglycol FCC. The solid composition can also include 1% by weight colloidal silica.

In a further embodiment, a solid composition of the present invention comprises an amorphous solid dispersion or solid solution which includes (1) 10% by weight Compound I_A, I_B, I_C or I_D (or a pharmaceutically acceptable salt thereof) (2) 82% by weight copovidone, and (3) 7% by weight propylene glycol monocaprylate (Capryol 90). The solid composition can also include 1% by weight colloidal silica.

A solid dispersion employed in the present invention preferably comprises or consists of a single-phase (defined in thermodynamics) in which the therapeutic agent(s) (e.g., Compound I_A, I_B, I_C or I_D, or a pharmaceutically acceptable salt thereof, with or without another anti-HCV agent) is molecularly dispersed in a matrix containing the pharmaceutically acceptable hydrophilic polymer(s). In such cases, thermal analysis of the solid dispersion using differential scanning calorimetry (DSC) typically shows only one single T_g, and the solid dispersion does not contain any detectable crystalline Compound I_A, I_B, I_C or I_D as measured by X-ray powder diffraction spectroscopy.

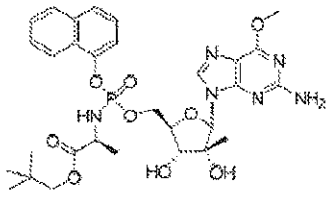
Compound I_A, I_B, I_C and I_D can be prepared according to the procedures described in Examples 37, 144, 250 and 237, respectively, of U.S. Patent Application Serial No. 12/813,301, filed June 10, 2010, now U.S. Patent Application Publication No. 2010/0317568, which is incorporated herein by reference in its entirety.

A solid composition of the present invention can further include one or more other anti-HCV agents. These other anti-HCV agents can be, for example, HCV polymerase inhibitors (including nucleoside or non-nucleoside type of polymerase inhibitors), HCV protease inhibitors, HCV helicase inhibitors, CD81 inhibitors, cyclophilin inhibitors, internal ribosome entry site inhibitors, or HCV NS5A inhibitors. Specific examples of these other anti-HCV agents include, but are not limited to, ribavirin, α-interferon, β-interferon, pegylated interferon-α, pegylated interferon-lambda, PSI-7851 (Pharmasset) (nucleoside polymerase inhibitor), PSI-938 (Pharmasset) (nucleoside polymerase inhibitor), PF-00868554, ANA-598, IDX184 (nucleoside polymerase inhibitor), IDX102, IDX375 (non-nucleoside polymerase inhibitor), GS-9190 (non-nucleoside polymerase inhibitor), VCH-759, VCH-916, MK-3281, BCX-4678, MK-3281, VBY708, ANA598, GL59728, GL60667, BMS-790052 (NS5A inhibitor), BMS-791325 (protease Inhibitor), BMS-650032, BMS-824393, GS-9132, ACH-1095 (protease inhibitor), AP-H005, A-831 (Arrow Therapeutics) (NS5A inhibitor), A-689 (Arrow Therapeutics) (NS5A inhibitor), INX08189 (Inhibitex) (polymerase inhibitor), AZD2836, telaprevir (protease Inhibitor), boceprevir (protease Inhibitor), ITMN-191 (Intermune/Roche), BI-201335 (protease Inhibitor), VBY-376, VX-500 (Vertex) (protease Inhibitor), PHX-B, ACH-1625, IDX136, IDX316, VX-813 (Vertex) (protease Inhibitor), SCH 900518 (Schering-Plough), TMC-435 (Tibotec) (protease Inhibitor), ITMN-191 (Intermune, Roche) (protease Inhibitor), MK-7009 (Merck) (protease Inhibitor), IDX-PI (Novartis), BI-201335 (Boehringer Ingelheim), R7128 (Roche) (nucleoside polymerase inhibitor), MK-3281 (Merck), MK-0608 (Merck) (nucleoside polymerase inhibitor), PF-868554 (Pfizer) (non-nucleoside polymerase inhibitor), PF-4878691 (Pfizer), IDX-184 (Novartis), IDX-375 (Pharmasset), PPI-461 (Presidio) (NS5A inhibitor), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), Albuferon (Novartis), ABT-333 (Abbott) (non-nucleoside polymerase inhibitor), and ABT-072 (Abbott) (non-nucleoside polymerase inhibitor).

