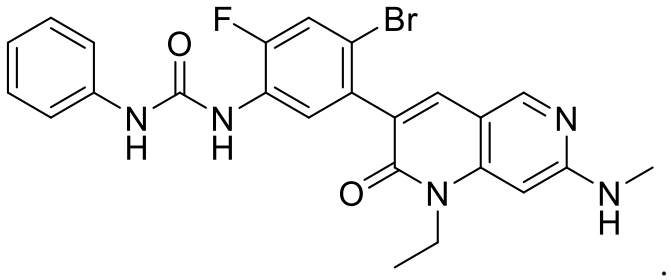
Formula (I), suitable for oral administration comprising an amorphous form of a compound of Formula (I):



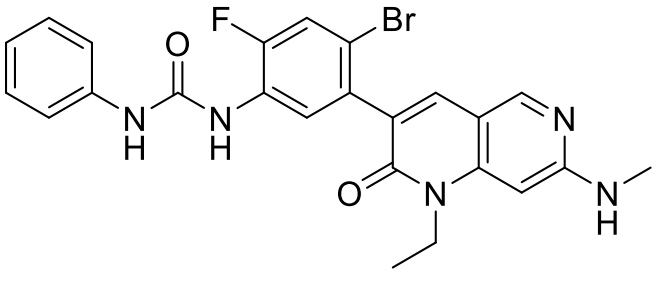
Formula (I)

For example, provided herein is a pharmaceutical composition comprising a solid spray-dried dispersion comprising an amorphous form of a compound represented by Formula (I) and a pharmaceutically acceptable polymer and one or more pharmaceutically acceptable carriers. Contemplated compositions provided herein, e.g., that include an amorphous form of Formula I, such as in a solid dispersion as described herein, may provide, in certain examples, enhanced pharmacokinetic profiles when administered to a patient, as for example, compared to administration of a crystalline form of Formula I. Disclosed composition (e.g., tablets) have, in at least some examples, may provide fast release (e.g., in 30 minutes or less) of Formula I and/or fast dissolution.

[0005a] In one aspect of the present disclosure, there is provided a pharmaceutically acceptable composition for oral administration, the composition comprising:

(i) a solid dispersion, wherein the solid dispersion comprises:

the amorphous form of a compound represented by Formula (I):



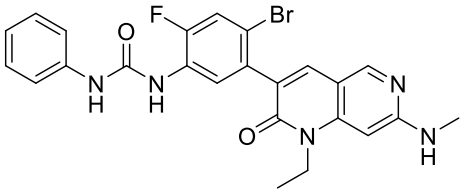
and

Formula (I)

a pharmaceutically acceptable polymer; and

(ii) one or more pharmaceutically acceptable excipients.

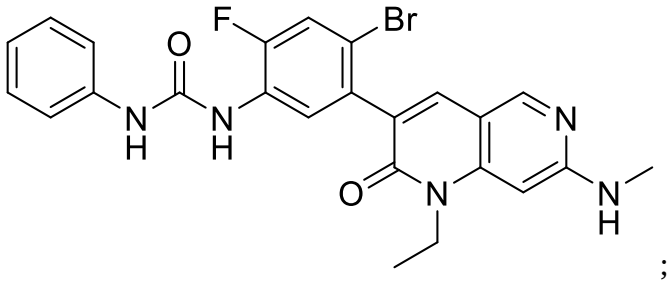
[0005b] In another aspect of the present disclosure, there is provided a pharmaceutically acceptable composition comprising a compound represented by Formula (I)



Formula (I)

and a pharmaceutically acceptable excipient, wherein greater than about 96% by weight of the compound present in the pharmaceutically acceptable composition is in the amorphous form.

[0005c] In a further aspect of the present disclosure, there is provided a pharmaceutically acceptable composition for orally delivering to a patient 50 mg of a compound represented by Formula (I):



;

Formula (I)

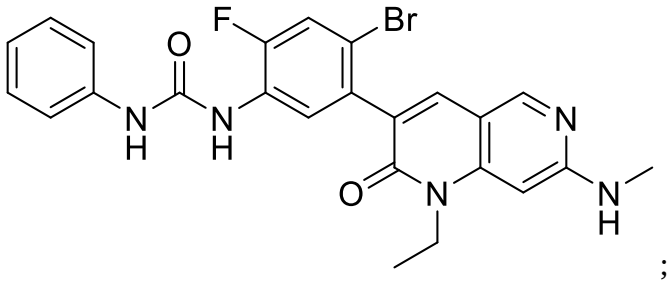
comprising:

an intragranular blend, wherein the intragranular blend comprises:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, hydroxypropyl methyl cellulose acetate succinate; a bulking agent and/or filler; and a lubricant and/or a glidant; and

an extragranular blend comprising a glidant and/or a lubricant.

[0005d] In another aspect of the present disclosure, there is provided a pharmaceutically acceptable composition for orally delivering to a patient 50 mg of a compound represented by Formula (I):



;

Formula (I)

comprising:

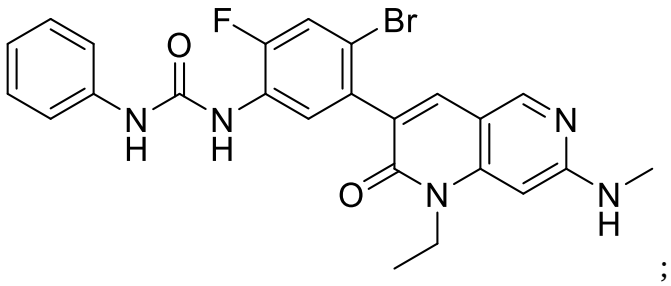
a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form and hydroxypropyl methyl cellulose acetate succinate;

a bulking agent,

a filler, and

a lubricant and/or a glidant.

[0005e] In a further aspect of the present disclosure, there is provided a pharmaceutically acceptable tablet having 50 mg of a compound represented by Formula (I):



;

Formula (I)

comprising:

an intragranular blend, wherein the intragranular blend comprises:

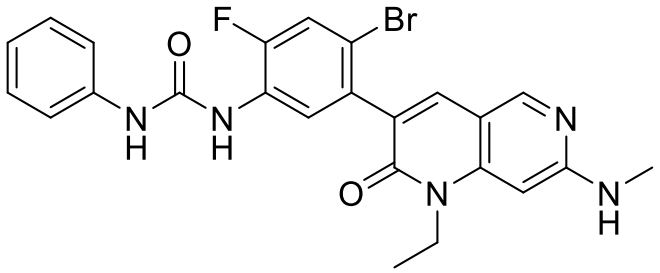
a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and hydroxypropyl methyl cellulose acetate succinate;

about 25-35% by weight of a bulking agent based on the total amount of the pharmaceutical composition;

about 25-35% by weight of a filler based on the total amount of the pharmaceutical composition; and

an extragranular blend comprising a glidant and/or a lubricant.

