FORMULATIONS OF A SOMATOSTATIN MODULATOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of U.S. Provisional Patent Application No. 63/076,024, filed on September 9, 2020, which is incoporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are pharmaceutical compositions and medicaments comprising a somatostatin modulator, methods of making such pharmaceutical compositions and medicaments and methods of using such pharmaceutical compositions and medicaments in the treatment of conditions, diseases, or disorders that would benefit from modulating somatostatin activity.

BACKGROUND OF THE INVENTION

[0003] Somatostatin is a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G-protein-coupled somatostatin receptors and inhibition of the release of numerous secondary hormones. Six subtype somatostatin receptor proteins have been identified (SSTR1, SSTR2a, SSTR2b, SSTR3, SSTR4, SSTR5) and are encoded by five different somatostatin receptor genes. Modulation of a particular subtype somatostatin receptor, or combination thereof, is attractive for the treatment of conditions, diseases, or disorders that would benefit from modulating somatostatin activity.

SUMMARY ~~OF THE INVENTION~~

[0003a] In an aspect of the present disclosure, there is provided a spray-dried solid dispersion comprising:

(a) 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt thereof; and

(b) a pharmaceutically acceptable polymer;

wherein 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt thereof, is dispersed in a polymer matrix formed from the pharmaceutically acceptable polymer.

[0003b] In another aspect of the present disclosure, there is provided a tablet comprising:

the spray-dried solid dispersion of any one of claims 1-5;

one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more lubricants, one or more glidants; and

optionally one or more film coating agents.

[0003c] In a further aspect of the present disclosure, there is provided a tablet comprising:

the spray-dried solid dispersion disclosed herein;

one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more disintegrant aid, one or more lubricants, one or more glidants; and

optionally one or more film coating agents.

[0003d] In another aspect of the present disclosure, there is provided a use of the tablet disclosed herein in the manufacture of a medicament for treating acromegaly or neuroendocrine tumors, or both, in a human, wherein one or more of the tablets are to be orally administered once daily to the human with acromegaly or neuroendocrine tumors.

[0003e] In a further aspect of the present di sclosure, there is provided a use of the spray-dried solid dispersion disclosed herein, in the manufacture of a medicament for the treatment of acromegaly or neuroendocrine tumors, or both, in a human.

[0003f] In another aspect of the present disclosure, there is provided a tablet disclosed herein, or a spray-dried solid dispersion disclosed herein, for use in therapy.

[0004] In one ~~aspect~~example, provided herein is a spray-dried solid dispersion comprising: (a) 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof; and (b) a pharmaceutically acceptable polymer; wherein 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof, is dispersed in a polymer matrix formed from the pharmaceutically acceptable polymer. In some ~~embodiment~~examples, the pharmaceutically acceptable polymer has a high glass transition temperature (Tg). In some ~~embodiment~~examples, the pharmaceutically acceptable polymer comprises polymers of: cellulose optionally functionalized with any combination of alkyl ethers, alkyl esters, phthalate esters; vinyl alcohol; vinyl acetate; propylene glycol; pyrrolidone; vinylpyrrolidone, oxyethylene; oxypropylene; methacrylic acid; methyl methacrylate; ethylene glycol; ethylene glycol glycerides; ethylene oxide; propylene oxide; 2-ethyl-2-oxazoline; maleic acid; methyl vinyl ether; vinyl caprolactam; or combinations thereof.

[0005] In some ~~embodiment~~examples, the pharmaceutically acceptable polymer is hydroxypropyl methylcellulose (HPMC), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropyl cellulose (HPC), methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, hydroxyethyl ethyl cellulose, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone polyvinyl acetate copolymers (PVP/VA), polyethylene polyvinyl alcohol copolymers, polyoxyethylene-polyoxypropylene block copolymers, cellulose acetate phthalate (CAP), hydroxypropyl methyl-cellulose phthalate (HPMCP), co-polymerc of methacrylic acid and methyl methacrylate, polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol, hydroxypropylcellulose, copolymers of ethylene oxide and propylene oxide blocks, poly(2-ethyl-2-oxazoline), poly(maleic acid/methyl vinyl ether), polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, ethylene oxide/propylene oxide tetra functional block copolymer, d-alpha tocopheryl polyethylene glycol 1000 succinate, or combinations thereof. In some ~~embodiment~~examples, the pharmaceutically acceptable polymer is hydroxypropyl methyl cellulose acetate succinate (HPMCAS), or polyvinylpyrrolidone polyvinyl acetate copolymers (PVP/VA). In some ~~embodiment~~examples, the pharmaceutically acceptable polymer is hydroxypropyl methyl cellulose acetate succinate grade M (HPMCAS-M). In some ~~embodiment~~examples, the pharmaceutically acceptable polymer is polyvinylpyrrolidone polyvinyl acetate copolymers in a 6:4 ratio (PVP/VA 64).