In one embodiment, a solid composition of the invention comprises Compound I_A, I_B, I_C or I_D (or a pharmaceutically acceptable salt thereof), and a HCV protease inhibitor. In another embodiment, a solid composition of the invention comprises Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), and a HCV polymerase inhibitor (e.g., a non-nucleoside polymerase inhibitor, or preferably a nucleoside polymerase inhibitor). In yet another embodiment, a solid composition of the invention comprises (1) Compound I_A, I_B, I_C or I_D (a

pharmaceutically acceptable salt thereof), (2) a HCV protease inhibitor, and (3) a HCV polymerase inhibitor (e.g., a non-nucleoside polymerase inhibitor, or preferably a nucleoside polymerase inhibitor). Non-limiting examples of protease and polymerase inhibitors are described above. For instance, the protease inhibitor can be selected from ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BI-201335 (Boehringer Ingelheim), BMS-650032 (BMS), boceprevir, danoprevir, GS-9132 (Gilead), GS-9256 (Gilead), GS-9451 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir, PHX-1766 (Phenomix), telaprevir, TMC-435 (Tibotec), vaniprevir, VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), or a combination thereof. And the HCV polymerase inhibitor can be selected from, without limitation, ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst), or a combination thereof. The polymerase inhibitor may be a nucleotide polymerase inhibitor, such as GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Pharmasset), PSI-938 (Pharmasset), RG7128 (Roche), TMC64912 (Medivir), or a combination therefore. The polymerase inhibitor may also be a non-nucleoside polymerase inhibitor, such as ABT-072 (Abbott), ABT-333 (Abbott), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), or a combination thereof. The present invention also contemplates the inclusion of both a nucleotide polymerase inhibitor and a non-nucleoside polymerase inhibitor in a solid composition of the invention.

In yet another embodiment, a solid composition of the invention comprises (1) Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), and (2) INX-189

(Inhibitex; ). In still another embodiment, a solid composition of the invention comprises (1) Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), and (2) RG7128, PSI-7977, PSI-938 or PSI-7851. In a further embodiment, a solid composition of the invention comprises (1) Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), (2) MK-5172, and optionally (3) RG7128. In another embodiment, a solid composition of the invention comprises (1) Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), (2) BMS-650032, and optionally (3) PSI-7977, PSI-938 or PSI-7851. In another embodiment, a solid composition of the invention comprises (1) Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), (2) danoprevir, and optionally (3) RG7128, PSI-7977, PSI-938 or PSI-7851. In another embodiment, a solid composition of the invention comprises (1) Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), (2) TMC-435, and optionally (3) RG7128, PSI-7977, PSI-938 or PSI-7851. In another embodiment, a solid composition of the invention comprises (1) Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), (2) BMS-650032, and optionally (3) BMS-790052. Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), and BMS-790052, can be co-formulated in an amorphous form, e.g., co-formulated in a solid dispersion or solid solution described herein. In still another embodiment, a solid composition of the invention comprises (1) Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), and (2) GS-9256, GS-9190, GS-9132, GS-9451, GS-9669, or GS-6620.

Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), and one or more other anti-HCV agents described herein (e.g., MX-5172 or danoprevir), can be co-formulated in amorphous forms, e.g., co-formulated in a solid dispersion or solid solution described herein. Alternatively, Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof) can be co-administered with one or more other anti-HCV agents described herein, either concurrently or sequentially, to a patient in need thereof for the treatment of HCV infection.

A solid composition of the present invention preferably is a solid oral dosage form. Common solid oral dosage forms suitable for the present invention include, but are not limited to, capsules, dragees, granules, pills, powders and tablets, with capsules and tablets being

preferred. A solid oral dosage form of the present invention can also include other excipients or inset diluents, such as sucrose, lactose or starch. Lubricants, coloring agents, releasing agents, coating agents, sweetening or flavoring agents, buffering agents, preservatives, or antioxidants can also be included in a solid oral dosage form of the present invention.