[0005f] In another aspect of the present disclosure, there is provided a pharmaceutically acceptable tablet having 50 mg of a compound represented by Formula (I):



;

Formula (I)

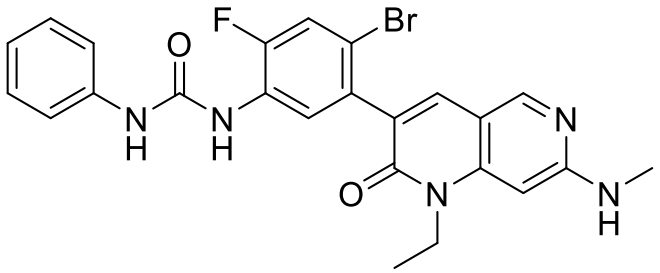
wherein the tablet comprises:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and hydroxypropyl methyl cellulose acetate succinate;

about 25-35% by weight microcrystalline cellulose based on the total weight of the tablet; and

about 25-35% by weight of lactose or a hydrate thereof based on the total amount of the pharmaceutical composition.

[0005g] In a further aspect of the present disclosure, there is provided a pharmaceutically acceptable composition for orally delivering 50 mg of a compound represented by Formula (I):



;

Formula (I)

comprising:

an intragranular blend, wherein the intragranular blend comprises:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form and hydroxypropyl methyl cellulose acetate succinate;

about 25-35% by weight microcrystalline cellulose based on the total amount of the pharmaceutical composition;

about 25-35%% by weight of lactose or a hydrate thereof based on the total amount of the pharmaceutical composition;

about 5% by weight of crospovidone based on the total amount of the of the pharmaceutical composition;

about 0.5% by weight of silicon dioxide based on the total amount of the of the pharmaceutical composition; and

about 0.5% by weight of magnesium stearate based on the total amount of the of the pharmaceutical composition; and

an extragranular blend comprising about 0.5% by weight of silicon dioxide based on the total amount of the pharmaceutical composition; and (ii) about 0.5% by weight of magnesium stearate based on the total amount of the of the pharmaceutical composition.

[0005h] In another aspect of the present disclosure, there is provided a use of the composition or one or more of the tablets disclosed herein, in the manufacture of a medicament for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, or non-small cell lung cancer.

[0005i] In a further aspect of the present disclosure, there is provided a use of the composition or one or more of the tablets disclosed herein, in the manufacture of a medicament for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, lung cancer, glioblastoma, a glioma, malignant peripheral nerve sheath sarcoma, or hypereosinophilic syndrome.

[0005j] In another aspect of the present disclosure, there is provided a use of the composition or one or more of the tablets disclosed herein, in the manufacture of a medicament for treating a disease selected from the group consisting of KIT driven germ cell tumor (e.g., testicular germ cell), KIT driven skin cancer, or KIT driven renal cell carcinoma.

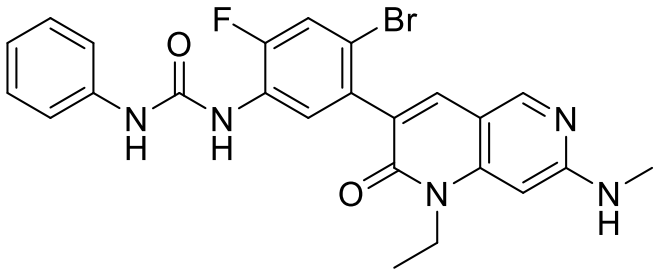
[0005k] In a further aspect of the present disclosure, there is provided a use of the composition or one or more of the tablets disclosed herein, in the manufacture of a medicament for treating a disease selected from the group consisting of penile cancer,

PDGFRA driven penile cancer, prostate cancer, PDGFRA driven prostate cancer, PDGFRA driven non-melanoma skin cancer, PDGFRA driven glioma, PDGFRA driven sarcoma, PDGFRA driven glioblastoma, or PDGFRA driven pancreatic cancer.

[0005l] In another aspect of the present disclosure, there is provided a use of the composition or one or more of the tablets disclosed herein, in the manufacture of a medicament for treating a disease selected from the group consisting of vaginal cancer, prostate cancer, penile cancer, non-melanoma skin cancer, melanoma, or breast sarcoma, wherein the disease comprises a PDGFRAB mutation.

[0005m] In a further aspect of the present disclosure, there is provided a use of the composition or tablets disclosed herein in the preparation of a medicament for the treatment of a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, or non-small cell lung cancer.

[0005n] In another aspect of the present disclosure, there is provided a process for the preparation of the solid dispersion comprising an amorphous form of a compound of Formula (I)



Formula (I)

disclosed herein, the process comprising:

(a) mixing the compound of Formula (I), a solvent, the polymer and water to obtain a suspension;

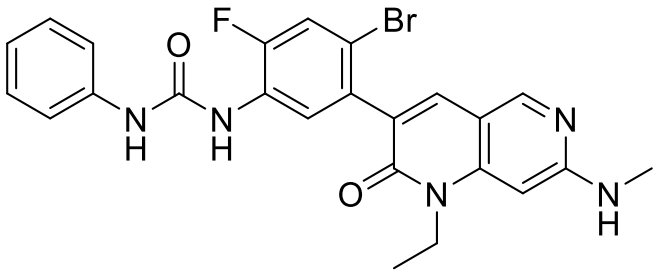
(b) optionally agitating and/or mixing the suspension while maintaining a temperature of about 10 to about 25 ºC;

(c) heating the suspension to dissolve the suspended particles prior to introduction into a spray-dryer; and

(d) spray-drying the suspension to obtain a spray-dried dispersion;

(e) drying the spray-dried dispersion; thereby obtaining the solid dispersion.

[0005o] In a further aspect of the present disclosure, there is provided a solid dispersion comprising an amorphous form of a compound of Formula (I)



Formula (I)

produced by the process of disclosed herein.

[0005p] In another aspect of the present disclosure, there is provided a composition or one or more of the tablets disclosed herein, for use in therapy.

[0006] Also provided herein, in an example, is a pharmaceutical composition comprising: (a) an intragranular blend comprising: (i) a solid dispersion comprising an amorphous form of a compound represented by Formula (I), and a pharmaceutically acceptable polymer; (ii) one or more fillers; (iii) a disintegrant; (iv) a glidant; and (v) a lubricant; and (b) an extragranular blend comprising: (i) a glidant; and (ii) a lubricant.

[0007] In some examples, provided herein is an amorphous form of a compound of Formula (I) having no detectable amounts of any crystalline form.

[0008] In some examples, provided herein is an amorphous form of a compound of Formula (I) having no detectable amounts of any crystalline form of compound of Formula (I).

[0009] In some examples, provided herein is an amorphous form of a compound of Formula (I) having no more than about 5% (w/w) of any crystalline form of compound of Formula (I).

[0010] Also provided herein, in an example, is an amorphous form of a compound of Formula (I) which contains not more than about 5% (w/w) of any crystalline form or any

detectable amount of any crystalline form of compound of Formula (I) when exposed to 0-100% relative humidity at between 25-40 ºC for at least 3 months.

[0011] Also provided herein, in an example, is a compound of Formula (I) wherein the compound is greater than about 95% amorphous. In some examples, a compound of Formula (I) wherein the compound is greater than about 95% amorphous by PXRD analysis.

