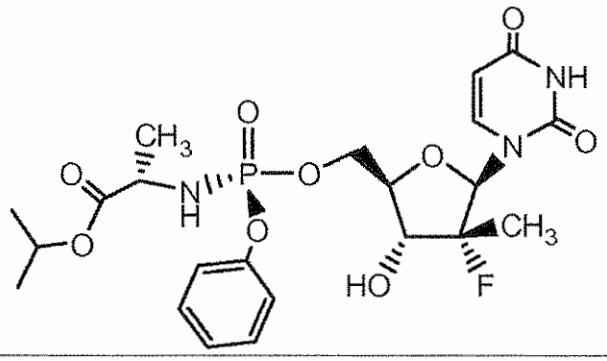
acceptable excipient, as well as methods for making said composition and unit dosage form.

In one aspect, there is provided a pharmaceutical composition comprising:

a) about 25% to about 35% w/w of crystalline GS-7977 having the structure



; and

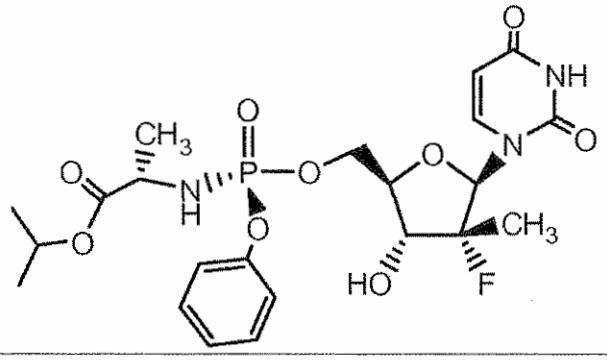
b) at least one pharmaceutically acceptable excipient,

wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about:

6.1 and 12.7.

In one aspect, there is provided a unit dosage form comprising:

a) about 400 mg of crystalline GS-7977 having the structure



; and

b) at least one pharmaceutically acceptable excipient,

wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about

6.1 and 12.7.

In one aspect, there is provided a process for preparing a tablet composition comprising the unit dosage form as described herein comprising:

blending an intragranular composition and an extragranular composition to obtain a blended composition;

compressing the blended composition to obtain the tablet composition; and

optionally coating the tablet composition;

wherein

the intragranular composition comprises GS-7977, a first intragranular diluent, optionally a second intragranular diluent, an intragranular disintegrant, an intragranular glidant, and an intragranular lubricant; and

the extragranular composition comprises a first extragranular diluent, optionally a second extragranular diluent, an extragranular glidant, an extragranular disintegrant, and an extragranular lubricant.

In one aspect, there is provided a tablet composition comprising about 400 mg of GS-7977 made according to the process as described herein.

Also disclosed herein is a method of treating a subject, preferably a human, infected with hepatitis C virus, said method comprising administering to the subject for a time period an effective amount of GS-7977 and an effective amount of ribavirin. In one ~~aspect~~embodiment, the method comprises administering to the subject an interferon-free treatment regimen comprising an effective amount of GS-7977 and an effective amount of ribavirin. In a particular ~~aspect~~embodiment, the method is sufficient to produce an undetectable amount of HCV RNA in the subject for at least 12 weeks after the end of the time period.

Brief Description of the Drawings

Figure 1. Plot of Mean HCV RNA (log_{10} IU/mL) versus time during treatment and for up to 12 weeks after the end of treatment ("EOT") for HCV GT2/GT3 treatment-naïve patients receiving a combination of GS-7977 (400 mg QD) and RBV (1000/1200 mg BID based on weight) for 12 weeks (ELECTRON Group 1).

Figure 2. Fold-change in EC_{50} for HCV replicons containing 1b, 1a, 2a, 2b, 3a, 4a, and 5a NS5B harboring the S282T mutation (compared to the corresponding wild-type) treated with GS-7977 or ribavirin.

Figure 3. Percentage of wild-type at S282 position in HCV replicons before and after treatment with GS-7977, ribavirin, and a combination of GS-7977 and ribavirin in long-term passaging study (15-30 days).

