formulation material will impact such things as control of the tablet weight, the uniformity of the content of the dosage unit and the ease with which the formulation is able to be fed into a die for compression. Compaction is another critical property necessary to produce tablets with adequate tensile strength and hardness. In addition, it is often desirable to increase the amount of active agent in the dosage form to achieve adequate efficacy in human without increasing the pill size and burden.

There are challenges to develop orally bioavailable dosage forms containing pyrimidinedione compounds due to their extremely low intrinsic aqueous solubility. Although the potassium- or sodium- salt of certain pyrimidinedione compounds possesses a rapid dissolution to form a supersaturated state in aqueous media, the formation of the insoluble free acid form in the physiological GI environment with pH < 8 (based on their pKa1 > 8.3) upon dissolution is inevitable. Therefore, rapid conversion of the salt into the free acid form with essentially extremely slow dissolution usually results in low oral bioavailability. There is therefore a need for improved formulations for poorly water-soluble drugs, and identifying appropriate functional excipients and developing a highly bioavailable drug product of pyrimidinedione compounds continues to be a challenging endeavor.

SUMMARY ~~OF THE INVENTION~~

The disclosure is directed to pharmaceutical compositions of pyrimidinedione derivative compounds, methods of using such compositions and methods of enhancing the bioavailability of such compounds. In particular, the disclosed pharmaceutical compositions comprise a pyrimidinedione derivative compound, or a salt or hydrate or solvate thereof, or tautomer or combination thereof, and at least one bioavailability enhancing agent.

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

N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof;

at least one bioavailability enhancing agent comprising a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers in an amount of at least about 5% by weight of the pharmaceutical composition.

In one aspect, there is provided the use of a pharmaceutical composition as disclosed herein in the manufacture of medicament for treating hepatitis C.

In one aspect, there is provided a method for preparing a pharmaceutical composition comprising N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof, said method comprising preparing a pharmaceutical composition comprising said Compound A, or salt thereof, and a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers in an amount of about 5% to about 25% by weight of the pharmaceutical composition.

In one aspect, there is provided the use of a pharmaceutical composition comprising Compound A, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers in the manufacture of a medicament for enhancing bioavailability of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof, in a subject, wherein the medicament is to be administered to the subject, and

wherein the bioavailability is enhanced by from at least 10% to at least 30% relative to a similar pharmaceutical composition that does not comprise the stabilizing polymer or combination of stabilizing polymers.

In one aspect, there is provided the use of a pharmaceutical composition comprising Compound A, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers in the manufacture of a medicament for reducing the amount of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof, in a pharmaceutical composition necessary to achieve in a subject substantially the same bioavailability of Compound A, or a pharmaceutically acceptable salt thereof, in the subject, wherein the medicament is to be administered to the subject, and

wherein the amount of Compound A, or a salt thereof, necessary to achieve a bioavailability in said pharmaceutical composition is reduced by at least 20% to at least 30% relative to a similar pharmaceutical composition that does not comprise the stabilizing polymer or combination of stabilizing polymers.

In one aspect, there is provided a method of improving tabletability of a pharmaceutical composition comprising N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof, said method comprising preparing a pharmaceutical composition comprising said Compound A, or salt thereof, and a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers, in an amount of about 5% to about 25% by weight of the pharmaceutical composition.

In embodiments, the compound is *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A).

In embodiments, the salt of Compound A is a sodium salt.

In embodiments, the sodium salt of Compound A is a pattern B crystalline monosodium salt.

In embodiments, the pattern B monosodium salt is a monohydrate.

In embodiments, the bioavailability enhancing agent is a polyvinylpyrrolidone.

What is claimed is:

1. A pharmaceutical composition comprising:
at least one pyrimidinedione derivative compound, or a salt thereof; and
at least one bioavailability enhancing agent.

2. The pharmaceutical composition of claim 1, wherein:
the compound, or salt thereof, is *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof;
the at least one bioavailability enhancing agent comprises a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers; and
the pharmaceutical composition comprises the stabilizing polymer, or combination of stabilizing polymers, in an amount of at least about 5% by weight of the pharmaceutical composition.

3. The pharmaceutical composition of claim 2, wherein the weight ratio of the stabilizing polymer, or combination of stabilizing polymers, to Compound A, or the salt thereof, on a free acid equivalent weight basis is from about 4:1 to about 1:8.

4. The pharmaceutical composition of claim 1, wherein:
the compound, or salt thereof, is *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof;
the at least one bioavailability enhancing agent is a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers;
the pharmaceutical composition comprises Compound A, or the salt thereof, in an amount of about 200 mg to about 300 mg on a free acid equivalent weight basis; and
the pharmaceutical composition comprises the stabilizing polymer, or combination of stabilizing polymers, in an amount of at least about 5% by weight of the pharmaceutical composition.