[0012] Also provided herein, in an example, is a compound of Formula (I) in amorphous form substantially free of any other crystalline forms of compound of Formula (I).

[0013] Also provided herein, in an example, is compound of Formula (I) in amorphous form essentially free of crystalline material having a purity of at least about 95% aside from residual solvents.

[0014] Also provided herein, in an example, is a pharmaceutical composition comprising an amorphous form of a compound of formula (I) having a purity by HPLC of greater than 95% and one or more pharmaceutically acceptable carriers, excipients or diluents.

[0015] Also provided herein, in an example, is a pharmaceutical composition comprising an amorphous form of a compound of Formula (I) having no detectable amounts of any crystalline form and one or more pharmaceutically acceptable carriers, excipients or diluents.

[0016] In some examples, provided herein is a pharmaceutical composition comprising an amorphous form of a compound of Formula (I) having no detectable amounts of any crystalline form of compound of Formula (I) and one or more pharmaceutically acceptable carriers, excipients or diluents.

[0017] In some examples, provided herein is a pharmaceutical composition comprising an amorphous form of a compound of Formula (I) having not more than about 5% (w/w) of any crystalline form of the compound of Formula (I) and one or more pharmaceutically acceptable carriers, excipients or diluents.

[0018] Also provided herein, in an example, is a pharmaceutical composition comprising an amorphous form of a compound of Formula (I) which contains not more than about 5% (w/w) of any crystalline form or any detectable amount of any crystalline form of compound of Formula (I) when exposed to 0-100% relative humidity at between 25-40 ºC for about at least 3 months, and one or more pharmaceutically acceptable carriers, excipients or diluents.

[0019] Also provided herein, in an example, is pharmaceutical composition comprising an amorphous form of a compound of Formula (I) wherein the compound is

greater than about 95% amorphous, and one or more pharmaceutically acceptable carriers, excipients or diluents. In some examples, a pharmaceutical composition comprises a compound of Formula (I) wherein the compound is greater than about 95% amorphous by PXRD analysis

[0020] Also provided herein, in an example, is a pharmaceutical composition comprising an amorphous form of a compound of Formula (I) substantially free of any other crystalline forms, and one or more pharmaceutically acceptable carriers, excipients or diluents.

[0021] Also provided herein, in an example, is pharmaceutical composition comprising an amorphous form of a compound of Formula (I) substantially free of crystalline form having a purity of at least about 95% by HPLC aside from residual solvents, and one or more pharmaceutically acceptable carriers, excipients or diluents.

[0022] Also provided herein, in an example, is a solid dispersion comprising an amorphous form of a compound of formula (I) having a purity by HPLC of greater than 95% and a polymer together with one or more pharmaceutically acceptable carriers, excipients or diluents.

[0023] Also provided herein, in an example, is an amorphous form of a solid dispersion comprising a compound of Formula (I) and a pharmaceutically acceptable polymer, e.g., hydroxypropylmethylcellulose acetate succinate, wherein the amorphous form is characterized by a powder X-ray diffraction having broad peaks in degrees 2θ, e.g., in degrees 2θ at about 9.5 and about 17 to about 29. In some examples, the amorphous form of a compound of Formula (I) is characterized by the x-ray diffraction pattern substantially as depicted in Figure 1.

[0024] Also provided herein, in an example, is a solid dispersion comprising an amorphous form of a compound of Formula (I) having no detectable amounts of any crystalline form and one or more pharmaceutically acceptable carriers, excipients or diluents.

[0025] In some examples, provided herein is a solid dispersion comprising an amorphous form of a compound of Formula (I) having no detectable amounts to any crystalline form of compound of Formula (I) and a polymer together with one or more pharmaceutically acceptable carriers, excipients or diluents.

[0026] Also provided herein, in an example, is a solid dispersion comprising an amorphous form of a compound of Formula (I) having not more than about 5% (w/w) of any

crystalline form for compound of Formula (I) and a polymer together with one or more pharmaceutically acceptable carriers, excipients or diluents.

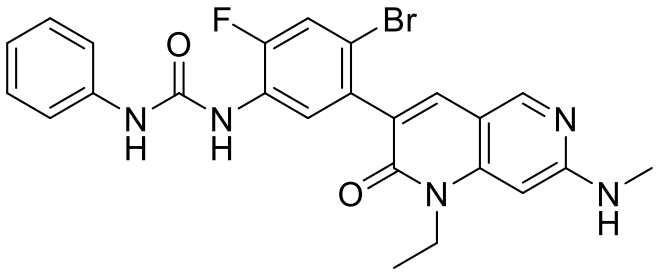
[0027] Also provided herein, in an example, is a solid dispersion comprising a amorphous form of a compound of Formula (I) which contains not more than about 5% (w/w) of any crystalline form or any detectable amount of any crystalline form of compound of Formula (I) when exposed to 0-100% relative humidity at between 25-40 ºC for about 3 months or more, and a polymer together with one or more pharmaceutically acceptable carriers, excipients or diluents.

[0028] Also provided herein, in an example, is solid dispersion comprising an amorphous form of a compound of Formula (I) wherein the compound is greater than about 95% amorphous, and a polymer together with one or more pharmaceutically acceptable carriers, excipients or diluents.

[0029] Also provided herein, in an example, is a solid dispersion comprising an amorphous form of a compound of Formula (I) substantially free of any other crystalline forms, and a polymer together with one or more pharmaceutically acceptable carriers, excipients or diluents.

[0030] Also provided herein, in an example, is a solid dispersion comprising an amorphous form of a compound of Formula (I) substantially free of crystalline form having a purity of at least about 95% by HPLC aside from residual solvents, and a polymer together with one or more pharmaceutically acceptable carriers, excipients or diluents.

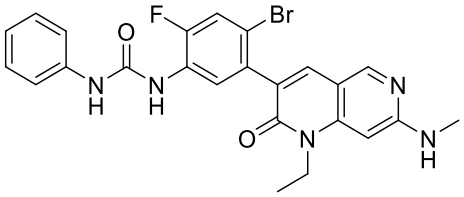
[0031] In one example, provided herein is a pharmaceutically acceptable composition for oral administration, the composition comprising:(i) a solid dispersion, wherein the solid dispersion comprises: the amorphous form of a compound represented by Formula (I):



Formula (I)

and a pharmaceutically acceptable polymer; and (ii) one or more pharmaceutically acceptable excipients.

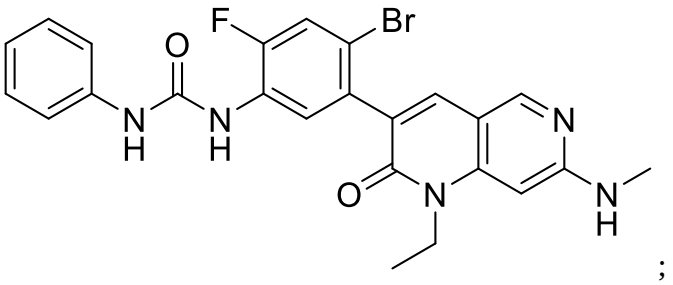
[0032] In another example, described herein is a pharmaceutically acceptable composition comprising a compound represented by Formula (I)



Formula (I)

and a pharmaceutically acceptable excipient, wherein greater than about 96% by weight of the compound present in the pharmaceutically acceptable composition is in the amorphous form.