[0006] In some ~~embodiment~~examples, the weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof, to the pharmaceutically acceptable polymer is from about 1:10 to about 10:1. In some ~~embodiment~~examples, the weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof, to the pharmaceutically acceptable polymer is from about 1:1 to about 1:10. In some ~~embodiment~~examples, the weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof, to the pharmaceutically acceptable polymer is from about 1:4 to about 1:6. In some ~~embodiment~~examples, the weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof, to the pharmaceutically acceptable polymer is from about 1:1.5 to about 1:6.

[0007] In some ~~embodiment~~examples, the spray-dried solid dispersion comprises at least about 5% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-

benzonitrile, or a pharmaceutically acceptable salt or solvate thereof. In some ~~embodiment~~examples, the spray-dried solid dispersion comprises at least about 10% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof. In some ~~embodiment~~examples, the spray-dried solid dispersion comprises about 15% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof.

[0008] In some ~~embodiment~~examples, the spray-dried solid dispersion further comprises a non-aqueous solvent. In some ~~embodiment~~examples, the non-aqueous solvent is selected from the group consisting of tert-butanol, n-propanol, n-butanol, isopropanol, ethanol, methanol, acetone, ethyl acetate, acetonitrile, methyl ethyl ketone, methyl isobutyl ketone, methyl acetate, and mixtures thereof. In some ~~embodiment~~examples, the non-aqueous solvent is selected from the group consisting of methanol, acetone, and mixtures thereof. In some ~~embodiment~~examples, the non-aqueous solvent is methanol.

[0009] In some ~~embodiment~~examples, 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof, is substantially amorphous.

[0010] In some ~~embodiment~~examples, 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof, is 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof.

[0011] In another ~~aspect~~example, provided herein is a tablet comprising: the spray-dried solid dispersion described herein; one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more lubricants, one or more glidants; and optionally one or more film coating agents.

[0012] In another ~~aspect~~example, provided herein is a tablet comprising: 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer; one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more lubricants, one or more glidants; and optionally one or more film coating agents. In some ~~embodiment~~examples, 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer is a spray-dried solid dispersion described herein. In some ~~embodiment~~examples, the one or more pharmaceutical acceptable ingredients comprise microcrystalline cellulose, mannitol, crospovidone, colloidal

silicon dioxide, and magnesium stearate. In some ~~embodiment~~examples, the one or more pharmaceutical acceptable ingredients comprise microcrystalline cellulose, mannitol, pregelatinized starch croscarmellose sodium crospovidone, sodium chloride, 1:1 sodium chloride:potassium chloride, colloidal silicon dioxide, and magnesium stearate.

[0013] In some ~~embodiment~~examples, the tablet comprises about 2% by weight to about 20% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof. In some ~~embodiment~~examples, the tablet comprises about 2% by weight to about 15% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof. In some ~~embodiment~~examples, the tablet comprises about 2% by weight, about 3% by weight, about 4% by weight, about 5% by weight, about 6% by weight, about 7% by weight, about 8% by weight, about 9% by weight, about 10% by weight, about 11% by weight, about 12% by weight, about 13% by weight, about 14% by weight, or about 15% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof. In some ~~embodiment~~examples, the tablet comprises about 10% by weight to about 30% by weight of the polymer matrix formed from the pharmaceutically acceptable polymer. In some ~~embodiment~~examples, the tablet comprises about 20% by weight to about 35% by weight of the polymer matrix formed from the pharmaceutically acceptable polymer.

[0014] In some ~~embodiment~~examples, the tablet comprises about 2% by weight to about 10% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, dispersed in about 10% by weight to about 30% by weight of a polymer matrix formed from a pharmaceutically acceptable polymer; about 40% by weight to about 80% by weight of one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more lubricants, one or more glidants; and optionally less than about 5% by weight of one or more film coating agents.

[0015] In some ~~embodiment~~examples, the tablet comprises: about 2% by weight to about 10% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, dispersed in about 10% by weight to about 35% by weight of a polymer matrix formed from a pharmaceutically acceptable polymer; about 40% by weight to about 80% by weight of one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more lubricants, one or more glidants; and optionally less than about 5% by weight of one or more film coating agents.

[0016] In some ~~embodiment~~examples, the tablet comprises: about 20% by weight to about 40% of a spray dried dispersion of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer; about 60% by weight to about 80% by weight of one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more disintegrant aids, one or more lubricants, one or more glidants; and optionally less than about 5% by weight of one or more film coating agents.

[0017] In some ~~embodiment~~examples, the spray dried dispersion comprises an about 15/85 to about 35/65 ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof to a polymer matrix of hydroxypropyl methyl cellulose acetate succinate (HPMCAS), or polyvinylpyrrolidone polyvinyl acetate copolymers (PVP/VA).

