

THERAPEUTIC COMPOUNDS, FORMULATIONS, AND USE THEREOF

CROSS-REFERENCE

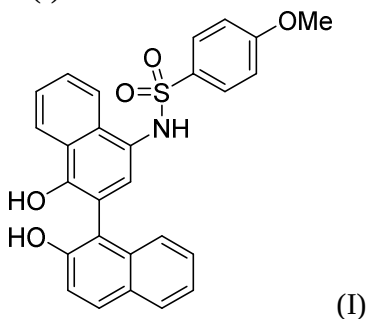
[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application No. 63/268,723, filed March 1, 2022, which is incorporated by reference in its entirety herein.

SUMMARY

[0002] Disclosed herein, in certain examples, are solid amorphous dispersions comprising a compound of Formula (I) and a polymer excipient, methods of making said dispersions, compositions comprising said dispersions, oral dosage forms comprising said compositions, as well as methods of treating diseases or disorders (e.g., cancer, fibrosis, inflammatory diseases or disorders) comprising administering oral dosage forms comprising said compositions.

[0003] Disclosed herein, in certain examples, are solid amorphous dispersions comprising:

a) a compound of formula (I):



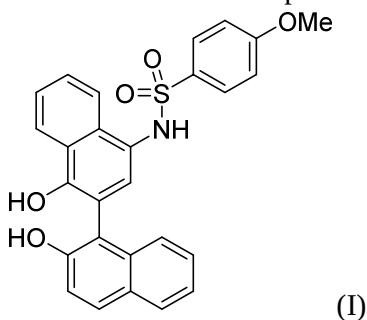
(I)

or a pharmaceutically acceptable salt thereof; and

b) a polymer excipient.

[0003a] In one aspect, the present disclosure refers to a solid amorphous dispersion comprising:

a) about 40 % w/w to about 80 % w/w of a compound of formula (I):



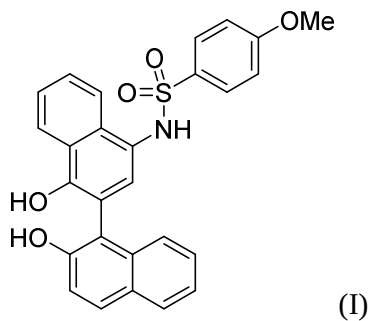
(I)

or a pharmaceutically acceptable salt thereof, in the dispersion; and

b) a polymer excipient.

[0004] Disclosed herein, in certain examples, are solid amorphous dispersions comprising:

a) a compound of formula (I):

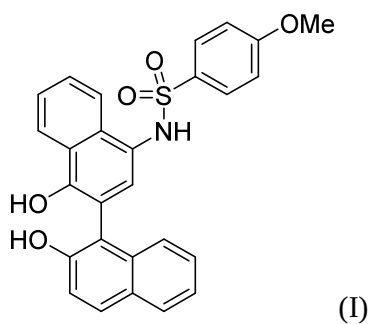


or a pharmaceutically acceptable salt thereof, in an amount of about 40% w/w to about 60% w/w of the dispersion; and

b) a polymer excipient in an amount of about 40% to about 60% w/w of the dispersion.

[0005] Disclosed herein, in certain examples, are solid amorphous dispersions comprising:

a) at least 150 mg of a compound of formula (I):



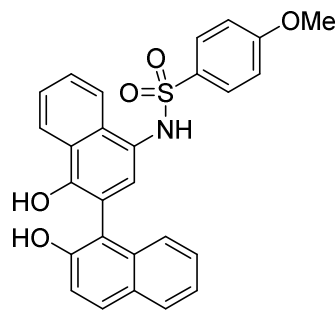
or a pharmaceutically acceptable salt thereof; and

b) a polymer excipient.