[0033] In another example, described herein is a pharmaceutically acceptable composition for orally delivering to a patient 50 mg of a compound represented by Formula (I):

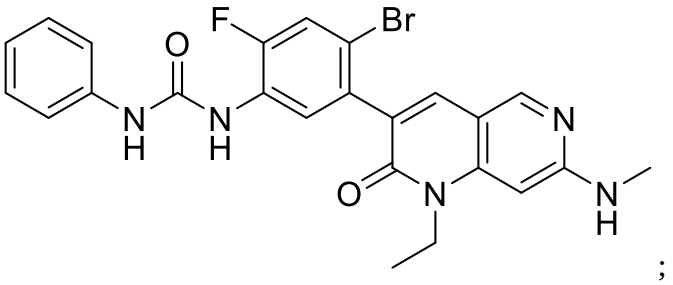


;

Formula (I)

comprising: an intragranular blend, wherein the intragranular blend comprises: a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, hydroxypropyl methyl cellulose acetate succinate; a bulking agent and/or filler; and a lubricant and/or a glidant; and an extragranular blend comprising a glidant and/or a lubricant.

[0034] In another example, described herein is a pharmaceutically acceptable composition for orally delivering to a patient 50 mg of a compound represented by Formula (I):

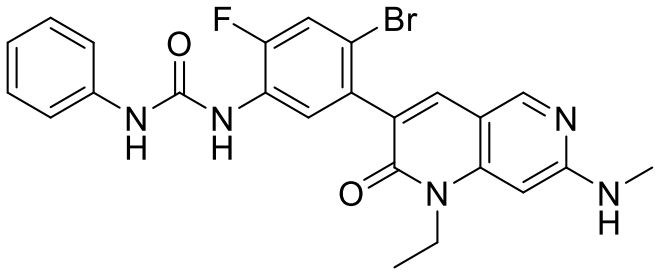


;

Formula (I)

comprising: a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form and hydroxypropyl methyl cellulose acetate succinate; a bulking agent, a filler, and a lubricant and/or a glidant.

[0035] In another example, described herein is a pharmaceutically acceptable tablet having 50 mg of a compound represented by Formula (I):

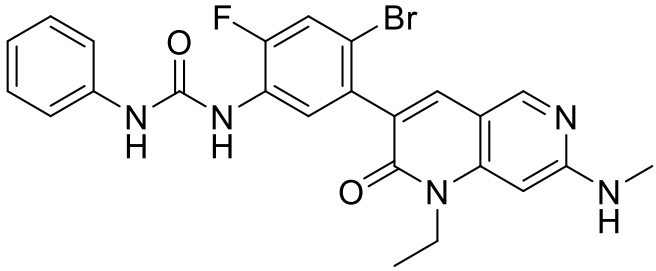


;

Formula (I)

comprising: an intragranular blend, wherein the intragranular blend comprises: a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and hydroxypropyl methyl cellulose acetate succinate; about 25-35% by weight of a bulking agent based on the total amount of the pharmaceutical composition; about 25-35% by weight of a filler based on the total amount of the pharmaceutical composition; and an extragranular blend comprising a glidant and/or a lubricant.

[0036] In another example, described herein is a pharmaceutically acceptable tablet having 50 mg of a compound represented by Formula (I):

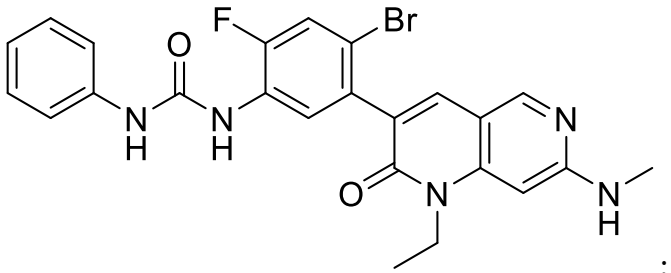


;

Formula (I)

wherein the tablet comprises: a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and hydroxypropyl methyl cellulose acetate succinate; about 25-35% by weight microcrystalline cellulose based on the total weight of the tablet; and about 25-35% by weight of lactose or a hydrate thereof based on the total amount of the pharmaceutical composition.

[0037] In another example, described herein is a pharmaceutically acceptable composition for orally delivering 50 mg of a compound represented by Formula (I):

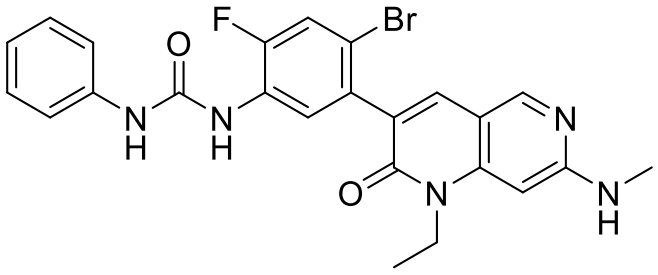


;

Formula (I)

comprising: an intragranular blend, wherein the intragranular blend comprises: a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form and hydroxypropyl methyl cellulose acetate succinate; about 25-35% by weight microcrystalline cellulose based on the total amount of the pharmaceutical composition; about 25-35%% by weight of lactose or a hydrate thereof based on the total amount of the pharmaceutical composition; about 5% by weight of crospovidone based on the total amount of the of the pharmaceutical composition; about 0.5% by weight of silicon dioxide based on the total amount of the of the pharmaceutical composition; and about 0.5% by weight of magnesium stearate based on the total amount of the of the pharmaceutical composition; and an extragranular blend comprising about 0.5% by weight of silicon dioxide based on the total amount of the pharmaceutical composition; and (ii) about 0.5% by weight of magnesium stearate based on the total amount of the of the pharmaceutical composition.

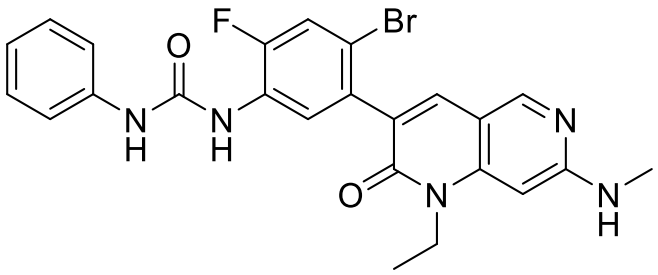
[0038] In another example, described herein is a process for the preparation of the solid dispersion comprising an amorphous form of a compound of Formula (I)



Formula (I)

e.g., an amorphous form described herein, the process comprising: (a) mixing the compound of Formula (I), a solvent, the polymer and water to obtain a suspension; (b) optionally agitating and/or mixing the suspension while maintaining a temperature of about 10 to about 25 ºC; (c) heating the suspension to dissolve the suspended particles prior to introduction into

a spray-dryer; and (d) spray-drying the suspension to obtain a spray-dried dispersion; (e) drying the spray-dried dispersion; thereby obtaining the solid dispersion. In some examples, a solid dispersion comprising an amorphous form of a compound of Formula (I)



Formula (I)

is produced by said process.

