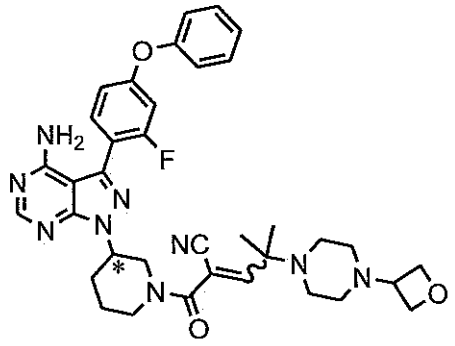
Claims

1. A solid oral dosage form, which is typically a tablet or capsule, comprising:

(A) a core material comprising the (E) isomer, (Z) isomer, or a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, (S)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, or a mixture of (R) and (S) isomers of 2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile (Compound (I)) having the structure:



Compound (I)

where *C is a stereochemical center;

and/or a pharmaceutically acceptable salt thereof;

(B) an enteric coating;

(C) a subcoat below the enteric coating, wherein the subcoat:

(1) is a water soluble or hydrophilic erodible polymer, said polymer being a low molecular weight polymer selected from hydroxymethyl cellulose (HPMC), hydroxyethyl cellulose, hydroxypropyl cellulose, microcrystalline cellulose, polyvinylpyrrolidones, polysaccharides, a polysaccharide derivative, polyvinyl alcohols, polyethylene glycol (PEG), polypropylene glycol (PPG), and a PEG-PPG block copolymer; or

(2) comprises a water insoluble composition comprising: (i) particles of a water soluble compound capable of forming channels in the water insoluble composition; or (ii) water insoluble hydrophilic particles which cause swelling of the subcoat when in contact with an aqueous media; and

(D) a pharmaceutically acceptable excipient,

wherein the solid oral dosage form is able to release Compound (I) and/or the pharmaceutically acceptable salt thereof in the jejuno-ileum portion of the intestine of a mammal after administration; and

wherein the solid oral dosage form is able to release at least about 80% of Compound (I) and/or the pharmaceutically acceptable salt thereof in about 120 minutes in a dissolution vessel comprising an aqueous solution at a pH of from about 6.4 to about 7.4.

2. The solid oral dosage form according to claim 1, wherein the solid oral dosage form is able to release less than about 10% by weight of Compound (I) and/or the pharmaceutically acceptable salt thereof in about 1.5 hours in a dissolution vessel comprising an aqueous solution at a pH of less than about 3 or a pH of from about 4.5 to about 5.0; and wherein the solid oral dosage form is able to release not less than about 80% by weight of Compound (I) and/or the pharmaceutically acceptable salt thereof from about twenty minutes to about two hours in a dissolution vessel comprising an aqueous solution at a pH of from about 6.4 to about 7.4.

3. The solid oral dosage form according to claim 1 or claim 2, wherein the subcoat (C) comprises a water insoluble composition comprising particles of a water soluble compound.

4. The solid oral dosage form according to claim 1 or claim 2, wherein the subcoat (C) comprises a water insoluble composition comprising water insoluble hydrophilic particles which cause swelling of the subcoat when in contact with an aqueous media.

5. The solid oral dosage form according to claim 1 or claim 2, wherein the subcoat (C) is a water insoluble composition comprising particles of a water soluble compound capable of forming channels in the water insoluble composition allowing influx of water into the solid oral dosage form and diffusion of Compound (I) and/or the pharmaceutically acceptable salt thereof into the intestine.

6. The solid oral dosage form according to claim 1 or claim 2, wherein the subcoat (C) is a water insoluble composition comprising particles of a water soluble compound capable of

forming channels that are impermeable to Compound (I) and/or the pharmaceutically acceptable salt thereof, but which allow entry of water and swelling and rupturing of the subcoat, causing release of Compound (I) and/or the pharmaceutically acceptable salt thereof.

7. The solid oral dosage form according to any one of claims 1 to 6, wherein:

(a) the aqueous solution is a simulated intestinal fluid at a pH from about 6.4 to 7.4; and/or

(b) the solid oral dosage form comprises a pharmaceutically acceptable acid salt of Compound (I); and/or

(c) the core material (A) further comprises a pharmaceutically acceptable acid in an amount sufficient to form an acidic aqueous solution within the solid oral dosage form prior to the release of Compound (I) and/or the pharmaceutically acceptable salt thereof from the solid oral dosage form; and/or

(d) the core material (A) further comprises a surfactant which is present at a concentration above its critical micelle concentration upon disintegration in about 50 mL of aqueous media; and/or

(e) the mean particle size of Compound (I) and/or the pharmaceutically acceptable salt thereof is from about 0.3 micron to about 100 microns.

8. The solid oral dosage form according to any one of claims 1 to 7, wherein the enteric coating (B):

(a) is from about 10% to about 150% of the weight of the core material; and/or

(b) is from about 5 to about 500 microns thick; and/or

(c) is selected from polymerized gelatin, shellac, methacrylic acid copolymer type CNF, cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose proprionate phthalate, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypropyl methylcellulose succinate, carboxymethyl ethylcellulose (CMEC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and

(meth)acrylic acid polymers and copolymers, wherein said polymers are made from one monomer and said copolymers are made from two or more monomers, wherein said monomers are selected from methyl acrylate, ethyl acrylate, methyl methacrylate and ethyl methacrylate, preferably wherein the enteric coating comprises a poly(meth)acrylate polymer; and/or

(d) comprises a cellulose derivative, preferably wherein the cellulose derivative is selected from methylcellulose, cellulose acetate phthalate, hydroxymethyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose succinate (HPMCS), and hydroxymethyl cellulose acetate succinate (HPMCAS); and/or

(e) comprises a polyvinyl acetate phthalate (PVAP) polymer.

9. The solid oral dosage form according to any one of claims 1 to 8, wherein the pharmaceutically acceptable excipient (D) is independently selected from binders, surfactants, diluents, buffers, antiadherents, glidants, disintegrants, antioxidants, antifoaming agents, fillers, flavors, colors, lubricants, sorbents, preservatives, plasticizers, and sweeteners.

10. The solid oral dosage form according to any one of claims 1 to 9, wherein Compound (I) is an (E) and (Z) mixture of a mixture of (R) and (S) isomers of 2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)-pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile.

11. The solid oral dosage form according to any one of claims 1 to 9, wherein Compound (I) is an (E) and (Z) mixture of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)-pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile.

12. The solid oral dosage form according to any one of claims 1 to 11, wherein at least about 85% by weight of Compound (I) and/or the pharmaceutically acceptable salt thereof is the (E) isomer.

13. The solid oral dosage form according to any one of claims 1 to 12, wherein Compound (I) and/or the pharmaceutically acceptable salt thereof is a substantially pure amorphous form.

14. Use of the solid oral dosage for according to any one of claims 1 to 13 in the manufacture of a medicament for treating a disease treatable by the inhibition of BTK in a patient in recognized need thereof, wherein a therapeutically effective amount of Compound (I) and/or the pharmaceutically acceptable salt thereof is to be administered to the patient.

15. The use according to claim 14, wherein the disease is selected from an autoimmune disease, cancer, and an inflammatory disease, preferably a leukemia or lymphoma, and further optionally wherein the leukemia is selected from chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), multiple myeloma, mantle cell lymphoma, and B-cell non-Hodgkin lymphoma.