5. The pharmaceutical composition of claim 4, wherein the weight ratio of the stabilizing polymer, or combination of stabilizing polymers, to Compound A, or the salt thereof, on a free acid equivalent weight basis is from about 4:1 to about 1:8.

6. The pharmaceutical composition of claim 4, wherein the pharmaceutical composition comprises a salt of Compound A.

7. The pharmaceutical composition of claim 6, wherein the salt of Compound A is a sodium salt.

8. The pharmaceutical composition of claim 7, wherein the sodium salt of Compound A is a pattern B crystalline monosodium salt.

9. The pharmaceutical composition of claim 8, wherein the pattern B monosodium salt is a monohydrate.

10. The pharmaceutical composition of claim 4, wherein the amount of Compound A, or salt thereof, is about 200 mg to about 300 mg on a free acid equivalent weight basis.

11. The pharmaceutical composition of claim 4, wherein the amount of Compound A, or salt thereof, is about 250 mg on a free acid equivalent weight basis.

12. The pharmaceutical composition of claim 4, wherein the amount of Compound A, or salt thereof, is at least about 20% by weight of the pharmaceutical composition on a free acid equivalent weight basis.

13. The pharmaceutical composition of claim 4, wherein the stabilizing polymer, or combination of stabilizing polymers, inhibits precipitation of Compound A, or a salt thereof.

14. The pharmaceutical composition of claim 4, wherein inhibition of precipitation of Compound A, or a salt thereof is determined by the process comprising:

(i) preparing a test solution comprising Compound A, or a salt thereof, and the stabilizing polymer, or combination of stabilizing polymers;

(ii) preparing a control solution, said control solution being substantially identical to the test solution except that said control solution does not contain the stabilizing polymer, or combination of stabilizing polymers;

(iii) maintaining the test mixture and the control solution under the same conditions for a test period; and

(iv) determining at the end of the test period the extent to which precipitation of Compound A, or a salt thereof, is inhibited in the test solution relative to the control solution.

15. The pharmaceutical composition of claim 4, wherein the stabilizing polymer, or combination of stabilizing polymers, is selected from the group consisting of copovidone, polyvinylpyrrolidone, hydroxymethylpropylcellulose, SOLUPLUS®, and combinations thereof; wherein the hydroxymethylpropylcellulose has a viscosity less than about 100 centipoise in a 2% solution of at a temperature of about 20°C.

16. The pharmaceutical composition of claim 4, wherein the stabilizing polymer, or combination of stabilizing polymers, comprises copovidone.

17. The pharmaceutical composition of claim 4, wherein the amount of the stabilizing polymer, or combination of stabilizing polymers, is at least about 10% by weight of the pharmaceutical composition.

18. The pharmaceutical composition of claim 4, wherein the amount of the stabilizing polymer, or combination of stabilizing polymers, is about 5% to about 25% by weight of the pharmaceutical composition.

19. The pharmaceutical composition of claim 4, wherein the pharmaceutical composition is an oral dosage form.

20. The pharmaceutical composition of claim 4, wherein the pharmaceutical composition is a tablet.

21. The pharmaceutical composition of claim 19, wherein the oral dosage form has a weight less than about 1500 mg.

22. The pharmaceutical composition of claim 4, wherein the pharmaceutical composition is a tablet having a weight from about 500 mg to about 900 mg.

23. The pharmaceutical composition of claim 20, wherein the tablet when administered as a single dose to a population of human subjects provides an average AUC_{24} value that is at least about 4500 ng·hr/mL for the population of human subjects.

24. The pharmaceutical composition of claim 20, wherein the tablet when administered as a single dose to a population of human subjects provides an average AUC_{24} value that is at least about 5000 ng·hr/mL and an average C_{max} value that is less than about 1200 ng/mL for the population of human subjects.

25. The pharmaceutical composition of claim 4, wherein:

the pharmaceutical composition is an oral dosage form having a weight less than about 1500 mg;

the oral dosage form comprises Compound A, or a salt thereof, in an amount of about 225 mg to about 275 mg on a free acid equivalent weight basis; and

the oral dosage form comprises the stabilizing polymer, or combination of stabilizing polymers, in an amount of at least about 5% by weight of the oral dosage form.