A solid composition of the present invention can be prepared by a variety of techniques such as, without limitation, melt-extrusion, spray-drying, co-precipitation, freeze drying, or other solvent evaporation techniques, with melt-extrusion and spray-drying being preferred. The melt-extrusion process typically comprises the steps of preparing a melt which includes the active ingredient(s), the hydrophilic polymer(s) and preferably the surfactant(s), and then cooling the melt until it solidifies. Melting often involves a transition into a liquid state in which it is possible for one component to get dissolved or embedded, preferably homogeneously dissolved or embedded, in the other component or components. In many cases, the polymer component(s) will melt and the other components including the active ingredient(s) and surfactant(s) will dissolve in the melt thereby forming a solution. In such a case, the polymer functions as a solvent. Melting usually involves heating above the softening point of the polymer(s). 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 the active ingredient(s) efficiently. In addition, it may be convenient first to melt the polymer(s) and then to mix in and homogenize the active ingredient(s). In one example, all materials except surfactant(s) are blended and fed into an extruder, while the surfactant(s) is molten externally and pumped in during extrusion.

In another example, the melt comprises Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), and one or more hydrophilic polymers 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.

In still another example, the melt comprises Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), at least another anti-HCV agent described above, and one or more hydrophilic polymers described above. The melt can also include a pharmaceutically acceptable surfactant described above.

To start a melt-extrusion process, the active ingredient(s) (e.g., Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), or a combination of Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof) with at least another anti-HCV agent) can be employed in their solid forms, such as their respective crystalline forms. The active ingredient(s) can also be employed as a solution or dispersion 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.

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

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.

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).

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 the active ingredient(s) in a matrix comprised of the hydrophilic polymer(s) and optionally the pharmaceutically acceptable surfactant(s). 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) and/or additive(s) before being milled or ground to granules. The granules can be further processed into suitable solid oral dosage forms.

In some cases, direct-shaping techniques such as injection moulding can be used in combination with melt extrusion to prepare suitable solid dosage forms.

In one example, copovidone and one or more surfactants are mixed and granulated, followed by the addition of aerosil and Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof). The mixture, which may contain for example at least 5% by weight of Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof) 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. Surfactant(s) employed in this example can also be added through liquid dosing during extrusion.

The approach of solvent evaporation, 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.

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.

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.

Like the solid extrudate described above, the spray dried product contains a solid dispersion, preferably a solid solution, of the active ingredient(s) in a matrix comprised of the hydrophilic polymer(s) and optionally the pharmaceutically acceptable surfactant(s). 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.

Before feeding into a spray dryer, the active ingredient(s) (e.g., Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof), or a combination of Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof) with at least another anti-HCV agent), the hydrophilic polymer(s), as well as other optional active ingredients or excipients such as the pharmaceutically acceptable surfactant(s), can be dissolved in a solvent. Suitable solvents include, but are not limited to, water, 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.

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 of the present invention comprises Compound I_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof) 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_A, I_B, I_C or I_D (a pharmaceutically acceptable salt thereof) and other active ingredient(s) can also be prepared in the same solid dispersion, optionally milled and/or blended with other additives, and then compressed into tablets.

At least one additive selected from flow regulators, binders, 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.

Various other additives may also be used in preparing a solid composition of the present 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.

Solid compositions according to certain embodiments of the present invention may contain several layers, for example laminated or multilayer tablets. They can be in open or closed form. "Closed dosage forms" are those in which one layer is completely surrounded by at least one other layer.

In order to facilitate the intake of a solid dosage form, it is advantageous to give the dosage form an appropriate shape. Large tablets that can be swallowed comfortably are therefore preferably elongated rather than round in shape.

A film coat on the tablet further contributes to the ease with which it can be swallowed. A film coat also improves taste and provides an elegant appearance. The film-coat usually includes a polymeric film-forming material such as hydroxypropyl methylcellulose, hydroxypropylcellulose, and acrylate or methacrylate copolymers. Besides a film-forming polymer, the film-coat may further comprise a plasticizer, e.g. polyethylene glycol, a surfactant, e.g. polysorbates, and optionally a pigment, e.g. titanium dioxide or iron oxides. The film-coating may also comprise talc as anti-adhesive. Preferably, the film coat accounts for less than 5 % by weight of a pharmaceutical composition of the present invention.

In another aspect, the present invention feature methods of using solid compositions of the present invention to treat HIV infection. The methods comprise administering a solid composition of the present invention to a patient in need thereof. A solid composition of the present invention can be administered either alone, or in combination with one or more other anti-HCV agents, such as those described hereinabove. The specific inhibitory dose for any particular patient will depend upon a variety of factors including the severity of the HCV infection; the activity of the active ingredient(s) in the particular patient; the specific solid composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration and rate of excretion; the duration of the treatment; drugs used in combination or coincidental with Compound I_A, I_B, I_C or I_D; and like factors well known in the medical arts.