[0039] Also provided herein, in another example, is a method of treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein.

[0040] Also provided herein, in another example, is a method of treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, lung cancer, glioblastoma, a glioma, malignant peripheral nerve sheath sarcoma, and hypereosinophilic syndrome in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein.

[0041] Also provided herein, in another example, is a method of treating a disease selected from the group consisting of KIT driven germ cell tumor (e.g., testicular germ cell), KIT driven skin cancer, or KIT driven renal cell carcinoma in a patient in need thereof,

comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein.

[0042] Also provided herein, in another example, is a method of treating a disease selected from the group consisting of penile cancer, PDGFRA driven penile cancer, prostate cancer, PDGFRA driven prostate cancer, PDGFRA driven non-melanoma skin cancer, PDGFRA driven glioma, PDGFRA driven sarcoma, PDGFRA driven glioblastoma, or PDGFRA driven pancreatic cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein.

[0043] Also provided herein, in another example, is a method of treating a disease comprising a PDGFRB mutation selected from the group consisting of vaginal cancer, prostate cancer, penile cancer, non-melanoma skin cancer, melanoma, or breast sarcoma in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein.

[0044] In some examples, provided herein is a method for treating diseases driven by KIT mutations or PDGFRA mutations in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein. In some examples, provided herein is a method for treating diseases driven by KIT mutations and PDGFRA mutations in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein. In some examples, provided herein is a method for treating diseases driven by KIT mutations or PDGFRA mutations, comprising passenger PDGFRB mutations in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein. In some examples, provided herein is a method for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma (e.g., KIT driven melanoma or PGDFRA driven melanoma or PGDFR driven melanoma), acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia,

lymphoblastic T-cell lymphoma, and non-small cell lung cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a composition or one or more tablets described herein. In some examples, the melanoma is cutaneous melanoma or noncutaneous melanaoma. In some examples, the melanoma is cutaneous melanoma. In some examples, the cutaneous melanoma is superficial spreading melanoma, nodular melanoma, acral-lentiginous melanoma, or amelanotic and desmoplastic melanoma. In some examples, the melanoma is noncutaneous (non-skin) melanoma. In some examples, the noncutaneous melanoma is ocular melanoma or mucosal melanoma. In some examples, the disease is caused by the kinase activity of c-KIT and/or PDGFRA, and/or oncogenic forms thereof. In some examples, the disease is selected from the group consisting of KIT driven germ cell tumor (e.g., testicular germ cell), KIT driven skin cancer (e.g., KIT driven cutaneous squamous cell carcinoma, KIT driven Merkel cell carcinoma, uveal melanoma, non-melanoma skin cancer), or KIT driven renal cell carcinoma (e.g., renal cell carcinoma, chromophobe renal cell carcinoma). In some examples, the disease is selected from the group consisting of penile cancer, PDGFRA driven penile cancer, prostate cancer, PDGFRA driven prostate cancer, PDGFRA driven non-melanoma skin cancer, PDGFRA driven glioma, PDGFRA driven sarcoma, PDGFRA driven glioblastoma, or PDGFRA driven pancreatic cancer. In some examples, the disease comprising a PDGFRB mutation is selected from the group consisting of vaginal cancer, prostate cancer, penile cancer, non-melanoma skin cancer, melanoma, or breast sarcoma.

[0045] Also provided herein, in another example, is a use of a composition or tablets described herein for the preparation of a medicament for the treatment of a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer.

BRIEF DESCRIPTION OF FIGURES AND DRAWINGS

[0046] Figure 1 depicts a powder X-ray diffraction (PXRD) of a solid dispersion comprising the amorphous form of a compound of Formula (I).

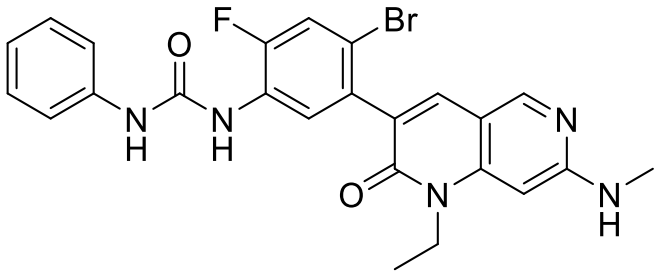
CLAIMS

What is claimed is:

1. A pharmaceutically acceptable composition for oral administration, the composition comprising:

(i) a solid dispersion, wherein the solid dispersion comprises:

the amorphous form of a compound represented by Formula (I):



and

Formula (I)

a pharmaceutically acceptable polymer; and

(ii) one or more pharmaceutically acceptable excipients.

2 . The pharmaceutically acceptable composition of claim 1, wherein the solid dispersion has no more than about 5% w/w of any crystalline form of the compound.

3. The pharmaceutically acceptable composition of claim 1 or 2, wherein the solid dispersion has substantially no detectable amount of any crystalline form of the compound.

4. The pharmaceutically acceptable composition of any one of claims 1-3, wherein the amorphous form has a powder X-ray diffraction pattern substantially as shown in Figure 1.

5. The pharmaceutically acceptable composition of any one of claims 1-4, wherein the composition contains not more than about 5% (w/w) of any crystalline form of the compound in the aggregate when exposed to 60% relative humidity at 25 ºC for 1 month, 3 months or 6 months.

6. The pharmaceutically acceptable composition of any one of claims 1-4, wherein the composition contains not more than about 5% (w/w) of any crystalline form of the compound

in the aggregate when exposed to 75% relative humidity at 40 ºC for 1 month, 3 months or 6 months.

7. The pharmaceutically acceptable composition of any one of claims 1-6 comprising about 10% to about 30% by weight of the compound based on the total weight of the solid dispersion.

8. The pharmaceutically acceptable composition of any one of claims 1-7, comprising about 20% to about 30% by weight of the compound based on the total weight of the solid dispersion.

9. The pharmaceutically acceptable composition of any one of claims 1-8, comprising about 25% by weight of the compound based on the total weight of the solid dispersion.