[0006] Disclosed herein, in certain examples, are compositions comprising:

a) a solid amorphous dispersion comprising:

i) at least 150 mg of a compound of formula (I):

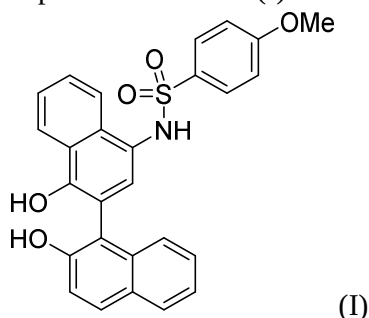


or a pharmaceutically acceptable salt thereof; and

- ii) a polymer excipient in an amount of about 20-35% w/w of the composition;
- b) a crystallization inhibiting polymer in an amount of about 15-35% w/w of the composition;
- c) a diluent or filler in an amount of about 5-25% of the composition;
- d) a disintegrant in an amount of about 1-8% w/w of the composition; and
- e) a lubricant in an amount of about 0.1-3% w/w of the composition.

[0006a] In one aspect, the present disclosure refers to a composition comprising a solid amorphous dispersion comprising:

- a) at least 150 mg of a compound of formula (I):

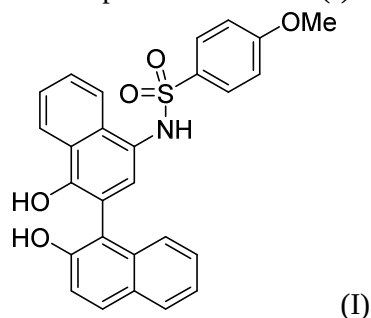


or a pharmaceutically acceptable salt thereof; and

- b) a polymer excipient.

[0007] Disclosed herein, in certain examples, are compositions comprising:

- a) a solid amorphous dispersion comprising:
 - i) at least 150 mg of a compound of formula (I):



or a pharmaceutically acceptable salt thereof; and

- ii) a polymer excipient in an amount of about 15-25% w/w of the composition;

- b) a crystallization inhibiting polymer in an amount of about 15-25% w/w of the composition;
- c) a diluent or filler in an amount of about 20-35% of the composition;
- d) a disintegrant in an amount of about 3-8% w/w of the composition; and
- e) a lubricant in an amount of about 1-3% w/w of the composition.

[0008] Disclosed herein, in certain examples, are solid oral dosage forms comprising a compound of formula (I).

[0009] Disclosed herein, in certain examples, are solid oral dosage forms comprising a composition disclosed herein.

[0009a] In one aspect, the present disclosure refers to a solid oral dosage form comprising a solid amorphous dispersion disclosed herein or a composition disclosed herein.

[0009b] In one aspect, the present disclosure refers to a composition disclosed herein or a solid oral dosage form disclosed herein, for use in therapy.

[00010] Disclosed herein, in certain examples, are methods of treating cancer in an individual in need thereof, the method comprising administering to the individual the oral dosage form disclosed herein.

[00010a] In one aspect, the present disclosure refers to use of a composition disclosed herein or a solid oral dosage form disclosed herein in the manufacturing of a medicament for treating cancer in an individual in need thereof, optionally wherein the cancer is head and neck cancer, lung cancer, liver cancer, breast cancer, skin cancer, kidney cancer, testicular cancer, colon cancer, rectal cancer, gastric cancer, skin cancer, metastatic melanoma, prostate cancer, ovarian cancer, cervical cancer, bone cancer, spleen cancer, gall bladder cancer, brain cancer, pancreatic cancer, stomach cancer, anal cancer, prostate cancer, multiple myeloma, post-transplant lymphoproliferative disease, restenosis, myelodysplastic syndrome, leukemia, or lymphoma.

[00011] Disclosed herein, in certain examples, are methods of treating fibrosis in an individual in need thereof, the method comprising administering to the individual the oral dosage form disclosed herein.

[00011a] In one aspect, the present disclosure refers to use of a composition disclosed herein or a solid oral dosage form disclosed herein in the manufacturing of a medicament for treating fibrosis in an individual in need thereof, optionally wherein the fibrosis is pulmonary fibrosis, bone marrow fibrosis, intestine fibrosis, pancreatic fibrosis, joint fibrosis, liver fibrosis, retroperitoneum, kidney fibrosis, myelofibrosis, dermal fibrosis, non-alcoholic fatty liver disease, steatohepatitis, or systemic sclerosis.