In one embodiment, a method of the present invention comprises administering to a patient in need thereof a solid composition of the present invention and at least another anti-HCV agent, wherein said another anti-HCV agent is selected from HCV polymerase inhibitors (e.g., nucleoside or non-nucleoside HCV polymerase inhibitors), HCV protease inhibitors, HCV helicase inhibitors, CD81 inhibitors, cyclophilin inhibitors, internal ribosome entry site inhibitors, or HCV NS5A inhibitors. Preferably, said another anti-HCV agent is an HCV polymerase inhibitor (e.g., nucleoside or non-nucleoside HCV polymerase inhibitor) or an HCV protease inhibitor. Also preferably, said another anti-HCV agent is interferon or ribavirin, or preferably a combination thereof. The interferon preferably is α-interferon, and more preferably, pegylated interferon-α such as PEGASYS (peginterferon alfa-2a). The administration of a solid

composition of the present invention and another anti-HCV agent(s) can be concurrent or sequential.

The present invention also features use of a solid composition of the present invention for the manufacture of medicaments for the treatment of HCV infection.

It should be understood that the above-described embodiments and the following examples are given by way of illustration, not limitation. Various changes and modifications within the scope of the present invention will become apparent to those skilled in the art from the present description.

Example 1

Compound I_A was extruded using melt-extrusion. Two extrudates were prepared, and then milled and filled into capsules. The 1st extrudate contained Compound I_A, copovidone, and Vitamin E-TPGS in a weight ratio of 5:88:7 (hereinafter Formulation 1). The 2nd extrudate contained Compound I_A, copovidone and Sorbitan monolaurate in a weight ratio of 5:90:5 (hereinafter Formulation 2). The extrusion mixtures were prepared by use of mortar and pestle. Both formulations were extruded at 140°C. The obtained extruded strands were milled and the fractions of over 0.2 mm were combined with 100 mg mannite / collidal silica (99:1) and then filled into capsules. Each of these extrudate capsules contained 5 mg Compound I_A.

Example 2

The pharmacokinetic profile of each formulation described in Example 1 was evaluated in dogs after single oral (PO) administration of the formulation. Four dogs (two male and two female dogs) were used in this study. The animals were fasted overnight and received food 30 min prior to dosing and throughout the duration of the study. Plasma samples were collected at 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours post-dose administration. Plasma samples were analyzed for Compound I_A by LC-MS/MS. $AUC_{0\text{-}inf}$ and C_{max} were normalized to a dose of 0.5 mg/kg Compound I_A.

Mean dose-normalized $AUC_{0\text{-}inf}$ values of Compound I_A were 512.2 and 432.0 ng·h/ml, at a 0.5 mg/kg dose in Formulations 1 and 2, respectively. Mean dose-normalized C_{max} values of Compound I_A were 36.1 and 15.2 ng/ml at a 0.5 mg/kg dose in Formulations 1 and 2, respectively.

Example 3

Compound I_A was mixed with hydrophilic polymers and pharmaceutically acceptable surfactants at various ratios, and dissolved in an organic solvent (acetone or acetone/water mixtures). The solvent was then removed from the system under heat (~75°C) and vacuum, using a Genevac rotary evaporator or Buchi Rotavap. Solid dispersions of Compound I_A at various drug loading levels and using different surfactants or polymers were sieved through a 30 mesh screen to reduce particle size. The resultant solid dispersion samples were used for amorphous characterization by X-ray powder diffraction (PXRD), chemical stability, in-vitro dissolution test and dog bioavailability studies.

For dog bioavailability studies, the solid dispersion powder was mixed with other excipients and compressed into tablets to achieve strengths of 0.5 mg, 5.0 mg, and 25.0 mg. For in-vitro dissolution studies, the release of Compound I_A was evaluated.

The hydrophilic polymers employed were copovidone, Soluplus, hydroxypropyl methylcellulose phthalate (HPMCP), and hydroxypropyl methylcellulose grade E5 (HPMC-E5). The surfactants employed were Vitamin E TPGS and Cremophor RH40. The amount of the surfactant(s) in each solid dispersion was no more than 10% by weight, and the amount of Compound I_A in each solid dispersion ranged from 5 to 20% by weight.