Detailed Description

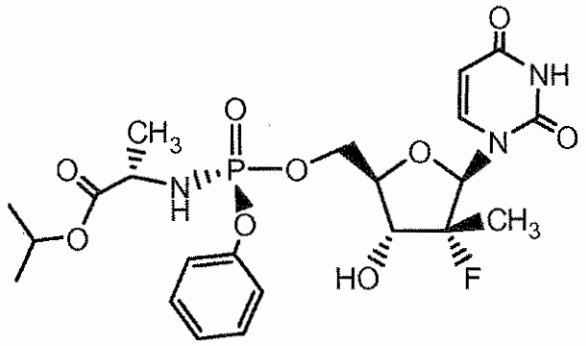
Definitions

The phrase "a" or "an" entity as used herein refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound. As

What is claimed is:

1. A pharmaceutical composition comprising:

a) about 25% to about 35% w/w of crystalline GS-7977 having the structure



; and

b) at least one pharmaceutically acceptable excipient,

wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about:

6.1 and 12.7.

2. The composition according to claim 1, wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about:

6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3.

3. The composition according to claim 1, wherein the at least one pharmaceutically acceptable excipient comprises at least one of a diluent, a disintegrant, a glidant, and a lubricant.

4. The composition according to claim 3, wherein the at least one pharmaceutically acceptable excipient comprises a diluent selected from the group consisting of dicalcium phosphate, cellulose, compressible sugars, dibasic calcium phosphate dehydrate, lactose, mannitol, microcrystalline cellulose, starch, tribasic calcium phosphate, and combinations thereof.

5. The composition according to claim 4, wherein the diluent is selected from the group consisting of mannitol, microcrystalline cellulose, and combinations thereof.

6. The composition according to claim 3, wherein the at least one pharmaceutically acceptable excipient comprises a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, microcrystalline cellulose, modified corn starch, povidone, pregelatinized starch, sodium starch glycolate, and combinations thereof.

7. The composition according to claim 6, wherein the disintegrant is croscarmellose sodium.

8. The composition according to claim 3, wherein the at least one pharmaceutically acceptable excipient comprises a glidant selected from the group consisting of colloidal silicon dioxide, talc, starch, starch derivatives, and combinations thereof.

9. The composition according to claim 8, wherein the glidant is colloidal silicon dioxide.

10. The composition according to claim 3, wherein the at least one pharmaceutically acceptable excipient comprises a lubricant selected from the group consisting of calcium stearate, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and combinations thereof.

11. The composition according to claim 10, wherein the lubricant is magnesium stearate.

12. The composition according to claim 1 further comprising a coating agent.

13. The composition according to claim 1, wherein the at least one pharmaceutically acceptable excipient comprises:

a) about 55% w/w to about 65% w/w of a diluent;

b) about 2.5 % w/w to about 7.5% w/w of a disintegrant;

c) about 0.25% w/w to about 0.75% w/w of a glidant; and

d) about 1.25% w/w to about 1.75% w/w of a lubricant.

14. The composition according to claim 1, wherein the at least one pharmaceutically acceptable excipient comprises:

a) about 30% w/w of mannitol and about 30% w/w of microcrystalline cellulose;

b) about 5% w/w of croscarmellose sodium;

c) about 0.5% w/w of colloidal silicon dioxide; and

d) about 1.5% w/w of magnesium stearate.

15. The composition according to claim 1, wherein the composition comprises:

a) about 33% w/w of crystalline GS-7977;

b) about 30% w/w of mannitol and about 30% w/w of microcrystalline cellulose;

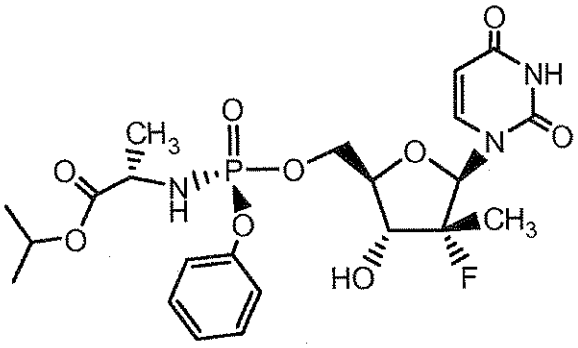
c) about 5% w/w of croscarmellose sodium;

d) about 0.5% w/w of colloidal silicon dioxide; and

e) about 1.5% w/w of magnesium stearate.

16. A unit dosage form comprising:

a) about 400 mg of crystalline GS-7977 having the structure



; and

b) at least one pharmaceutically acceptable excipient,

wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about 6.1 and 12.7.

17. The unit dosage form according to claim 16, wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about:

6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3.