10. The pharmaceutically acceptable composition of any one of claims 1-9, wherein the pharmaceutically acceptable polymer is selected from the group consisting of: polyvinyl pyrrolidone, polyethyleneoxide, polyethylene glycol, poly(vinyl pyrrolidone-co-vinyl acetate), polyoxyethylene-polyoxypropylene block copolymers, graft copolymers comprised of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate, polymethacrylates, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polycaprolactam, polylactic acid, polyglycolic acid, poly(lactic-glycolic)acid, lipids, cellulose, pullulan, dextran, maltodextrin, hyaluronic acid, polysialic acid, chondroitin sulfate, heparin, fucoidan, pentosan polysulfate, spirulan, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose propionate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate phthalate, hydroxypropyl methylcellulose propionate phthalate, hydroxypropyl methylcellulose acetate trimellitate, hydroxypropyl methylcellulose propionate trimellitate, cellulose acetate succinate, methyl cellulose acetate succinate, dextran, dextran acetate, dextran propionate, dextran succinate, dextran acetate propionate, dextran acetate succinate, dextran propionate succinate, dextran acetate propionate succinate, poly(methacrylic acid-co-methyl methacrylate) 1:1, poly(methacrylic acid-co-methyl methacrylate) 1:2, poly(methacrylic acid-co-ethyl acrylate) 1:1, hydroxyethyl cellulose, methyl cellulose and hydroxy propyl cellulose, poly methacrylic acid-ethyl acrylate, poly methacrylic acid-methyl methacrylate, poly methyl methacrylate-ethyl acrylate, poly

trimethylammonioethyl methacrylate chloride-methyl methacrylate-ethyl acrylate and poly(butylmethacrylate-co-(2-dimethylaminoethyl)methacrylate-co-methyl methacrylate), and mixtures thereof.

11. The pharmaceutically acceptable composition of any one of claims 1-10, wherein the pharmaceutically acceptable polymer is selected from the group consisting of: polyvinyl pyrrolidone, polyethyleneoxide, polyethylene glycol, poly(vinyl pyrrolidone-co-vinyl acetate), polyoxyethylene-polyoxypropylene block copolymers, graft copolymers comprised of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate, polymethacrylates, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polycaprolactam, polylactic acid, polyglycolic acid, poly(lactic-glycolic)acid, lipids, cellulose, pullulan, dextran, maltodextrin, hyaluronic acid, polysialic acid, chondroitin sulfate, heparin, fucoidan, pentosan polysulfate, spirulan, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose propionate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate phthalate, hydroxypropyl methylcellulose propionate phthalate, hydroxypropyl methylcellulose acetate trimellitate, hydroxypropyl methylcellulose propionate trimellitate, cellulose acetate succinate, methyl cellulose acetate succinate, dextran, dextran acetate, dextran propionate, dextran succinate, dextran acetate propionate, dextran acetate succinate, dextran propionate succinate, dextran acetate propionate succinate, poly(methacrylic acid-co-methyl methacrylate) 1:1, poly(methacrylic acid-co-methyl methacrylate) 1:2, poly(methacrylic acid-co-ethyl acrylate) 1:1, and mixtures thereof.

12. The pharmaceutically acceptable composition of any one of claims 1-11, wherein the pharmaceutically acceptable polymer is hydroxypropyl methyl cellulose acetate succinate.

13. The pharmaceutically acceptable composition of any one of claims 1-12, wherein the compound and the pharmaceutically acceptable polymer are present in a ratio of compound:polymer from about 40:60 to about 10:90.

14. The pharmaceutically acceptable composition of any one of claims 1-13, wherein the compound and the pharmaceutically acceptable polymer are present in a ratio of compound:polymer from about 30:70 to about 20:80.

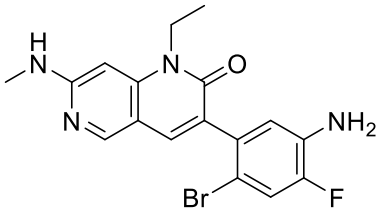
15. The pharmaceutically acceptable composition of any one of claims 1-14, wherein the compound and the pharmaceutically acceptable polymer are present in a ratio of compound:polymer of about 25:75.

16. The pharmaceutically acceptable composition of anyone of claims 1-15, wherein the solid dispersion is a solid spray-dried dispersion.

17. The pharmaceutically acceptable composition of any one of claims 1-16, wherein the solid dispersion has a solubility in water at pH 6.5 of about 120 □g/mL at 25 °C.

18. The pharmaceutically acceptable composition of any one of claims 1-17, wherein the solid dispersion has a solubility in water at pH 2 of about 178 □g/mL at 25 °C.

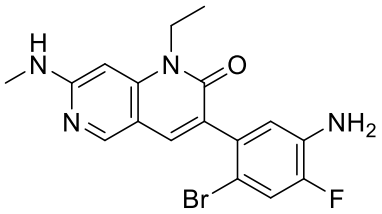
19. The pharmaceutically acceptable composition of any one of claims 1-18, comprising less than about 10 % by weight of a compound represented by Formula (II):



Formula (II)

based on the weight of the compound of Formula (I).

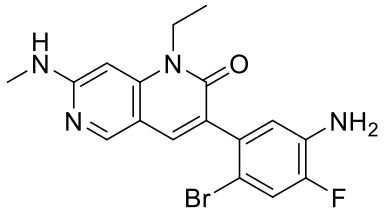
20. The pharmaceutically acceptable composition of any one of claims 1-19, comprising less than about 3 % by weight of a compound represented by Formula (II):



Formula (II)

based on the weight of the compound of Formula (I).

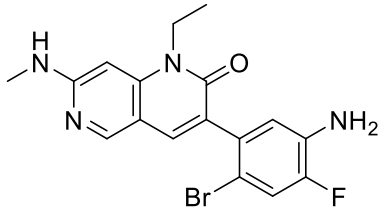
21. The pharmaceutically acceptable composition of any one of claims 1-20, comprising less than about 1 % by weight of a compound represented by Formula (II):



Formula (II)

based on the weight of the compound of Formula (I).

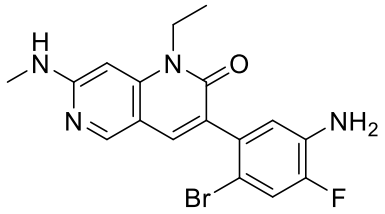
22. The pharmaceutically acceptable composition of any one of claims 1-21, comprising about 0.1 % by weight to about 0.5% by weight of a compound represented by Formula (II):



Formula (II)

based on the weight of the compound of Formula (I).

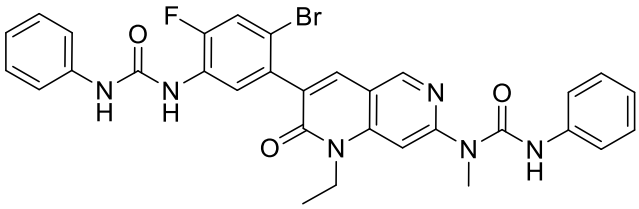
23. The pharmaceutically acceptable composition of any one of claims 1-22, comprising about 0.01 % by weight to about 0.1% by weight of a compound represented by Formula (II):



Formula (II)

based on the weight of the compound of Formula (I).