All solid dispersions showed that Compound I_A was in an amorphous form, as indicated by their PXRD patterns. Solid dispersions containing copovidone were evaluated for stability and showed chemical stability after 4 weeks at 40 °C and 75% relative humidity in closed dish studies. These solid dispersions also exhibited rapid dissolution rate.

Example 4

One solid dispersion formulation was prepared using spray-drying to produce a solid dispersion powder of amorphous Compound I_A within a polymer matrix. The spray dried powder contained 10% by weight of Compound I_A, 85% by weight of copovidone, and 5% by weight of Vitamin E TPGS. Acetone and water in a 9:1 ratio was used as a solvent for spray-drying.

The spray dried powder was further dried under vacuum to remove residual solvent. The vacuum dried powder was blended with microcrystalline cellulose, lactose monohydrate,

colloidal silicon dioxide, sodium stearyl fumarate, and optionally croscarmellose sodium. This blend was then compressed into the final tablet dosage form.

Example 5

Compound I_B was formulated using melt-extrusion as well as spray-drying. Both formulations contained 10% Compound I_B, 82% copovidone, 2% Vitamin E TPGS, 5% lauroglycol FCC, and 1% Aerosil 200, and were processed further into compressed tablets. Both forms were tested in an accelerated stability test over 4 weeks. The pharmacokinetic study in dogs showed excellent bioavailability of Compound I_B.

Example 6

Compound I_C was mixed with Copovidone at drug loading of 10%, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_C from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

The solid dispersion showed that Compound I_C was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_C in neat amorphous state.

Example 7

Compound I_C was mixed with Copovidone and Vitamin E TPGS at drug loading of 10% and 20%, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum (rotary evaporation or vacuum oven). Solid dispersion of Compound I_C at 10% drug loading level was ground to fine particles using mortar and pestle, and was then characterized by X-ray powder diffraction (PXRD), DSC and TGA, and in vitro dissolution test. The resultant amorphous solid dispersion at 20% drug loading was also characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_C from above

amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

Both solid dispersions showed that Compound I_C was in an amorphous form, as indicated by PXRD, DSC or PLM. These solid dispersions exhibited rapid dissolution rate in comparison with Compound I_C in neat amorphous state.

Example 8

Compound I_C was mixed with Copovidone and Tween 80 or Cremophor RH40 at drug loading of 10% and 20%, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_C from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

All four solid dispersions showed that Compound I_C was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_C in neat amorphous state.

Example 9

Compound I_C was mixed with Copovidone and Vitamin E TPGS and Lauroglycol FCC at drug loading of 10% and 20%, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_C from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

Both solid dispersions showed that Compound I_C was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_C in neat amorphous state.

Example 10

Compound I_C was mixed with Soluplus and Vitamin E TPGS or Tween 80 or Cremophor RH40 at drug loading of 10% and 20%, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_C from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

All six solid dispersions showed that Compound I_C was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_C in neat amorphous state.

Example 11

Compound I_C was mixed with Soluplus (a graft copolymer of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate) and Vitamin E TPGS and Lauroglycol FCC at drug loading of 10% and 20%, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_C from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

Both solid dispersions showed that Compound I_C was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_C in neat amorphous state.

Example 12

One solid dispersion formulation was prepared using spray-drying to produce a solid dispersion powder of amorphous Compound I_C within a polymer matrix. The spray dried powder contained 10% by weight of Compound I_C, 85% by weight of Copovidone, and 5% by weight of Vitamin E TPGS. Methanol was used as a solvent for spray drying. The spray dried powder was further dried under vacuum to further remove residual solvent. The dried amorphous solid dispersion was characterized by X-ray powder diffraction (PXRD), DSC and TGA.

The solid dispersion showed that Compound I_C was in an amorphous form, as indicated by either PXRD and DSC.

Example 13

Compound I_D was mixed with Copovidone at drug loading of 10%, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_D from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

The solid dispersion showed that Compound I_D was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_D in neat amorphous state.

Example 14

Compound I_D was mixed with Copovidone and Vitamin E TPGS or Tween 80 or Cremophor RH40 at drug loading of 10% and 20%, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_D from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

All six solid dispersions showed that Compound I_D was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_D in neat amorphous state.

Example 15

Compound I_D was mixed with Copovidone and Vitamin E TPGS and Lauroglycol FCC at drug loading of 10% and 20%, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_D from

above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

Both solid dispersions showed that Compound I_D was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_D in neat amorphous state.