26. The pharmaceutical composition of claim 4, wherein:

the pharmaceutical composition is an oral dosage form having a weight less than about 1500 mg;

the oral dosage form comprises Compound A, or a salt thereof, in an amount of about 240 mg to about 260 mg on a free acid equivalent weight basis; and

the oral dosage form comprises the stabilizing polymer, or combination of stabilizing polymers, in an amount of at least about 10% by weight of the oral dosage form.

27. The pharmaceutical composition of claim 4, wherein:

the pharmaceutical composition is an oral dosage form having a weight less than about 1500 mg;

the oral dosage form comprises Compound A, or a salt thereof, in an amount of about 240 mg to about 260 mg on a free acid equivalent weight basis; and

the oral dosage form comprises the stabilizing polymer, or combination of stabilizing polymers, in an amount of about 10% to about 25% by weight of the oral dosage form.

28. The pharmaceutical composition of claim 4, wherein:

the pharmaceutical composition is an oral dosage form having a weight less than about 1500 mg;

the oral dosage form comprises Compound A, or a salt thereof, in an amount of about 245 mg to about 255 mg on a free acid equivalent weight basis;

the oral dosage form comprises the stabilizing polymer, or combination of stabilizing polymers in an amount of at from about 10% to about 25% by weight of the oral dosage form; and

the stabilizing polymer, or combination of stabilizing polymers, are selected from the group consisting of copovidone, polyvinylpyrrolidone, hydroxymethylpropylcellulose, SOLUPLUS®, and combinations thereof; wherein the hydroxymethylpropylcellulose has a viscosity less than about 100 centipoise in a 2% solution of at a temperature of about 20°C.

29. The pharmaceutical composition of claim 4, wherein:

the pharmaceutical composition is an oral dosage form having a weight less than about 1500 mg;

the oral dosage form comprises Compound A, or a salt thereof, in an amount of about 245 mg to about 255 mg on a free acid equivalent weight basis;

the oral dosage form comprises the stabilizing polymer, or combination of stabilizing polymers in an amount of at from about 10% to about 25% by weight of the oral dosage form; and

the stabilizing polymer, or combination of stabilizing polymers, comprises copovidone.

30. The pharmaceutical composition of claim 4, wherein:

the pharmaceutical composition is an oral dosage form having a weight less than about 1500 mg;

the oral dosage form comprises Compound A, or a salt thereof, in an amount of about 240 mg to about 260 mg on a free acid equivalent weight basis; and

the weight ratio of the stabilizing polymer, or combination of stabilizing polymers, to Compound A, or the salt thereof, on a free acid equivalent weight basis is from about 1:1 to about 1:4.

31. The pharmaceutical composition of claim 4, wherein:

the pharmaceutical composition is an oral dosage form having a weight less than about 1500 mg;

the oral dosage form comprises Compound A, or a salt thereof, in an amount of about 245 mg to about 255 mg on a free acid equivalent weight basis;

the weight ratio of the stabilizing polymer, or combination of stabilizing polymers, to Compound A, or the salt thereof, on a free acid equivalent weight basis is from about 1:1 to about 1:4; and

the stabilizing polymer, or combination of stabilizing polymers, is selected from the group consisting of copovidone, polyvinylpyrrolidone, hydroxymethylpropylcellulose, SOLUPLUS®, and combinations thereof; wherein the hydroxymethylpropylcellulose has a viscosity less than about 100 centipoise in a 2% solution of at a temperature of about 20°C.

32. The pharmaceutical composition of claim 4, wherein:

the pharmaceutical composition is an oral dosage form having a weight less than about 1500 mg;

the oral dosage form comprises Compound A, or a salt thereof, in an amount of about 245 mg to about 255 mg on a free acid equivalent weight basis;

the weight ratio of the stabilizing polymer, or combination of stabilizing polymers, to Compound A, or the salt thereof, on a free acid equivalent weight basis is from about 1:1 to about 1:4; and

the stabilizing polymer, or combination of stabilizing polymers, comprises copovidone.

33. A method for treating hepatitis C in a subject in need of such treatment, wherein the method comprises administering to the subject a pharmaceutical composition according to claim 1.

34. The method of claim 33 wherein the method further comprises administering to the subject one or more additional therapeutic agents.

35. A method for preparing a pharmaceutical composition comprising *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof, said method comprising preparing a pharmaceutical composition comprising said Compound A, or salt thereof, and a pharmaceutically

acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers in an amount of about 5% to about 25% by weight of the pharmaceutical composition.

36. A method of enhancing bioavailability of *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof, in a subject comprising:

preparing a pharmaceutical composition comprising Compound A, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers; and

administering the pharmaceutical composition to the subject.

