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

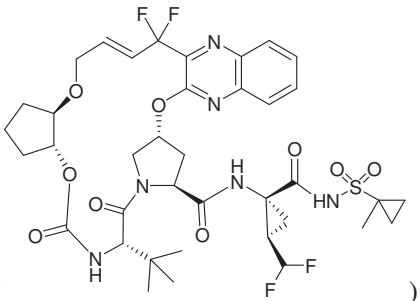
[0002] The hepatitis C virus (HCV) is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises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

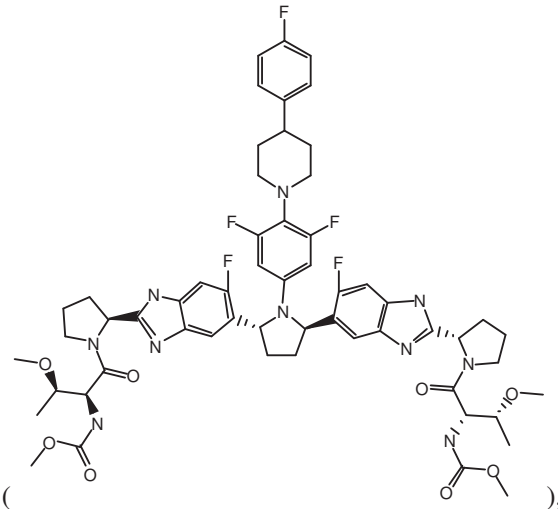
[0003] Chronic HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often incomplete. Also, although there are commercially available therapies for adults and pediatric populations aged 12-18, few options are available for pediatric populations aged 3-11. Therefore, there is a need for new drugs to treat HCV infection for these pediatric subpopulations.

SUMMARY OF THE DISCLOSURE

[0004] The present disclosure features solid pharmaceutical compositions comprising Compound 1 and Compound 2. In one example, the solid pharmaceutical composition includes (1) a first type of film-coated granules which comprise 50 mg of Compound 1, as well as a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant, all of which are formulated in amorphous solid dispersion; and (2) a second type of film-coated granules which comprise 20 mg of Compound 2, as well as a pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant, all of which are formulated in amorphous solid dispersion.

[0004a] In one aspect, provided herein is a use of a film-coated granule composition comprising

50 mg of Compound 1 () and

20 mg of Compound 2 (), in the manufacture of a medicament for treating hepatitis C virus (HCV) infection in a pediatric patient,

wherein the film-coated granule composition is provided in a sachet, and

wherein

(i) the patient is from 3 years old to less than 6 years old and three sachets are to be administered, comprising a total of about 150 mg of Compound 1, and about 60 mg of Compound 2, and the patient obtains a sustained virologic response about 12 weeks post treatment (SVR12);

(ii) the patient is from 6 years old to less than 9 years old and four sachets are to be administered, comprising a total of about 200 mg of Compound 1, and about 80 mg of Compound 2, and the patient obtains a sustained virologic response about 12 weeks post treatment (SVR12); or

[0005] (iii) the patient is from 9 years old to less than 12 years old and five sachets are to be administered, comprising a total of about 250 mg of Compound 1, and about 100 mg of Compound 2, and the patient obtains a sustained virologic response about 12 weeks post treatment (SVR12).In one example, the present disclosure provides a method for treating hepatitis C virus (HCV) infection in a pediatric patient, comprising administering (1) Compound 1 and (2) Compound 2, wherein (i) the patient is from 3 years old to less than 6 years old, Compound 1 is administered at a dose of about 150 mg, and Compound 2 is administered at a dose of about 60 mg; (ii) the patient is from 6 years old to less than 9 years old, Compound 1 is administered at a dose of about 200 mg, and Compound 2 is

administered at a dose of about 80 mg; or (iii) the patient is from 9 years old to less than 12 years old, Compound 1 is administered at a dose of about 250 mg, and Compound 2 is administered at a dose of about 100 mg.