18. The unit dosage form according to claim 16, wherein the at least one pharmaceutically acceptable excipient comprises at least one of a diluent, a disintegrant, a glidant, and a lubricant.

19. The unit dosage form according to claim 18, wherein the at least one pharmaceutically acceptable excipient comprises a diluent selected from the group consisting of dicalcium phosphate, cellulose, compressible sugars, dibasic calcium phosphate dehydrate, lactose, mannitol, microcrystalline cellulose, starch, tribasic calcium phosphate, and combinations thereof.

20. The unit dosage form according to claim 19, wherein the diluent is selected from the group consisting of mannitol, microcrystalline cellulose, and combinations thereof.

21. The unit dosage form according to claim 18, wherein the at least one pharmaceutically acceptable excipient comprises a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, microcrystalline cellulose, modified corn starch, povidone, pregelatinized starch, sodium starch glycolate, and combinations thereof.

22. The unit dosage form according to claim 21, wherein the disintegrant is croscarmellose sodium.

23. The unit dosage form according to claim 18, wherein the at least one pharmaceutically acceptable excipient comprises a glidant selected from the group consisting of colloidal silicon dioxide, talc, starch, starch derivatives, and combinations thereof.

24. The unit dosage form according to claim 23, wherein the glidant is colloidal silicon dioxide.

25. The unit dosage form according to claim 18, wherein the at least one pharmaceutically acceptable excipient comprises a lubricant selected from the group consisting

of calcium stearate, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and combinations thereof.

26. The unit dosage form according to claim 25, wherein the lubricant is magnesium stearate.

27. The unit dosage form according to claim 16 further comprising a coating agent.

28. The unit dosage form according to claim 16, wherein the at least one pharmaceutically acceptable excipient comprises:

a) about 660 mg to about 780 mg of a diluent;

b) about 30 mg to about 90 mg of a disintegrant;

c) about 3 mg to about 9 mg of a glidant; and

d) about 15 mg to about 21 mg of a lubricant.

29. The unit dosage form according to claim 16, wherein the unit dosage form comprises:

a) about 400 mg of crystalline GS-7977;

b) about 360 mg of mannitol and about 356 mg of microcrystalline cellulose;

c) about 60 mg of croscarmellose sodium;

d) about 6 mg of colloidal silicon dioxide; and

e) about 18 mg of magnesium stearate.

30. The unit dosage form according to claim 16, wherein the unit dosage form comprises a capsule or a tablet.

31. A process for preparing a tablet composition comprising the unit dosage form of claim 16 comprising:

blending an intragranular composition and an extragranular composition to obtain a blended composition;

compressing the blended composition to obtain the tablet composition; and

optionally coating the tablet composition;

wherein

the intragranular composition comprises GS-7977, a first intragranular diluent, optionally a second intragranular diluent, an intragranular disintegrant, an intragranular glidant, and an intragranular lubricant; and

the extragranular composition comprises a first extragranular diluent, optionally a second extragranular diluent, an extragranular glidant, an extragranular disintegrant, and an extragranular lubricant.

32. A tablet composition comprising about 400 mg of GS-7977 made according to the process of claim 31.

What is claimed is:

1. A pharmaceutical composition comprising:

a) about 25% to about 35% w/w of GS-7977; and

b) at least one pharmaceutically acceptable excipient.

2. The composition according to claim 1, wherein the composition comprises about 30% to about 35% w/w of GS-7977.

3. The composition according to claim 1, wherein the composition comprises about 30% w/w of GS-7977.

4. The composition according to claim 1, wherein the composition comprises about 33% w/w of GS-7977.

5. The composition according to claim 1, wherein the composition comprises crystalline GS-7977.

6. The composition according to claim 5, wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about:

(1) 5.2, 7.5, 9.6, 16.7, 18.3, and 22.2;

(2) 5.0, 7.3, 9.4, and 18.1;

(3) 4.9, 6.9, 9.8, 19.8, 20.6, 24.7, and 26.1;

(4) 6.9, 9.8, 19.7, 20.6, and 24.6;

(5) 5.0, 6.8, 19.9, 20.6, 20.9, and 24.9;

(6) 5.2, 6.6, 7.1, 15.7, 19.1, and 25.0; or

(7) 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3.

7. The composition according to claim 6, wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about:

(1) 5.0, 7.3, 9.4, and 18.1; or

(2) 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3.

8. The composition according to claim 5, wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about:

(1) 5.0 and 7.3; or

(2) 6.1 and 12.7.