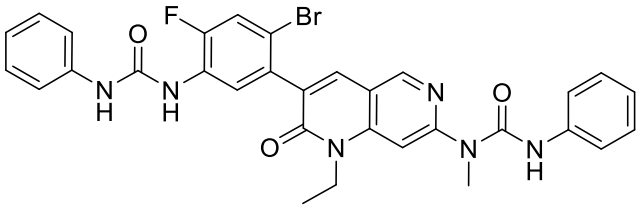
24. The pharmaceutically acceptable composition of any one of claims 1-23, comprising less than about 10 % by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

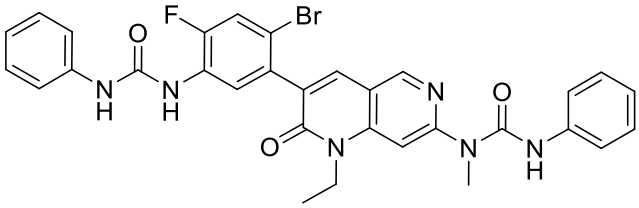
25. The pharmaceutically acceptable composition of any one of claims 1-24, comprising less than about 3 % by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

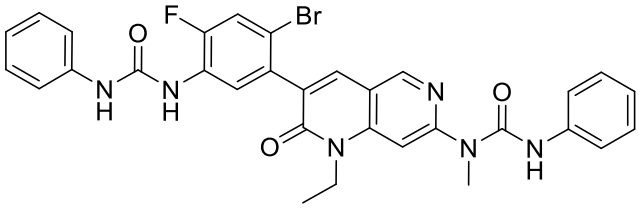
26. The pharmaceutically acceptable composition of any one of claims 1-25, comprising less than about 1 % by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

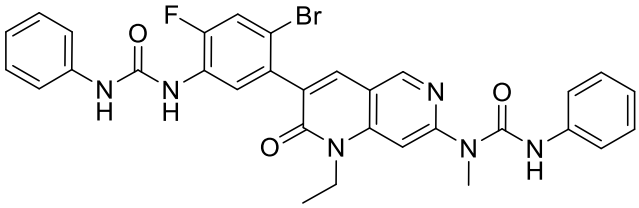
27. The pharmaceutically acceptable composition of any one of claims 1-26, comprising about 0.1 % by weight to about 0.5% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

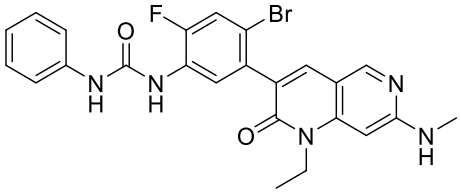
28. The pharmaceutically acceptable composition of any one of claims 1-28, comprising about 0.01 % by weight to about 0.1% by weight of a compound represented by Formula (III):



Formula (III)

based on the weight of the compound of Formula (I).

29. A pharmaceutically acceptable composition comprising a compound represented by Formula (I)



Formula (I)

and a pharmaceutically acceptable excipient, wherein greater than about 96% by weight of the compound present in the pharmaceutically acceptable composition is in the amorphous form.

30. The pharmaceutically acceptable composition of claim 29, wherein the amorphous form has a characteristic amorphous powder X-ray diffraction halo pattern.

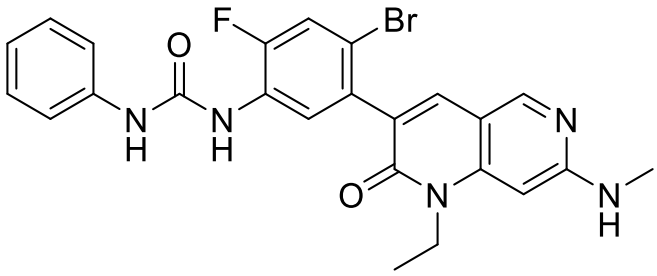
31 The pharmaceutically acceptable composition of claim 29 or 30 of any one of claims 1-3, where the amorphous form has a powder X-ray diffraction pattern substantially as shown in Figure 1.

32. The pharmaceutically acceptable composition of claim 29 or 30, wherein the powder X-ray diffraction spectrum is obtained using Cu Kα radiation.

33. The pharmaceutically acceptable composition of any one of claims 29-32, wherein the amorphous form of the compound has a glass transition temperature of about 125 °C.

34. The pharmaceutically acceptable composition of any one of claims 29-33, wherein the composition has no detectable amounts of any crystalline form of the compound of Formula (I).

35. A pharmaceutically acceptable composition for orally delivering to a patient 50 mg of a compound represented by Formula (I):



;

Formula (I)

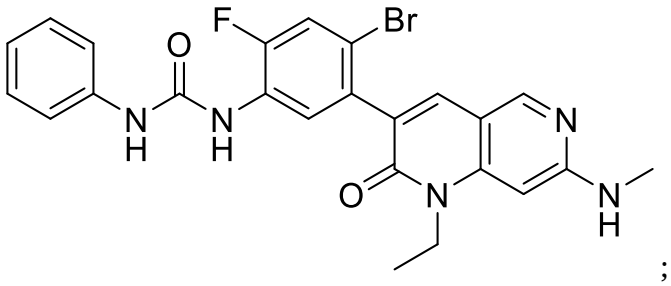
comprising:

an intragranular blend, wherein the intragranular blend comprises:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, hydroxypropyl methyl cellulose acetate succinate; a bulking agent and/or filler; and a lubricant and/or a glidant; and

an extragranular blend comprising a glidant and/or a lubricant.

36. A pharmaceutically acceptable composition for orally delivering to a patient 50 mg of a compound represented by Formula (I):



;

Formula (I)

comprising:

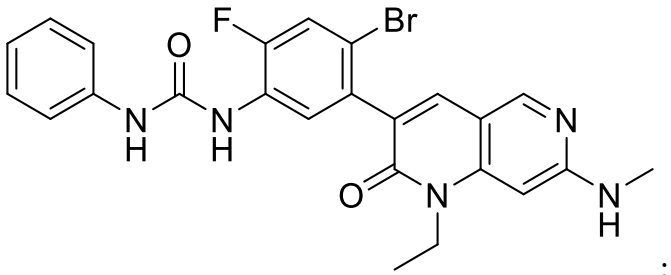
a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form and hydroxypropyl methyl cellulose acetate succinate;

a bulking agent,

a filler, and

a lubricant and/or a glidant.

37. A pharmaceutically acceptable tablet having 50 mg of a compound represented by Formula (I):



;

Formula (I)

comprising:

an intragranular blend, wherein the intragranular blend comprises:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and hydroxypropyl methyl cellulose acetate succinate;

about 25-35% by weight of a bulking agent based on the total amount of the pharmaceutical composition;

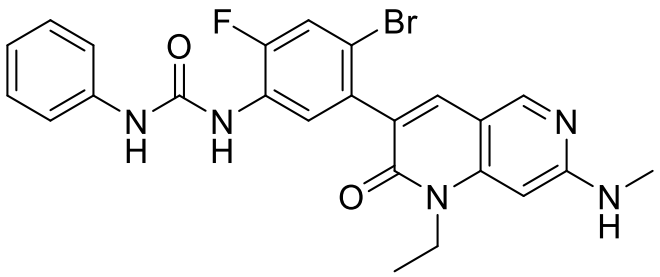
about 25-35% by weight of a filler based on the total amount of the pharmaceutical composition; and

an extragranular blend comprising a glidant and/or a lubricant.

