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

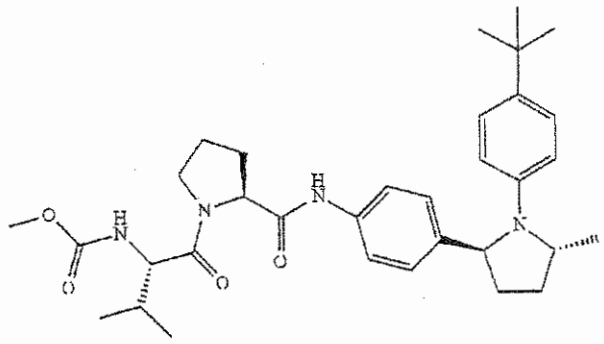
The hepatitis C virus (HCV) is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately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

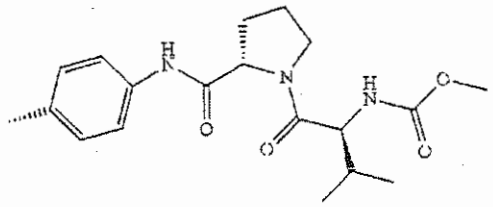
SUMMARY ~~OF THE INVENTION~~

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



(



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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~~invention~~ 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-

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~~invention~~ 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~~invention~~, 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~~invention~~, 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~~invention~~, 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~~invention~~ 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~~invention~~ 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~~invention~~ 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~~invention~~ 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~~invention~~ 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~~invention~~ 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~~invention~~ further features methods of using a solid composition of the present disclosure~~invention~~ to treat HCV infection. The methods comprise administering a solid composition of the present disclosure~~invention~~ 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~~invention~~ are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating preferred embodiments of the disclosure~~invention~~, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the disclosure~~invention~~ 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