Example 16

Compound I_D was mixed with Soluplus and Vitamin E TPGS or Tween 80 or Cremophor RH40 at drug loading of 10% and 20%, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_D from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

All six solid dispersions showed that Compound I_D was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_D in neat amorphous state.

Example 17

Compound I_D was mixed with Soluplus and Vitamin E TPGS and Lauroglycol FCC at drug loading of 10% and 20%, respectively, and dissolved in an organic solvent (e.g. methanol). The solvent was then removed from the system under heat (~40°C) and vacuum. The resultant amorphous solid dispersions were characterized by polarized light microscopy (PLM) and in vitro dissolution test. For in-vitro dissolution studies, the release of Compound I_D from above amorphous solid dispersions was evaluated in pH 6.8 phosphate buffer by in situ UV dip probe and HPLC assay.

Both solid dispersions showed that Compound I_D was in an amorphous form, as indicated by PLM. These solid dispersions also exhibited rapid dissolution rate in comparison with Compound I_D in neat amorphous state.

Example 18

Granulation of one formulation containing 15% Compound I_B, 7.1% Lauroglycol FCC, 2.9% Vitamin E TPGS and 75% copovidone was performed using a lab mill. Liquid excipients such as Lauroglycol FCC were granulated with the solid raw material, stored in the refrigerator over night for setting and mixed again. The resultant blends were used directly for extrusion. Extrusion was carried out on a small-scale twin-screw extruder (rotation speed of 80 rpm) at a temperature of 140°C. Drug recovery and purity analysis after processing was evaluated by HPLC assay. The solid dispersion was characterized by DSC and polarized light microscopy (PLM). For in-vitro dissolution studies, the release of Compound I_B from above amorphous solid dispersion was evaluated in pH 6.8 phosphate buffer by HPLC assay.

DSC and PLM analysis of the solid dispersion revealed that Compound I_B was in an amorphous form and showed negligible degradation upon processing at high temperature. The solid dispersion exhibited rapid dissolution rate at pH 6.8.

It turned out that Compound I_B can be processed via melt extrusion at temperatures as high as about 170°C, which is far beyond the degradation temperature of the drug substance of around 130°C without an increase in API degradation.

Example 19

Compound I_B was formulated using melt-extrusion as well as spray-drying. Both formulations included 10% Compound I_B, 82% copovidone, 5% Lauroglycol FCC, 2% Vitamin E TPGS, and 1% Aerosil 200. Preparation of the granulate for melt extrusion was performed using a lab mill. Liquid excipients such as Lauroglycol FCC were granulated with the solid raw material, stored in the refrigerator over night for setting and mixed again. The resultant blends were used directly for extrusion. Extrusion was carried out on a small-scale twin-screw extruder (rotation speed of 80 rpm) at a temperature of 150°C. The resultant amorphous solid dispersion was characterized by DSC and polarized light microscopy (PLM). For in-vitro dissolution studies, the release of Compound I_B from above amorphous solid dispersion was evaluated in pH 6.8 phosphate buffer by HPLC assay.

For spray drying, the same composition as applied for melt extrusion was dissolved in a isopropyl alcohol/water mixture, giving a feed solution formulation of 2 % Compound I_B, 16.4% copovidone, 1% Lauroglycol FCC, 0.4% Vitamin E TPGS, 0.2% Aerosil 200, 70% isopropyl alcohol and 10% DI water. The solid dispersion was manufactured using a

lab-scale spray drier at an inlet temperature of 110 °C and a rotavapor for post-drying at 40 °C and 40 mbar abs. to remove remaining solvents. The spray dried solid dispersion was tested for residual solvent content.

The yielded solid dispersions were compressed each into a 100 mg tablet by applying a direct-blend / direct-compression process of 50% solid dispersion, 28% Avicel 102, 14% Di-CAFOS A, 5% croscarmellose sodium, 1% Aerosil 200 and 2% sodium stearyl fumarate.

The pharmacokinetic study in dogs showed excellent bioavailability of Compound I_B in the spray dried as well as in the melt extrusion tablet form compared to in vivo administration of a reference liquid formulation of compound I_B. Compressed tablets of both forms exhibited no degradation of compound I_B when stored at 40°C and 75% rel. humidity over 4 weeks. Dissolution behavior as well as the glass transition temperature remains constant.