[0006] In one example, the present disclosure provides a method for treating hepatitis C virus (HCV) infection in a pediatric patient, comprising administering a film-coated granule composition comprising 50 mg of Compound 1 and 20 mg of Compound 2, wherein the film-coated granule composition is provided in a sachet, and wherein the patient is from 3 years old to less than 6 years old and three sachets are administered, comprising a total of about 150 mg of Compound 1, and about 60 mg of Compound 2, and the patient obtains a sustained virologic response about 12 weeks post treatment (SVR12).

[0007] In one example, the present disclosure provides a method for treating hepatitis C virus (HCV) infection in a pediatric patient, comprising administering a film-coated granule composition comprising 50 mg of Compound 1 and 20 mg of Compound 2, wherein the film-coated granule composition is provided in a sachet, and wherein the patient is from 6 years old to less than 9 years old and four sachets are administered, comprising a total of about 200 mg of Compound 1, and about 80 mg of Compound 2, and the patient obtains a sustained virologic response about 12 weeks post treatment (SVR12).

[0008] In one example, the present disclosure provides a method for treating hepatitis C virus (HCV) infection in a pediatric patient, comprising administering a film-coated granule composition comprising 50 mg of Compound 1 and 20 mg of Compound 2, wherein the film-coated granule composition is provided in a sachet, and wherein the patient is from 9 years old to less than 12 years old and five sachets are administered, comprising a total of about 250 mg of Compound 1, and about 100 mg of Compound 2, and the patient obtains a sustained virologic response about 12 weeks post treatment (SVR12).

[0009] In another example, the patient is from 3 years old to less than 6 years old, Compound 1 is administered at a dose of about 150 mg, and Compound 2 is administered at a dose of about 60 mg.

[0010] In yet another example, the patient is from 6 years old to less than 9 years old, Compound 1 is administered at a dose of about 200 mg, and Compound 2 is administered at a dose of about 80 mg.

[0011] In another example, the patient is from 9 years old to less than 12 years old, Compound 1 is administered at a dose of about 250 mg, and Compound 2 is administered at a dose of about 100 mg.

[0012] In one example, Compound 1 is administered from a first type of film-coated granule comprising an amorphous solid dispersion including (i) Compound 1, (ii) copovidone and (iii) Vitamin E TPGS. Further, the total amount of Compound 1 comprised in the first type of granules is 50 mg.

[0013] In another example, Compound 2 is administered from a second type of film-coated granules comprising an amorphous solid dispersion including (i) Compound 2, (ii) copovidone and (iii) Vitamin E TPGS and propylene glycol monocaprylate. Further, the total amount of Compound 2 comprised in the second type of granules is 20 mg.

[0014] One example, provides a solid pharmaceutical composition comprising: (1) 50 mg of 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) 20 mg of Compound 2 formulated in amorphous solid dispersion which further comprises from 50% to 90% by weight of a second pharmaceutically acceptable polymer and from 5% to 15% by weight of a second pharmaceutically acceptable surfactant. Further, in one example, the composition is a mixture of (1) a first type of film-coated granules including said 50 mg of Compound 1 and (2) a second type of film-coated granules including said 20 mg of Compound 2. Furthermore, in one example, the amorphous solid dispersion in which Compound 1 is formulated comprises 20% by weight of Compound 1, and the amorphous solid dispersion in which Compound 2 is formulated comprises 10% by weight of Compound 2. In one example, the composition is a mixture of (1) a first type of film-coated granules including said 50 mg of Compound 1 and (2) a second type of film-coated granules including said 20 mg of Compound 2. Further said first and second polymers are copovidone, and said first and second surfactants are Vitamin E TPGS. In one example, said first and second polymers are copovidone, and said first surfactant is Vitamin E TPGS, and said second surfactant is a combination of Vitamin E TPGS and propylene glycol monocaprylate.