9. The composition according to claim 1, wherein the at least one pharmaceutically acceptable excipient comprises at least one of a diluent, a disintegrant, a glidant, and a lubricant.

10. The composition according to claim 9, wherein the at least one pharmaceutically acceptable excipient comprises a diluent selected from the group consisting of dicalcium phosphate, cellulose, compressible sugars, dibasic calcium phosphate dehydrate, lactose, mannitol, microcrystalline cellulose, starch, tribasic calcium phosphate, and combinations thereof.

11. The composition according to claim 10, wherein the diluent is selected from the group consisting of mannitol, microcrystalline cellulose, and combinations thereof.

12. The composition according to claim 9, wherein the at least one pharmaceutically acceptable excipient comprises a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, microcrystalline cellulose, modified corn starch, povidone, pregelatinized starch, sodium starch glycolate, and combinations thereof.

13. The composition according to claim 12, wherein the disintegrant is croscarmellose sodium.

14. The composition according to claim 9, wherein the at least one pharmaceutically acceptable excipient comprises a glidant selected from the group consisting of colloidal silicon dioxide, talc, starch, starch derivatives, and combinations thereof.

15. The composition according to claim 14, wherein the glidant is colloidal silicon dioxide.

16. The composition according to claim 9, wherein the at least one pharmaceutically acceptable excipient comprises a lubricant selected from the group consisting of calcium stearate, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and combinations thereof.

17. The composition according to claim 16, wherein the lubricant is magnesium stearate.

18. The composition according to claim 1 further comprising a coating agent.

19. The composition according to claim 1, wherein the at least one pharmaceutically acceptable excipient comprises:

a) about 55% w/w to about 65% w/w of a diluent;

b) about 2.5 % w/w to about 7.5% w/w of a disintegrant;

c) about 0.25% w/w to about 0.75% w/w of a glidant; and

d) about 1.25% w/w to about 1.75% w/w of a lubricant.

20. The composition according to claim 1, wherein the at least one pharmaceutically acceptable excipient comprises:

a) about 30% w/w of mannitol and about 30% w/w of microcrystalline cellulose;

b) about 5 %w/w of croscarmellose sodium;

c) about 0.5% w/w of colloidal silicon dioxide; and

d) about 1.5% w/w of magnesium stearate.

21. The composition according to claim 1, wherein the composition comprises:

a) about 33% w/w of crystalline GS-7977;

b) about 30% w/w of mannitol and about 30% w/w of microcrystalline cellulose;

c) about 5 %w/w of croscarmellose sodium;

d) about 0.5% w/w of colloidal silicon dioxide; and

e) about 1.5% w/w of magnesium stearate.

22. The composition according to claim 21, wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about:

(1) 5.0, 7.3, 9.4, and 18.1; or

(2) 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3.

23. The composition according to claim 21, wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about:

(1) 5.0 and 7.3; or

(2) 6.1 and 12.7.

24. A unit dosage form comprising:

a) about 400 mg of GS-7977; and

b) at least one pharmaceutically acceptable excipient.

25. The unit dosage form according to claim 24 comprising crystalline GS-7977.

26. The unit dosage form according to claim 25, wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about:

(1) 5.2, 7.5, 9.6, 16.7, 18.3, and 22.2;

(2) 5.0, 7.3, 9.4, and 18.1;

(3) 4.9, 6.9, 9.8, 19.8, 20.6, 24.7, and 26.1;

(4) 6.9, 9.8, 19.7, 20.6, and 24.6;

(5) 5.0, 6.8, 19.9, 20.6, 20.9, and 24.9;

(6) 5.2, 6.6, 7.1, 15.7, 19.1, and 25.0; or

(7) 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3.

27. The unit dosage form according to claim 25, wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about:

(1) 5.0, 7.3, 9.4, and 18.1; or

(2) 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3.

28. The unit dosage form according to claim 25, wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about

(1) 5.0 and 7.3; or

(2) 6.1 and 12.7.

29. The unit dosage form according to claim 24, wherein the at least one pharmaceutically acceptable excipient comprises at least one of a diluent, a disintegrant, a glidant, and a lubricant.

30. The unit dosage form according to claim 29, wherein the at least one pharmaceutically acceptable excipient comprises a diluent selected from the group consisting of dicalcium phosphate, cellulose, compressible sugars, dibasic calcium phosphate dehydrate, lactose, mannitol, microcrystalline cellulose, starch, tribasic calcium phosphate, and combinations thereof.