[00012] Disclosed herein, in certain examples, are methods of treating an inflammatory disease or disorder in an individual in need thereof, the method comprising administering to the individual the oral dosage form disclosed herein.

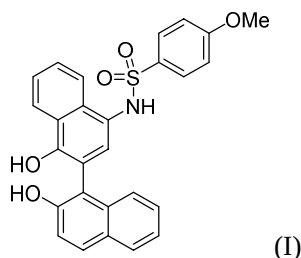
[00013] Disclosed herein, in certain examples, are methods of treating chemotherapy-induced peripheral neuropathy, diabetic neuropathy, or familial amyloid polyneuropathy in an individual in need thereof, the method comprising administering to the individual the oral dosage form disclosed herein.

[00014] Disclosed herein, in certain examples, are methods of treating cachexia in an individual in need thereof, the method comprising administering to the individual the oral dosage form disclosed herein.

[00015] Disclosed herein, in certain examples, are methods of treating anaphylaxis in an individual in need thereof, the method comprising administering to the individual the oral dosage form disclosed herein.

[00015a] In one aspect, the present disclosure refers to use of a composition disclosed herein or a solid oral dosage form disclosed herein in the manufacturing of a medicament for treating: i) an inflammatory disease or disorder in an individual in need thereof, optionally wherein the inflammatory disease or disorder is inflammatory bowel disease, ulcerative colitis, psoriasis, uveitis, scleritis, multiple sclerosis, pancreatitis, or asthma; ii) chemotherapy-induced peripheral neuropathy, diabetic neuropathy, or familial amyloid polyneuropathy in an individual in need thereof; iii) cachexia in an individual in need thereof; or iv) anaphylaxis in an individual in need thereof.

[00015b] In one aspect, the present disclosure refers to a method of preparing a solid amorphous dispersion comprising a) a compound of formula (I):



or a pharmaceutically acceptable salt thereof, and b) a polymer excipient, the method comprising: i) dissolving the compound of formula (I), or a pharmaceutically acceptable salt thereof, and the polymer excipient in a solvent to form a solution, optionally further comprising dissolving a crystallization inhibiting polymer; and ii) atomizing the solution of step (i) into a drying chamber in a spray dried dispersion apparatus to prepare the solid amorphous dispersion.

[00016] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing **Detailed Description**, **Examples**, and **Claims**.

BRIEF DESCRIPTION OF THE DRAWINGS

[00017] **FIG. 1** shows the kinetic solubility of TTI-101 compositions with 10%, 15%, or 25% CIP in FaSSIF (pH 6.5) monitored for 6 hours.

DETAILED DESCRIPTION

[00018] As generally described herein, the present disclosure, in part, provides solid amorphous dispersions comprising a compound of Formula (I) and a polymer excipient, methods of making said dispersions, compositions comprising said dispersions, oral dosage forms comprising said compositions, as well as methods of treating diseases or disorders (e.g., cancer, fibrosis, inflammatory diseases or disorders) comprising administering oral dosage forms comprising said compositions.

Definitions

[00019] As used herein the specification, “a” or “an” may mean one or more. As used herein, when used in conjunction with the word “comprising”, the words “a” or “an” may mean one or more than one. As used herein “another” may mean at least a second or more. Still further, the terms “having”, “including”, “containing” and “comprising” are interchangeable and one of skill in the art is cognizant that these terms are open ended terms. Some embodiments of the invention may consist of or consist essentially of one or more elements, method steps, and/or methods of the invention. It is contemplated that any method, compound, or composition described herein can be implemented with respect to any other method, compound, or composition described herein.

[00020] “About” and “approximately” shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees of error are within 20 percent (%), typically, within 10%, and more typically, within 5% of a given value or range of values.