[0015] In another aspect, provided herein is a stable, oral, immediate release solid pharmaceutical composition comprising: (1) 50 mg of Compound 1 formulated in an 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) 20 mg of Compound 2 formulated in an amorphous solid dispersion which further comprises from 50% to 90% by weight of a second pharmaceutically acceptable polymer and from 5% to 15% by weight of a second pharmaceutically acceptable surfactant, wherein the composition is provided in a sachet and is stable for the duration of a shelf life of about 24 months in the sachet.

[0016] In one example, the composition is a mixture of (1) a first type of film-coated granule including the 50 mg of Compound 1 and (2) a second type of film-coated granule including the 20 mg of Compound 2.

[0017] In one example, the amorphous solid dispersion in which Compound 1 is formulated comprises 20% by weight of Compound 1, and the amorphous solid dispersion in which Compound 2 is formulated comprises 10% by weight of Compound 2.

[0018] In one example, the composition is a mixture of (1) a first type of film-coated granule including the 50 mg of Compound 1 and (2) a second type of film-coated granule including the 20 mg of Compound 2.

[0019] In one example, the first and second polymers are copovidone, and the first and second surfactants are Vitamin E TPGS.

[0020] In one example, the first and second polymers are copovidone, and the first surfactant is Vitamin E TPGS, and the second surfactant is a combination of Vitamin E TPGS and propylene glycol monocaprylate.

[0021] In one example, the composition has an in vitro release profile according to at least one of the following profiles: (i) 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 ºC, at least 80% of Compound 1 in the composition is released within 3 hours and at least 80% of Compound 2 in the composition is released within 3 hours, wherein the dissolution medium is 0.1 M Acetate buffer (pH 4.0) with 1% Polysorbate 80; (ii) 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 ºC, at least 30% of Compound 1 in the composition is released within 50 minutes and at least 45% 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; or (iii) 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 ºC, at least 5% of Compound 1 in the composition is released within 25 minutes and at least 10% 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.

[0022] In one example, the composition has an in vitro release profile according to at least one of the following profiles: (i) when the composition is dissolved in 500 mL of a dissolution medium using a standard USP dissolution Apparatus 1 (basket) operating at 75 RPM at 37 ºC, at least 80% of Compound 1 in the composition is released within 40 minutes and at least 80% of Compound 2 in the composition is released within 40 minutes, wherein the dissolution medium is 0.1 M Acetate buffer (pH 4.0) with 1% Polysorbate 80; (ii) when the composition is dissolved in 500 mL of a dissolution medium using a standard USP dissolution Apparatus 1 (basket) operating at 75 RPM at 37 ºC, at least 30% of Compound 1 in the composition is released within 20 minutes and at least 45% of Compound 2 in the composition is released within 20 minutes, wherein the dissolution medium is 0.1 M Acetate buffer (pH 4.0) with 1% Polysorbate 80; or (iii) when the composition is dissolved in 500 mL of a dissolution medium using a standard USP dissolution Apparatus 1 (basket) operating at 75 RPM at 37 ºC, at least 5% of Compound 1 in the composition is released within 10 minutes and at least 10% of Compound 2 in the composition is released within 10 minutes, wherein the dissolution medium is 0.1 M Acetate buffer (pH 4.0) with 1% Polysorbate 80.

[0023] In one example, a single dose of three sachets administered to a population of healthy, non-fasted patients from 3 years old to less than 6 years old results in a mean AUC value between about 6936 ng·h/mL and about 10838 ng·h/mL for Compound 1, and a mean AUC value between about 1840 ng·h/mL and about 2875 ng·h/mL for Compound 2.

[0024] In one example, a single dose of four sachets administered to a population of healthy, non-fasted patients from 6 years old to less than 9 years old results in a mean AUC value between about 4776 ng·h/mL and about 7463 ng·h/mL for Compound 1, and a mean AUC value between about 1216 ng·h/mL and about 1900 ng·h/mL for Compound 2.

[0025] In one example, a single dose of five sachets administered to a population of healthy, non-fasted patients from 9 years old to less than 12 years old results in a mean AUC value between about 5360 ng·h/mL and about 8375 ng·h/mL for Compound 1, and a mean AUC value between about 1328 ng·h/mL and about 2075 ng·h/mL for Compound 2.