37. A method of reducing the amount of *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof, in a pharmaceutical composition necessary to achieve in a subject substantially the same bioavailability of Compound A, or a pharmaceutically acceptable salt thereof, in the subject comprising:

preparing a pharmaceutical composition comprising Compound A, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers; and

administering the pharmaceutical composition to the subject.

38. A method of improving tabletability of a pharmaceutical composition comprising *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof, said method comprising preparing a pharmaceutical composition comprising said Compound A, or salt thereof, and a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers, in an amount of about 5% to about 25% by weight of the pharmaceutical composition.

What is claimed is:

1. A pharmaceutical composition comprising:

N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof;

at least one bioavailability enhancing agent comprising a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers in an amount of at least about 5% by weight of the pharmaceutical composition.

2. The pharmaceutical composition of claim 1, wherein the weight ratio of the stabilizing polymer, or combination of stabilizing polymers, to Compound A, or the salt thereof, on a free acid equivalent weight basis, is from about 4:1 to about 1:8.

3. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises a salt of Compound A wherein the salt is a sodium salt or a pattern B crystalline monohydrate monosodium salt.

4. The pharmaceutical composition of claim 1, wherein the amount of Compound A, or salt thereof, is about 200 mg to about 300 mg on a free acid equivalent weight basis.

5. The pharmaceutical composition of claim 1, wherein the stabilizing polymer inhibits the precipitation of Compound A, or a salt thereof, by from at least 10% to at least 80% relative to a substantially identical pharmaceutical composition that does not contain the stabilizing polymer wherein inhibition of precipitation is determined by a method comprising:

(i) preparing a test solution comprising Compound A, or a salt thereof, and the stabilizing polymer, or combination of stabilizing polymers;

(ii) preparing a control solution, said control solution being substantially identical to the test solution except that said control solution does not contain the stabilizing polymer, or combination of stabilizing polymers;

(iii) maintaining the test mixture and the control solution under the same conditions for a test period; and

(iv) determining at the end of the test period the extent to which precipitation of Compound A, or a salt thereof, is inhibited in the test solution relative to the control solution.

6. The pharmaceutical composition of claim 1, wherein the stabilizing polymer, or combination of stabilizing polymers, is selected from the group consisting of copovidone, polyvinylpyrrolidone, hydroxymethylpropylcellulose, SOLUPLUS®, and combinations thereof; wherein the hydroxymethylpropylcellulose has a viscosity less than about 100 centipoise in a 2% solution of at a temperature of about 20°C.

7. The pharmaceutical composition of claim 1, wherein the stabilizing polymer, or combination of stabilizing polymers, comprises copovidone.

8. The pharmaceutical composition of claim 1, wherein the amount of the stabilizing polymer, or combination of stabilizing polymers, is about 5% to about 25% by weight of the pharmaceutical composition.

9. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is a tablet when administered as a single dose to a population of human subjects provides an average AUC_{24} value that is at least about 5000 ng·hr/mL and an average C_{max} value that is less than about 1200 ng/ml for the population of human subjects.

10. Use of a pharmaceutical composition according to claim 1 in the manufacture of medicament for treating hepatitis C.

11. A method for preparing a pharmaceutical composition comprising N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof, said method comprising preparing a pharmaceutical composition comprising said Compound A, or salt thereof, and a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers in an amount of about 5% to about 25% by weight of the pharmaceutical composition.

12. Use of a pharmaceutical composition comprising Compound A, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers in the manufacture of a medicament for enhancing bioavailability of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof, in a subject, wherein the medicament is to be administered to the subject, and

wherein the bioavailability is enhanced by from at least 10% to at least 30% relative to a similar pharmaceutical composition that does not comprise the stabilizing polymer or combination of stabilizing polymers.

13. Use of a pharmaceutical composition comprising Compound A, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers in the manufacture of a medicament for reducing the amount of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof, in a pharmaceutical composition necessary to achieve in a subject substantially the same bioavailability of Compound A, or a pharmaceutically acceptable salt thereof, in the subject, wherein the medicament is to be administered to the subject, and

wherein the amount of Compound A, or a salt thereof, necessary to achieve a bioavailability in said pharmaceutical composition is reduced by at least 20% to at least 30% relative to a similar pharmaceutical composition that does not comprise the stabilizing polymer or combination of stabilizing polymers.

14. A method of improving tabletability of a pharmaceutical composition comprising N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (Compound A), or a pharmaceutically acceptable salt thereof, said method comprising preparing a pharmaceutical composition comprising said Compound A, or salt thereof, and a pharmaceutically acceptable stabilizing polymer, or combination of pharmaceutically acceptable stabilizing polymers, in an amount of about 5% to about 25% by weight of the pharmaceutical composition.