SOLID PHARMACEUTICAL COMPOSITIONS FOR TREATING HCV

FIELD OF THE INVENTION

[0001] The present invention relates to solid pharmaceutical compositions comprising anti-HCV compounds and methods of using the same for treating HCV infection.

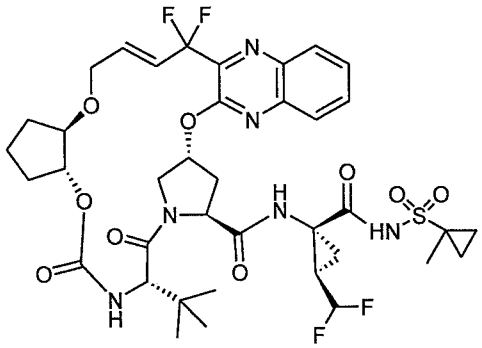
BACKGROUND OF THE INVENTION

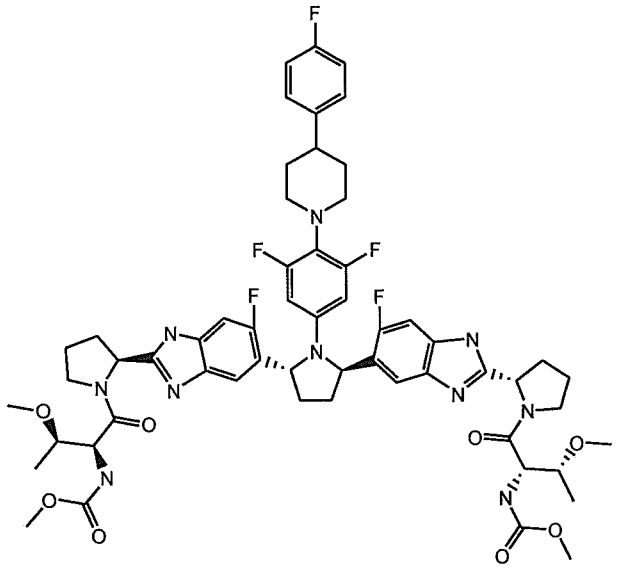
[0002] The hepatitis C virus (HCV) is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises 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.

[0003] Chronic 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 incomplete. Therefore, there is a need for new drugs to treat HCV infection.

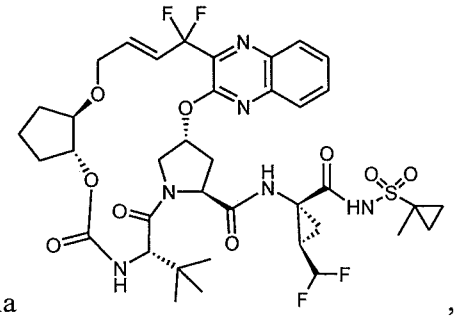
SUMMARY

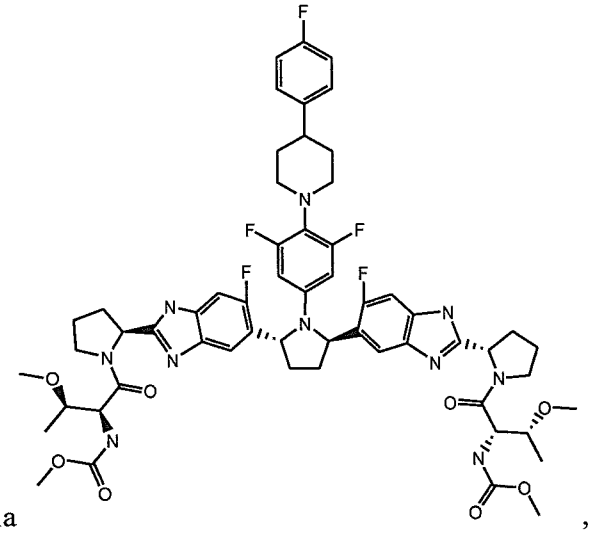
[0003a] In one aspect, there is provided a solid pharmaceutical composition comprising:

(1) 100 mg Compound 1 having the formula , formulated in amorphous solid dispersion which further comprises from 50% to 80% by weight of a first pharmaceutically acceptable hydrophilic polymer and from 5% to 15% by weight of a first pharmaceutically acceptable surfactant; and

(2) 40 mg Compound 2 having the formula  , formulated in amorphous solid dispersion which further comprises from 50% to 90% by weight of a second pharmaceutically acceptable hydrophilic polymer and from 5% to 15% by weight of a second pharmaceutically acceptable surfactant, wherein Compound 1 and Compound 2 are separately formulated in different amorphous solid dispersions, with the proviso that the solid pharmaceutical composition is not a solid pharmaceutical composition comprising: (1) 100 mg Compound 1 formulated in amorphous solid dispersion which further comprises from 50% to 80% by weight of a first pharmaceutically acceptable polymer and from 5% to 15% by weight of a first pharmaceutically acceptable surfactant; and (2) 40 mg Compound 2 formulated in amorphous solid dispersion which further comprises from 50% to 80% by weight of a second pharmaceutically acceptable polymer and from 5% to 15% by weight of a second pharmaceutically acceptable surfactant.

[0003b] In another aspect, there is provided a solid pharmaceutical composition comprising:

(1) 100 mg Compound 1 having the formula  , formulated in amorphous solid dispersion which further comprises from 50% to 80% by weight of a first pharmaceutically acceptable hydrophilic polymer and from 5% to 15% by weight of a first pharmaceutically acceptable surfactant; and

(2) 40 mg Compound 2 having the formula  ,

formulated in amorphous solid dispersion which further comprises from 50% to 90% by weight of a second pharmaceutically acceptable hydrophilic polymer and from 5% to 15% by weight of a second pharmaceutically acceptable surfactant,

wherein Compound 1 and Compound 2 are separately formulated in different amorphous solid dispersions,

wherein the composition has the following *in vitro* release profile:

(a) when the composition is dissolved in 1000 mL of a dissolution medium using a standard USP dissolution Apparatus 2 (paddle) with Japanese sinker operating at 75 RPM at 37 °C, 75-100% of Compound 1 in the composition is released within 105 minutes and 80-100% of Compound 2 in the composition is released within 105 minutes, wherein the dissolution medium is 0.1 M Acetate buffer (pH 4.0) with 1% Polysorbate 80;

(b) when the composition is dissolved in 1000 mL of a dissolution medium using a standard USP dissolution Apparatus 2 (paddle) with Japanese sinker operating at 75 RPM at 37 °C, 30-60% of Compound 1 in the composition is released within 50 minutes and 45-80% of Compound 2 in the composition is released within 50 minutes, wherein the dissolution medium is 0.1 M Acetate buffer (pH 4.0) with 1% Polysorbate 80; and/or

(c) when the composition is dissolved in 1000 mL of a dissolution medium using a standard USP dissolution Apparatus 2 (paddle) with Japanese sinker operating at 75 RPM at 37 °C, 5-30% of Compound 1 in the composition is released within 25 minutes and 10-40% of Compound 2 in the composition is released within 25 minutes, wherein the dissolution medium is 0.1 M Acetate buffer (pH 4.0) with 1% Polysorbate 80.

[0003c] In another aspect, there is provided a process for preparing a solid pharmaceutical composition as described herein, wherein each said amorphous solid dispersion is prepared by a method selected from melt-extrusion and spray-drying.

[0003d] In another aspect, there is provided a process for preparing a solid pharmaceutical composition as described herein, the process comprising: i) preparing a melt comprising said Compound 1, said pharmaceutically acceptable hydrophilic polymer, and said pharmaceutically acceptable surfactant, and solidifying said melt; and ii) preparing a melt comprising said Compound 2, said pharmaceutically acceptable hydrophilic polymer, and said pharmaceutically acceptable surfactant, and solidifying said melt, the process optionally further comprising the steps of milling the solidified melt, followed by compressing the milled product with one or more other excipients or ingredients to form a tablet, a minitablet, or a layer in a tablet.