[0026] In another aspect, provided herein is a pharmaceutical composition that is bioequivalent to the composition described herein.

[0027] Another example provides method for treating hepatitis C virus (HCV) infection, comprising administering the solid pharmaceutical composition described herein to a patient in need thereof, wherein the patient obtains a sustained virologic response about 12 weeks post treatment (SVR12).

[0027a] In another aspect, provided herein is a use of a pharmaceutical composition as described herein in the manufacture of a medicament for treating hepatitis C virus (HCV) infection, wherein the medicament is to be administered to a patient in need thereof, wherein the patient obtains a sustained virologic response about 12 weeks post treatment (SVR12).

[0028] Another example provides a dispensing container containing a solid pharmaceutical composition described above. Further, the dispensing container is a sachet.

[0029] One example provides a method for treating hepatitis C virus (HCV) infection, comprising administering a solid pharmaceutical composition as described above to a patient in need thereof.

[0030] Yet another example provides a solid pharmaceutical composition comprising: (1) 50 mg of 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; (2) 20 mg of Compound 2 formulated in amorphous solid dispersion which further comprises from 50% to 90% by weight of a second pharmaceutically acceptable polymer and from 5% to 15% by weight of a second pharmaceutically acceptable surfactant; and wherein the composition is provided in a dispensing container comprising a sachet. In another example, the composition provides a mixture of (1) a first type of film-coated granules including said 50 mg of Compound 1 and (2) a second type of film-coated granules including said 20 mg of Compound 2.

[0031] The above objectives of the present disclosure is not intended to be exhaustive or to limit the disclosure to the precise one disclosed. Modifications and variations are possible in light of the teachings or may be acquired from practice of the disclosure. Thus, it is noted that the scope of the disclosure is defined by the claims and their equivalents.

BRIEF DESCRIPTION OF THE DRAWINGS

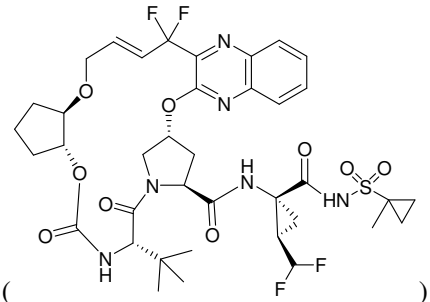
[0032] FIG 1 and FIG. 2 each depict an exemplary sachet for use as a dispensing container in accordance with the oral dosage forms (e.g., film-coated granules) described herein.

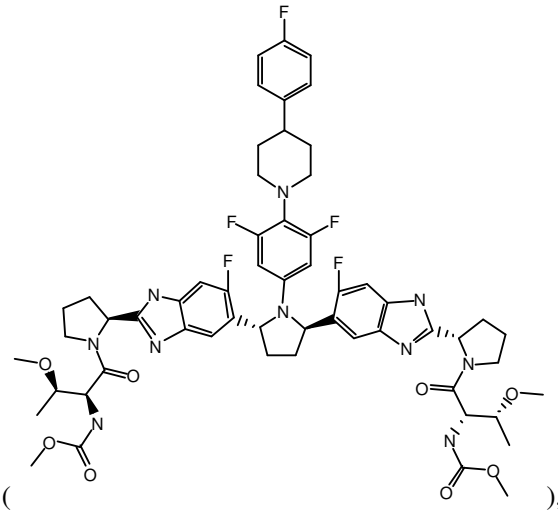
DETAILED DESCRIPTION

[0033] The present invention features solid pharmaceutical compositions useful for treating HCV. These solid pharmaceutical compositions comprise:

WHAT IS CLAIMED IS:

1. Use of a film-coated granule composition comprising

50 mg of Compound 1 () and



20 mg of Compound 2 ( ), in the manufacture of a medicament for treating hepatitis C virus (HCV) infection in a pediatric patient,

wherein the film-coated granule composition is provided in a sachet, and

wherein

(i) the patient is from 3 years old to less than 6 years old and three sachets are to be administered, comprising a total of about 150 mg of Compound 1, and about 60 mg of Compound 2, and the patient obtains a sustained virologic response about 12 weeks post treatment (SVR12);

(ii) the patient is from 6 years old to less than 9 years old and four sachets are to be administered, comprising a total of about 200 mg of Compound 1, and about 80 mg of Compound 2, and the patient obtains a sustained virologic response about 12 weeks post treatment (SVR12); or

(iii) the patient is from 9 years old to less than 12 years old and five sachets are to be administered, comprising a total of about 250 mg of Compound 1, and about 100 mg of Compound 2, and the patient obtains a sustained virologic response about 12 weeks post treatment (SVR12).

2. The use of claim 1, wherein the patient is from 3 years old to less than 6 years old, and the film-coated granule composition is to be administered in three sachets, comprising a total of about 150 mg of Compound 1, and about 60 mg of Compound 2.

3. The use of claim 1, wherein the patient is from 6 years old to less than 9 years old, and the film-coated granule composition is to be administered in four sachets, comprising a total of about 100 mg of Compound 1, and about 80 mg of Compound 2.

4. The use of claim 1, wherein the patient is from 9 years old to less than 12 years old, and the film-coated granule composition is to be administered in five sachets, comprising a total of about 250 mg of Compound 1, and about 100 mg of Compound 2.

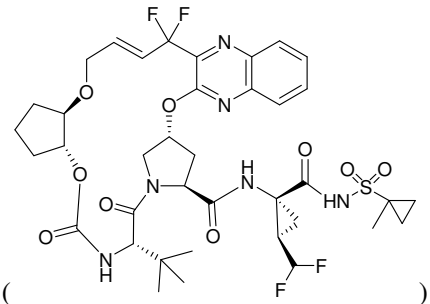
5. The use of claim 1, wherein Compound 1 is present in a first type of film-coated granule comprising an amorphous solid dispersion including (i) Compound 1, (ii) copovidone and (iii) Vitamin E TPGS.

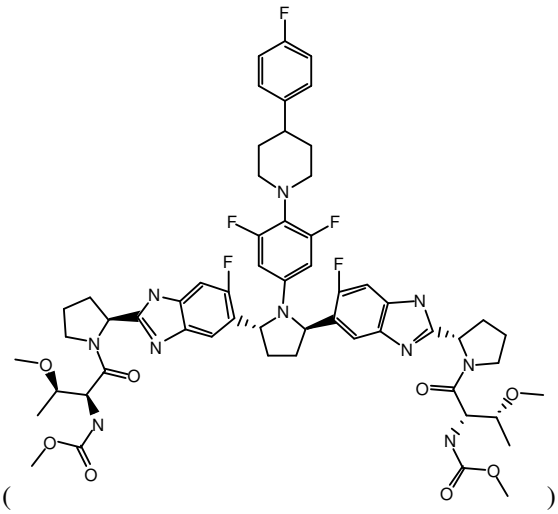
6. The use of claim 5, wherein the total amount of Compound 1 comprised in the first type of granule is 50 mg.

7. The use of claim 1, wherein Compound 2 is present in a second type of film-coated granule comprising an amorphous solid dispersion including (i) Compound 2, (ii) copovidone and (iii) Vitamin E TPGS and propylene glycol monocaprylate.

8. The use of claim 7, wherein the total amount of Compound 2 comprised in the second type of granule is 20 mg.

9. A stable, oral, immediate release solid pharmaceutical composition comprising:

(1) 50 mg of Compound 1 () formulated in an 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) 20 mg of Compound 2 () formulated in an amorphous solid dispersion which further comprises from 50% to 90% by weight of a second pharmaceutically acceptable polymer and from 5% to 15% by weight of a second pharmaceutically acceptable surfactant,

wherein the composition is provided in a sachet and is stable for the duration of a shelf life of about 24 months in the sachet.