31. The unit dosage form according to claim 30, wherein the diluent is selected from the group consisting of mannitol, microcrystalline cellulose, and combinations thereof.

32. The unit dosage form according to claim 29, wherein the at least one pharmaceutically acceptable excipient comprises a disintegrant selected from the group consisting of croscarmellose sodium, crospovidone, microcrystalline cellulose, modified corn starch, povidone, pregelatinized starch, sodium starch glycolate, and combinations thereof.

33. The unit dosage form according to claim 32, wherein the disintegrant is croscarmellose sodium.

34. The unit dosage form according to claim 29, wherein the at least one pharmaceutically acceptable excipient comprises a glidant selected from the group consisting of colloidal silicon dioxide, talc, starch, starch derivatives, and combinations thereof.

35. The unit dosage form according to claim 34, wherein the glidant is colloidal silicon dioxide.

36. The unit dosage form according to claim 29, wherein the at least one pharmaceutically acceptable excipient comprises a lubricant selected from the group consisting of calcium stearate, magnesium stearate, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, and combinations thereof.

37. The unit dosage form according to claim 36, wherein the lubricant is magnesium stearate.

38. The unit dosage form according to claim 24 further comprising a coating agent.

39. The unit dosage form according to claim 24, wherein the at least one pharmaceutically acceptable excipient comprises:

a) about 660 mg to about 780 mg of a diluent;

b) about 30 mg to about 90 mg of a disintegrant;

c) about 3 mg to about 9 mg of a glidant; and

d) about 15 mg to about 21 mg of a lubricant.

40. The unit dosage form according to claim 24, wherein the unit dosage form comprises:

a) about 400 mg of crystalline GS-7977;

b) about 360 mg of mannitol and about 356 mg of microcrystalline cellulose;

c) about 60 mg of croscarmellose sodium;

d) about 6 mg of colloidal silicon dioxide; and

e) about 18 mg of magnesium stearate.

41. The unit dosage form according to claim 40, wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about:

(1) 5.0, 7.3, 9.4, and 18.1; or

(2) 6.1, 8.2, 10.4, 12.7, 17.2, 17.7, 18.0, 18.8, 19.4, 19.8, 20.1, 20.8, 21.8, and 23.3.

42. The unit dosage form according to claim 40, wherein the crystalline GS-7977 has XRPD 2θ-reflections (°) at about:

(1) 5.0 and 7.3; or

(2) 6.1 and 12.7.

43. The unit dosage form according to claim 24, wherein the unit dosage form comprises a capsule or a tablet.

44. A process for preparing a tablet composition comprising about 400 mg of GS-7977 comprising:

blending an intragranular composition and an extragranular composition to obtain a blended composition;

compressing the blended composition to obtain a tablet composition; and

optionally coating the tablet composition;

wherein

the intragranular composition comprises GS-7977, a first intragranular diluent, optionally a second intragranular diluent, an intragranular disintegrant, an intragranular glidant, and an intragranular lubricant; and

the extragranular composition comprises a first extragranular diluent, optionally a second extragranular diluent, an extragranular glidant, an extragranular disintegrant, and an extragranular lubricant.

45. A tablet composition comprising about 400 mg of GS-7977 made according to the process of claim 44.

46. A method of treating a human infected with hepatitis C virus comprising administering to the human the composition according to claim 1.

47. The method according to claim 46, wherein the composition according to claim 1 is administered to the human in combination with ribavirin.

48. A method of treating a human infected with hepatitis C virus comprising administering to the human the unit dosage form according to claim 24.

49. The method according to claim 48, wherein the unit dosage form according to claim 24 is administered to the human in combination with ribavirin.

50. The method according to claim 49, wherein the unit dosage form according to claim 24 is administered to the human in combination with ribavirin as part of an interferon-free treatment regimen.

51. Use of the composition according to claim 1 to treat hepatitis C virus infection in a human in need thereof.

52. The use according to claim 51, wherein the composition according to claim 1 is administered to the human in combination with ribavirin.

53. Use of the unit dosage form according to claim 24 to treat hepatitis C virus infection in a human in need thereof.

54. The use according to claim 53, wherein the unit dosage form according to claim 24 is administered to the human in combination with ribavirin.

55. The use according to claim 54, wherein the unit dosage form according to claim 24 is administered to the human in combination with ribavirin as part of an interferon-free treatment regimen.