[0003e] In another aspect, there is provided a solid pharmaceutical composition obtainable by a process as described herein.

[0003f] In another aspect, there is provided a solid pharmaceutical composition described herein, for use in the treatment of HCV infection.

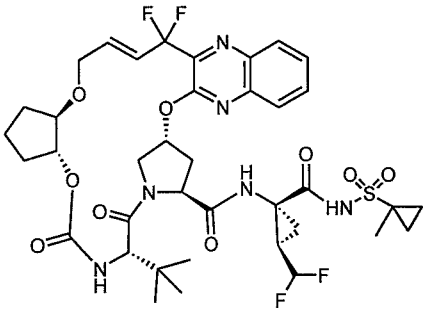
[0003g] In another aspect, there is provided a solid pharmaceutical composition described herein, for use in the treatment of HCV infection in a patient, wherein the solid pharmaceutical composition is to be administered to the patient with food.

[0003h] In another aspect, there is provided use of a solid pharmaceutical composition described herein in the manufacture of a medicament for the treatment of HCV infection.

[0003i] In another aspect, there is provided use of a solid pharmaceutical composition described herein in the manufacture of a medicament for the treatment of HCV infection in a patient, wherein the medicament is to be administered to the patient with food.

DETAILED DESCRIPTION

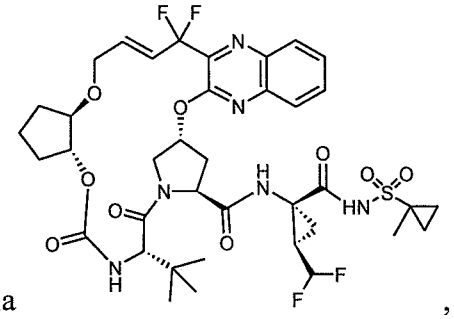
[0004] The present invention features solid pharmaceutical compositions useful for treating HCV. These solid pharmaceutical compositions comprise:

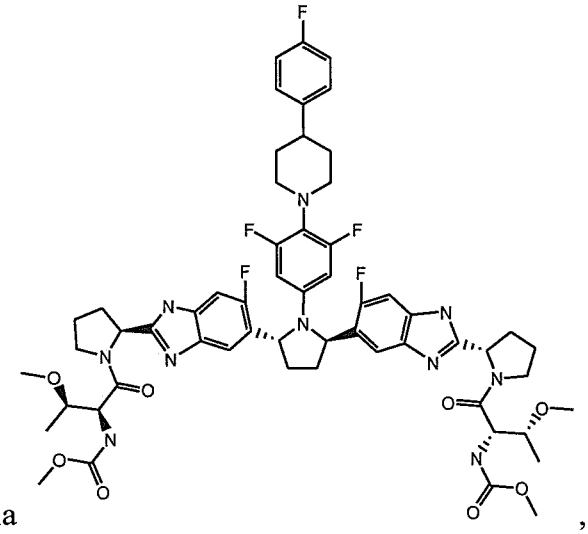


(1) (Compound 1) or a pharmaceutically acceptable salt thereof, formulated in amorphous solid dispersion, and

CLAIMS

1. A solid pharmaceutical composition comprising:

(1) 100 mg Compound 1 having the formula , formulated in amorphous solid dispersion which further comprises from 50% to 80% by weight of a first pharmaceutically acceptable hydrophilic polymer and from 5% to 15% by weight of a first pharmaceutically acceptable surfactant; and

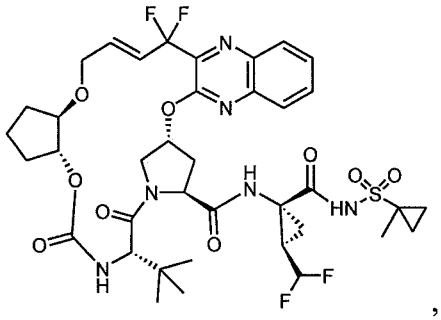
(2) 40 mg Compound 2 having the formula , formulated in amorphous solid dispersion which further comprises from 50% to 90% by weight of a second pharmaceutically acceptable hydrophilic polymer and from 5% to 15% by weight of a second pharmaceutically acceptable surfactant,

