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

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, in an amount of from about 200 mg to about 300 mg on a free acid equivalent weight basis; and

a bioavailability enhancing agent which is copovidone in an amount of from about 5% to about 25% 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, in an amount of from about 200 mg to about 300 mg on a free acid equivalent weight basis, said method comprising preparing a pharmaceutical composition comprising said Compound A, or salt thereof, and a bioavailability enhancing agent which is copovidone 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 bioavailability enhancing agent comprising copovidone 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 bioavailability enhancing agent.

In one aspect, there is provided the use of a pharmaceutical composition comprising Compound A, or a pharmaceutically acceptable salt thereof, and a bioavailability enhancing agent comprising copovidone 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 bioavailability enhancing agent.

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, in an amount of from about 200 mg to about 300 mg on a free acid equivalent weight basis,and a bioavailability enhancing agent which is copovidone, 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.

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

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, or a pharmaceutically acceptable salt thereof, in an amount of from about 200 mg to about 300 mg on a free acid equivalent weight basis; and a bioavailability enhancing agent which is copovidone in an amount of from about 5% to about 25% by weight of the pharmaceutical composition, wherein the solubility of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, or a pharmaceutically acceptable salt thereof, as measured by a biphasic dissolution test is at least 20 mcg per mL at 100 minutes.

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 the use of a pharmaceutical composition as described herein, in the manufacture of a medicament for treating hepatitis C, wherein the bioavailability of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, or a pharmaceutically acceptable salt thereof, is enhanced by from at least 10% to at least 30% relative to a similar pharmaceutical composition that does not comprise the bioavailability enhancing agent.

In one aspect, there is provided the use of a pharmaceutical composition as described herein, in the manufacture of a medicament for treating hepatitis C wherein the amount of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, or a pharmaceutically acceptable salt thereof is reduced to achieve substantially the same bioavailability of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, or a pharmaceutically acceptable salt thereof, wherein the amount of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, or a salt thereof, is reduced by at least 20% to at least 30% relative to a similar pharmaceutical composition that does not comprise the bioavailability enhancing agent.

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, in an amount of from about 200 mg to about 300 mg on a free acid equivalent weight basis,and a bioavailability enhancing agent which is copovidone, 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:

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 an amount of from about 200 mg to about 300 mg on a free acid equivalent weight basis; and

a bioavailability enhancing agent which is copovidone in an amount of from about 5% to about 25% by weight of the pharmaceutical composition.

2. The pharmaceutical composition of claim 1, wherein the weight ratio of the bioavailability enhancing agent 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 bioavailability enhancing agent 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 bioavailability enhancing agent wherein inhibition of precipitation is determined by a method comprising:

(i) preparing a test solution comprising Compound A, or a salt thereof, and the bioavailability enhancing agent;

(ii) preparing a control solution, said control solution being substantially identical to the test solution except that said control solution does not contain the bioavailability enhancing agent;

(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.

5. 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.

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

7. 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, in an amount of from about 200 mg to about 300 mg on a free acid equivalent weight basis, said method comprising preparing a pharmaceutical composition comprising said Compound A, or salt thereof, and a bioavailability enhancing agent which is copovidone in an amount of about 5% to about 25% by weight of the pharmaceutical composition.

8. Use of a pharmaceutical composition comprising Compound A, or a pharmaceutically acceptable salt thereof, and a bioavailability enhancing agent comprising copovidone 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 bioavailability enhancing agent.

9. Use of a pharmaceutical composition comprising Compound A, or a pharmaceutically acceptable salt thereof, and a bioavailability enhancing agent comprising copovidone 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 bioavailability enhancing agent.

10. 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, in an amount of from about 200 mg to about 300 mg on a free acid equivalent weight basis, and a bioavailability enhancing agent which is copovidone, 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, or a pharmaceutically acceptable salt thereof, in an amount of from about 200 mg to about 300 mg on a free acid equivalent weight basis; and

a bioavailability enhancing agent which is copovidone in an amount of from about 5% to about 25% by weight of the pharmaceutical composition,

wherein the solubility of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, or a pharmaceutically acceptable salt thereof, as measured by a biphasic dissolution test is at least 20 mcg per mL at 100 minutes.

2. The pharmaceutical composition of claim 1, wherein the weight ratio of the bioavailability enhancing agent to N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, 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 N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide wherein the salt is a sodium salt or a pattern B crystalline monohydrate monosodium salt having an X-ray powder diffraction pattern comprising three or more peaks selected from the group consisting of 5.4±0.2, 10.8±0.2, 14.4±0.2, 16.3±0.2, 17.0±0.2, 21.6±0.2, 22.1±0.2, and 23.7±0.2 degrees 2θ.

4. The pharmaceutical composition of claim 1, wherein the bioavailability enhancing agent inhibits the precipitation of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, 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 bioavailability enhancing agent wherein inhibition of precipitation is determined by a method comprising:

(i) preparing a test solution comprising N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, or a salt thereof, and the bioavailability enhancing agent;

(ii) preparing a control solution, said control solution being substantially identical to the test solution except that said control solution does not contain the bioavailability enhancing agent;

(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 N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, or a salt thereof, is inhibited in the test solution relative to the control solution.

5. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is a single dose tablet that 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 in a population of human subjects.

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

7. Use of a pharmaceutical composition of claim 1, in the manufacture of a medicament for treating hepatitis C, wherein the bioavailability of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, or a pharmaceutically acceptable salt thereof, is enhanced by from at least 10% to at least 30% relative to a similar pharmaceutical composition that does not comprise the bioavailability enhancing agent.

8. Use of a pharmaceutical composition of claim 1, in the manufacture of a medicament for treating hepatitis C wherein the amount of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, or a pharmaceutically acceptable salt thereof, is reduced to achieve substantially the same bioavailability of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, or a pharmaceutically acceptable salt

thereof, wherein the amount of N-(6-(3-tert-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1 (2H)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide, or a salt thereof, is reduced by at least 20% to at least 30% relative to a similar pharmaceutical composition that does not comprise the bioavailability enhancing agent.

9. The pharmaceutical composition of claim 1, wherein the weight ratio of the bioavailability enhancing agent to Compound A, or the salt thereof, on a free acid equivalent weight basis is from 1:1 to 1:3.5.

10. The pharmaceutical composition of claim 1, wherein the copovidone is present in an amount of from 10% to 25% by weight of the pharmaceutical composition.

11. The pharmaceutical composition of claim 1, wherein the copovidone is present in an amount of from 10% to 20% by weight of the pharmaceutical composition.

12. The pharmaceutical composition of claim 1 wherein the pharmaceutical composition is a tablet and wherein copovidone is present as an intragranular component.

13. The pharmaceutical composition of claim 1 wherein the solubility of Compound A as measured by a biphasic dissolution test is at least 30 mcg per mL at 100 minutes.