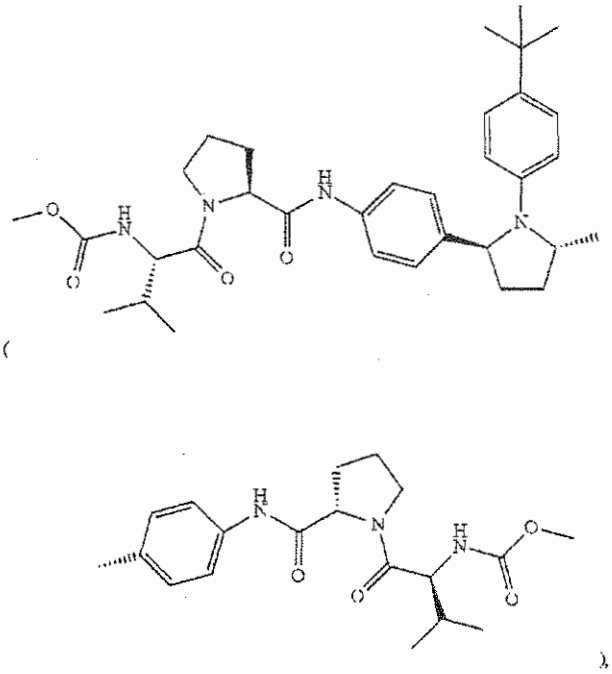
Compound I_B was also formulated in solid dispersion with other surfactants such as Tween 80 or Cremophor RH40.

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 solid composition comprising

(1) dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate



or a pharmaceutically acceptable salt thereof, in an amorphous form;

(2) a pharmaceutically acceptable hydrophilic polymer; and

(3) a pharmaceutically acceptable surfactant.

2. The composition of claim 1, comprising a solid dispersion which includes:

(1) said dimethyl (2S,2'S)-1,1'-((2S,2'S)-2,2'-(4,4'-((2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl)bis(oxomethylene)bis(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-2,1-diyl)dicarbamate, or said pharmaceutically acceptable salt thereof,

(2) said polymer, and

(3) said surfactant.

3. The composition of claim 2, wherein said polymer has a T_g of at least 50° C.

4. The composition of claim 3, wherein said surfactant has a HLB value of at least 10.

5. The composition of claim 4, further comprising another surfactant having a HLB value of below 10.

6. The composition of claim 3, wherein said solid dispersion is an amorphous solid dispersion which further comprises said surfactant.

7. The composition of claim 3, wherein said polymer is a homopolymer or copolymer of N-vinyl pyrrolidone.

8. The composition of claim 2, wherein said polymer is copovidone.

9. The composition of claim 8, wherein said surfactant is D-alpha-tocopheryl polyethylene glycol 1000 succinate.

10. The composition of claim 8, wherein said surfactant is sorbitan mono laurate.

11. The composition of claim 8, wherein said solid dispersion is an amorphous solid dispersion.

12. The composition of claim 8, where said solid dispersion is a solid solution which comprises said surfactant.

13. The composition of claim 1, further comprising another anti-HCV agent.

14. The composition of claim 1, further comprising an HCV protease inhibitor.

15. The composition of claim 1, further comprising an HCV polymerase inhibitor.

16. The composition of claim 1, further comprising telaprevir or boceprevir.

17. The composition of claim 1, further comprising an anti-HCV agent selected from the group consisting of ITMN-191, BI-201335, VBY-376, VX-500, PHX-B, ACH-1625, IDX136, IDX316, VX-813, SCH 900518, TMC-435, ITMN-191, MK-7009, IDX-PI, BI-201335, R7128, MK-3281, PF-868554, PF-4878691, IDX-184, IDX-375, PPI-461, BILB-1941, GS-9190, BMS-790052, ABT-333, and ABT-072.

18. The composition of claim 1, wherein said composition comprises at least two pharmaceutically acceptable surfactants, one having an HLB value of at least 10 and the other having an HLB value of below 10.

19. The composition of claim 6, wherein said composition comprises at least two pharmaceutically acceptable surfactants, one having an HLB value of at least 10 and the other having an HLB value of below 10.

20. The composition of claim 11, wherein said composition comprises at least two pharmaceutically acceptable surfactants, one having an HLB value of at least 10 and the other having an HLB value of below 10.

21. The composition of claim 12, wherein said composition comprises at least two pharmaceutically acceptable surfactants, one having an HLB value of at least 10 and the other having an HLB value of below 10.