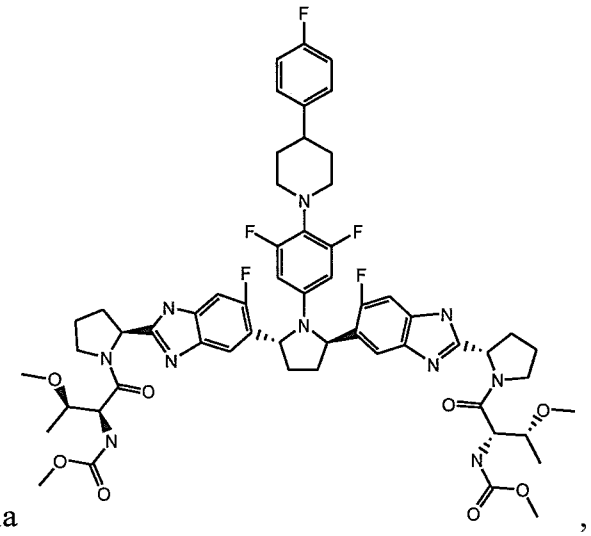
wherein Compound 1 and Compound 2 are separately formulated in different amorphous solid dispersions,

with the proviso that the solid pharmaceutical composition is not a solid pharmaceutical composition comprising: (1) 100 mg Compound 1 formulated in amorphous solid dispersion which further comprises from 50% to 80% by weight of a first pharmaceutically acceptable polymer and from 5% to 15% by weight of a first pharmaceutically acceptable surfactant; and (2)

40 mg Compound 2 formulated in amorphous solid dispersion which further comprises from 50% to 80% by weight of a second pharmaceutically acceptable polymer and from 5% to 15% by weight of a second pharmaceutically acceptable surfactant.

2. A solid pharmaceutical composition comprising:

(1) 100 mg Compound 1 having the formula , formulated in amorphous solid dispersion which further comprises from 50% to 80% by weight of a first pharmaceutically acceptable hydrophilic polymer and from 5% to 15% by weight of a first pharmaceutically acceptable surfactant; and

(2) 40 mg Compound 2 having the formula , formulated in amorphous solid dispersion which further comprises from 50% to 90% by weight of a second pharmaceutically acceptable hydrophilic polymer and from 5% to 15% by weight of a second pharmaceutically acceptable surfactant,

wherein Compound 1 and Compound 2 are separately formulated in different amorphous solid dispersions,

wherein the composition has the following *in vitro* release profile:

(a) when the composition is dissolved in 1000 mL of a dissolution medium using a standard USP dissolution Apparatus 2 (paddle) with Japanese sinker operating at 75 RPM at 37 °C, 75-100% of Compound 1 in the composition is released within 105 minutes and 80-100% of Compound 2 in the composition is released within 105 minutes, wherein the dissolution medium is 0.1 M Acetate buffer (pH 4.0) with 1% Polysorbate 80;

(b) when the composition is dissolved in 1000 mL of a dissolution medium using a standard USP dissolution Apparatus 2 (paddle) with Japanese sinker operating at 75 RPM at 37 °C, 30-60% of Compound 1 in the composition is released within 50 minutes and 45-80% of Compound 2 in the composition is released within 50 minutes, wherein the dissolution medium is 0.1 M Acetate buffer (pH 4.0) with 1% Polysorbate 80; and/or

(c) when the composition is dissolved in 1000 mL of a dissolution medium using a standard USP dissolution Apparatus 2 (paddle) with Japanese sinker operating at 75 RPM at 37 °C, 5-30% of Compound 1 in the composition is released within 25 minutes and 10-40% of Compound 2 in the composition is released within 25 minutes, wherein the dissolution medium is 0.1 M Acetate buffer (pH 4.0) with 1% Polysorbate 80.

3. The solid pharmaceutical composition of claim 1 or claim 2, wherein the amorphous solid dispersion in which Compound 1 is formulated comprises 10% to 40% (optionally 15% to 30%, or 20%) by weight of Compound 1, and the amorphous solid dispersion in which Compound 2 is formulated comprises 5% to 20% (optionally 5% to 15%, or 10%) by weight of Compound 2.