38. The pharmaceutically acceptable tablet of claim 37, wherein the bulking agent is microcrystalline cellulose.

39. The pharmaceutically acceptable tablet of claim 37 or 38, wherein the filler is lactose or a hydrate thereof.

40. A pharmaceutically acceptable tablet having 50 mg of a compound represented by Formula (I):



;

Formula (I)

wherein the tablet comprises:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and hydroxypropyl methyl cellulose acetate succinate;

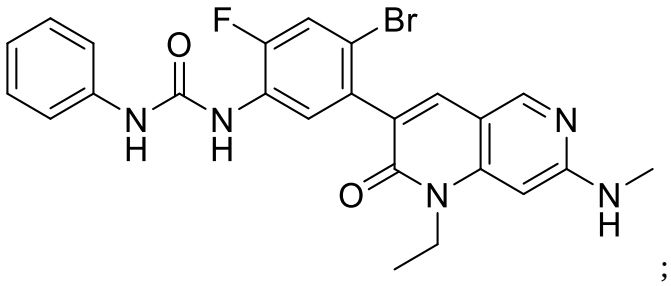
about 25-35% by weight microcrystalline cellulose based on the total weight of the tablet; and

about 25-35% by weight of lactose or a hydrate thereof based on the total amount of the pharmaceutical composition.

41. The pharmaceutically acceptable tablet of claim 40, further comprising at least one of: magnesium stearate, crospovidone and silicon dioxide.

42. The pharmaceutically acceptable tablet of any one of claims 40 or 41, wherein the tablet disintegrates in less than 1 minute as tested using USP <701> for uncoated tablets.

43. A pharmaceutically acceptable composition for orally delivering 50 mg of a compound represented by Formula (I):



;

Formula (I)

comprising:

an intragranular blend, wherein the intragranular blend comprises:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form and hydroxypropyl methyl cellulose acetate succinate;

about 25-35% by weight microcrystalline cellulose based on the total amount of the pharmaceutical composition;

about 25-35%% by weight of lactose or a hydrate thereof based on the total amount of the pharmaceutical composition;

about 5% by weight of crospovidone based on the total amount of the of the pharmaceutical composition;

about 0.5% by weight of silicon dioxide based on the total amount of the of the pharmaceutical composition; and

about 0.5% by weight of magnesium stearate based on the total amount of the of the pharmaceutical composition; and

an extragranular blend comprising about 0.5% by weight of silicon dioxide based on the total amount of the pharmaceutical composition; and (ii) about 0.5% by weight of magnesium stearate based on the total amount of the of the pharmaceutical composition.

44. The pharmaceutically acceptable composition or tablet of any one of claims 1-43, wherein the composition or tablet releases at least 80% of the compound after 10 minutes to 40 minutes when the composition is tested in 900 mL sodium acetate buffer at pH 4.5 using a USP Apparatus II (Paddle Method) at 37 °C, with a paddle speed of 75 rpm.

45. The pharmaceutically acceptable composition or tablet of any one of claims 1-44, wherein the composition or tablet releases at least 80% of the compound after 20 minutes when the composition is tested in 900 mL sodium acetate buffer at pH 4.5 using a USP Apparatus II (Paddle Method) at 37 °C, with a paddle speed of 75 rpm.

46. Use of the composition or one or more of the tablets of claims 1-42, in the manufacture of a medicament for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, or non-small cell lung cancer.

47. Use of the composition or one or more of the tablets of claims 1-45, in the manufacture of a medicament for treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, lung cancer, glioblastoma, a glioma, malignant peripheral nerve sheath sarcoma, or hypereosinophilic syndrome.

48. Use of the composition or one or more of the tablets of claims 1-45, in the manufacture of a medicament for treating a disease selected from the group consisting of KIT driven germ cell tumor (e.g., testicular germ cell), KIT driven skin cancer, or KIT driven renal cell carcinoma.

49. Use of the composition or one or more of the tablets of claims 1-45, in the manufacture of a medicament for treating a disease selected from the group consisting of penile cancer, PDGFRA driven penile cancer, prostate cancer, PDGFRA driven prostate cancer, PDGFRA driven non-melanoma skin cancer, PDGFRA driven glioma, PDGFRA driven sarcoma, PDGFRA driven glioblastoma, or PDGFRA driven pancreatic cancer.

50. Use of the composition or one or more of the tablets of claims 1-45, in the manufacture of a medicament for treating a disease selected from the group consisting of

vaginal cancer, prostate cancer, penile cancer, non-melanoma skin cancer, melanoma, or breast sarcoma, wherein the disease comprises a PDGFRAB mutation.

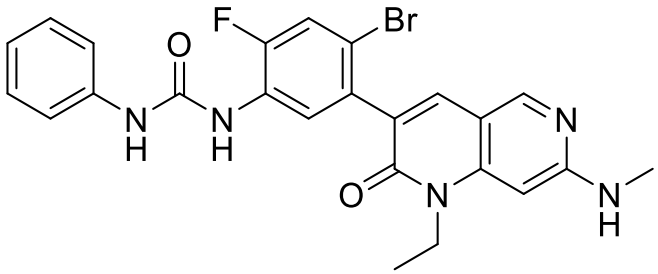
51. The use of claim 46, wherein the disease is gastrointestinal stromal tumors (GIST).

52. Use of the composition or tablets according to any one of claims 1-45 in the preparation of a medicament for the treatment of a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, or non-small cell lung cancer.

53. The use of claim 49, wherein the disease is gastrointestinal stromal tumors (GIST).

54. The use of any one of claims 46-53, wherein the disease is caused by the kinase activity of: c-KIT and/or PDGFRA, and/or oncogenic forms thereof.

55. A process for the preparation of the solid dispersion comprising an amorphous form of a compound of Formula (I)



Formula (I)

according to any one of claims 1-37, the process comprising:

(a) mixing the compound of Formula (I), a solvent, the polymer and water to obtain a suspension;

(b) optionally agitating and/or mixing the suspension while maintaining a temperature of about 10 to about 25 ºC;

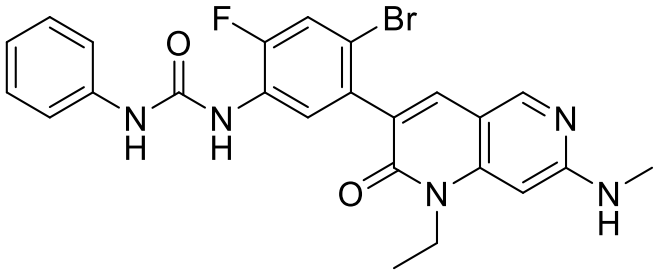
(c) heating the suspension to dissolve the suspended particles prior to introduction into a spray-dryer; and

(d) spray-drying the suspension to obtain a spray-dried dispersion;

(e) drying the spray-dried dispersion; thereby obtaining the solid dispersion.

56. The process of claim 55, wherein heating comprises passing the suspension through an in-line heat exchanger.

57. A solid dispersion comprising an amorphous form of a compound of Formula (I)



Formula (I)

produced by the process of claim 54 or 55.

58. The composition or one or more of the tablets of claims 1-45, for use in therapy.