10. The solid pharmaceutical composition of claim 9, where the composition is a mixture of (1) a first type of film-coated granule including the 50 mg of Compound 1 and (2) a second type of film-coated granule including the 20 mg of Compound 2.

11. The solid pharmaceutical composition of claim 9, wherein the amorphous solid dispersion in which Compound 1 is formulated comprises 20% by weight of Compound 1, and the amorphous solid dispersion in which Compound 2 is formulated comprises 10% by weight of Compound 2.

12. The solid pharmaceutical composition of claim 11, where the composition is a mixture of (1) a first type of film-coated granule including the 50 mg of Compound 1 and (2) a second type of film-coated granule including the 20 mg of Compound 2.

13. The solid pharmaceutical of claim 12, wherein the first and second polymers are copovidone, and the first and second surfactants are Vitamin E TPGS.

14. The solid pharmaceutical composition of claim 12, wherein the first and second polymers are copovidone, and the first surfactant is Vitamin E TPGS, and the second surfactant is a combination of Vitamin E TPGS and propylene glycol monocaprylate.

15. The solid pharmaceutical composition of any one of claims 9-14, wherein the composition has an in vitro release profile according to at least one of the following profiles:

(i) when the composition is dissolved in 500 mL of a dissolution medium using a standard USP dissolution Apparatus 1 (basket) operating at 75 RPM at 37 ºC, at least 80% of

Compound 1 in the composition is released within 40 minutes and at least 80% of Compound 2 in the composition is released within 40 minutes, wherein the dissolution medium is 0.1 M Acetate buffer (pH 4.0) with 1% Polysorbate 80;

(ii) when the composition is dissolved in 500 mL of a dissolution medium using a standard USP dissolution Apparatus 1 (basket) operating at 75 RPM at 37 ºC, at least 30% of Compound 1 in the composition is released within 20 minutes and at least 45% of Compound 2 in the composition is released within 20 minutes, wherein the dissolution medium is 0.1 M Acetate buffer (pH 4.0) with 1% Polysorbate 80; or

(iii) when the composition is dissolved in 500 mL of a dissolution medium using a standard USP dissolution Apparatus 1 (basket) operating at 75 RPM at 37 ºC, at least 5% of Compound 1 in the composition is released within 10 minutes and at least 10% of Compound 2 in the composition is released within 10 minutes, wherein the dissolution medium is 0.1 M Acetate buffer (pH 4.0) with 1% Polysorbate 80.

16. The solid pharmaceutical composition of any one of claims 9-15, wherein a single dose of three sachets administered to a population of healthy, non-fasted patients from 3 years old to less than 6 years old results in a mean AUC value between about 6936 ng·h/mL and about 10838 ng·h/mL for Compound 1, and a mean AUC value between about 1840 ng·h/mL and about 2875 ng·h/mL for Compound 2.

17. The solid pharmaceutical composition of any one of claims 9-15, wherein a single dose of four sachets administered to a population of healthy, non-fasted patients from 6 years old to less than 9 years old results in a mean AUC value between about 4776 ng·h/mL and about 7463 ng·h/mL for Compound 1, and a mean AUC value between about 1216 ng·h/mL and about 1900 ng·h/mL for Compound 2.

18. The solid pharmaceutical composition of any one of claims 9-15, wherein a single dose of five sachets administered to a population of healthy, non-fasted patients from 9 years old to less than 12 years old results in a mean AUC value between about 5360 ng·h/mL and about 8375 ng·h/mL for Compound 1, and a mean AUC value between about 1328 ng·h/mL and about 2075 ng·h/mL for Compound 2.

19. A pharmaceutical composition that is bioequivalent to the composition of any one of claims 9-18.

20. Use of a pharmaceutical composition of any one of claims 9-19 in the manufacture of a medicament for treating hepatitis C virus (HCV) infection, wherein the medicament is to be administered to a patient in need thereof, wherein the patient obtains a sustained virologic response about 12 weeks post treatment (SVR12).