4. The solid pharmaceutical composition of any one of claims 1-3, wherein the composition is a tablet which comprises: (1) a first layer comprising a first amorphous solid dispersion, wherein the first amorphous solid dispersion comprises Compound 1, a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant; and (2) second layer comprising a second amorphous solid dispersion, wherein the second amorphous solid dispersion comprises Compound 2, a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant.

5. The solid pharmaceutical composition according to any one of claims 1, where the composition is a tablet comprising (1) a first layer including said 100 mg Compound 1 and (2) a second layer including said 40 mg Compound 2.

6. The solid pharmaceutical composition according to any one of claims 1-5, wherein said first and second polymers are copovidone.

7. The solid pharmaceutical composition according to any one of claims 1-5, wherein said first and second polymers are copovidone, and said first and second surfactants are or include Vitamin E TPGS;

or wherein said first and second polymers are copovidone, and said first surfactant is or includes Vitamin E TPGS, and said second surfactant is or includes a combination of Vitamin E TPGS and propylene glycol monocaprylate.

8. A process for preparing a solid pharmaceutical composition as claimed in any one of claims 1-7, wherein each said amorphous solid dispersion is prepared by a method selected from melt-extrusion and spray-drying.

9. A process for preparing a solid pharmaceutical composition as claimed in any one of claims 1-7, the process comprising:

i) preparing a melt comprising said Compound 1, said pharmaceutically acceptable hydrophilic polymer, and said pharmaceutically acceptable surfactant, and solidifying said melt; and

ii) preparing a melt comprising said Compound 2, said pharmaceutically acceptable hydrophilic polymer, and said pharmaceutically acceptable surfactant, and solidifying said melt,

the process optionally further comprising the steps of milling the solidified melt, followed by compressing the milled product with one or more other excipients or ingredients to form a tablet, a minitablet, or a layer in a tablet.

10. The process of claim 8 or claim 9, wherein Compound 1 and Compound 2 are comprised in separate layers in a tablet, and wherein Compound 1 is melt-extruded at a temperature of from 155 to 180 °C, and Compound 2 is melt-extruded at a temperature of from 150 to 195 °C.

11. The process of any one of claims 8-10, wherein Compound 1 and Compound 2 are comprised in separate layers in a tablet, and wherein, before melt-extrusion, Compound 2 is milled to particles with a median particle size (D50) of no more than 15 μm (optionally no more than 10 μm, or no more than 9 μm).

12. The process of any one of claims 8-11, wherein Compound 1 and Compound 2 are comprised in separate layers in a tablet, and wherein, before melt-extrusion, Compound 2 is milled to particles with a D90 of no more than 80 μm (optionally no more than 60 μm).

13. The process of any one of claims 8-12, wherein the solid dispersions are milled and/or mixed with other excipients, to form a solid pharmaceutical composition that contains both Compound 1 and Compound 2.

14. The process of any one of claims 8-12, wherein the solid dispersion comprising Compound 1 is milled and/or mixed with other excipients, and then compressed into a first layer of a tablet; and the solid dispersion comprising Compound 2 is likewise milled and/or mixed with other excipients, and compressed into a second layer of the same tablet.

15. A solid pharmaceutical composition obtainable by a process as claimed in any one of claims 8-14.

16. A solid pharmaceutical composition according to any one of claims 1-7 and 15, for use in the treatment of HCV infection.

17. A solid pharmaceutical composition according to any one of claims 1-7 and 15, for use in the treatment of HCV infection in a patient, wherein the solid pharmaceutical composition is to be administered to the patient with food.

18. Use of a solid pharmaceutical composition according to any one of claims 1-7 and 15 in the manufacture of a medicament for the treatment of HCV infection.

19. Use of a solid pharmaceutical composition according to any one of claims 1-7 and 15 in the manufacture of a medicament for the treatment of HCV infection in a patient, wherein the medicament is to be administered to the patient with food.