[0018] In some ~~embodiment~~examples, the tablet comprises: about 20% by weight to about 35% of a spray dried dispersion of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer; wherein the spray dried dispersion comprises an about 15/85 to about 35/65 ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof to a polymer matrix of hydroxypropyl methyl cellulose acetate succinate (HPMCAS), or polyvinylpyrrolidone polyvinyl acetate copolymers (PVP/VA); about 60% by weight to about 80% by weight of one or more pharmaceutical acceptable ingredients selected from the group consisting of microcrystalline cellulose, mannitol, pregelatinized starch, croscarmellose sodium, crospovidone, sodium chloride, 1:1 sodium chloride:potassium chloride, silicon dioxide, and magnesium stearate; optionally less than about 5% by weight of one or more film coating agents.

[0019] In some ~~embodiment~~examples, the tablet comprises: about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, or about 35% by weight of a spray dried dispersion of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer; wherein the spray dried dispersion comprises an about 15/85 or about 35/65 ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof to a polymer matrix of hydroxypropyl methyl cellulose acetate succinate (HPMCAS), or polyvinylpyrrolidone polyvinyl

acetate copolymers (PVP/VA); about 60% by weight to about 80% by weight of one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more disintegrant aids, one or more lubricants, one or more glidants; and optionally less than about 5% by weight of one or more film coating agents.

[0020] In some ~~embodiment~~examples, the tablet comprises: about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, or about 35% by weight of a spray dried dispersion of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer; wherein the spray dried dispersion comprises an about 15/85 or about 35/65 ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof to a polymer matrix of hydroxypropyl methyl cellulose acetate succinate (HPMCAS), or polyvinylpyrrolidone polyvinyl acetate copolymers (PVP/VA); about 60% by weight to about 80% by weight of one or more pharmaceutical acceptable ingredients selected from the group consisting of microcrystalline cellulose, mannitol, pregelatinized starch, croscarmellose sodium, crospovidone, sodium chloride, 1:1 sodium chloride:potassium chloride, silicon dioxide, and magnesium stearate; optionally less than about 5% by weight of one or more film coating agents.

[0021] In some ~~embodiment~~examples, the tablet comprises about 5 mg, about 10 mg, about 20 mg, about 40 mg, about 60 mg or about 80 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof. In some ~~embodiment~~examples, the tablet comprises about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, or about 80 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof.

[0022] In some ~~embodiment~~examples, the tablet comprises about 10 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof. In some ~~embodiment~~examples, the tablet comprises about 20 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof. In some ~~embodiment~~examples, the tablet comprises about 30 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof. In some ~~embodiment~~examples, the tablet comprises about 40 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof. In some ~~embodiment~~examples, the tablet comprises about 50 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate

thereof. In some ~~embodiment~~examples, the tablet comprises about 60 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof.

[0023] In one ~~aspect~~example, described herein is a method of treating acromegaly or neuroendocrine tumors, or both, in a human comprising orally administering to the human with acromegaly or neuroendocrine tumors any one of the spray-dired dispersion tablets described herein.

[0024] In some ~~embodiment~~examples, the tablet is administered once daily. In some ~~embodiment~~examples, the tablet is administered at least 30 minutes before a meal. In some ~~embodiment~~examples, the tablet is administered at least 60 minutes before a meal. In some ~~embodiment~~examples, the tablet is administered with a glass of water on an empty stomach at least 30 minutes before a meal. In some ~~embodiment~~examples, the bioavailability of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, from the tablet is not substatntially affected by the coadministration of proton pump inhibitors, histamine H2-receptor antagonists, or antacids.

[0025] Other features and advantages of the compositions, compounds, and methods described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific ~~embodiment~~examples, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] **Figure 1.** Illustrates the observed dose proportionality in humans administered the HMG capsule formulation or the SDD tablet formulation of Compound A-HCl.

[0027] **Figure 2.** Illustrates the performance of the HMG capsule formulation and the SDD tablet formulation of Compound A-HCl in dogs with or without pentagastrin pretreatment.

DETAILED DESCRIPTION OF THE INVENTION

[0028] Somatostatin (SST), also known as somatotropin release inhibiting factor (SRIF) was initially isolated as a 14-amino acid peptide from ovine hypothalamii (Brazeau *et al.*, *Science* 179, 77-79, 1973). An *N*-terminal extended 28-amino acid peptide with similar biological activity to 14-amino acid somatostatin was subsequently isolated (Pradayrol *et, al.*, *FEBS Letters*, 109, 55-58, 1980; Esch *et al.*, *Proc. Natl. Acad. Sci. U S A*, 77, 6827–6831, 1980). SST is a regulatory peptide produced by several cell types in response to other neuropeptides, neurotransmitters, hormones, cytokines, and growth factors. SST acts through both endocrine

CLAIMS

WHAT IS CLAIMED IS:

1. A spray-dried solid dispersion comprising:

(a) 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt ~~or solvate~~ thereof; and

(b) a pharmaceutically acceptable polymer;

wherein 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, is dispersed in a polymer matrix formed from the pharmaceutically acceptable polymer.

~~2. The spray-dried solid dispersion of claim 1, wherein:~~

~~the pharmaceutically acceptable polymer has a high glass transition temperature (Tg).~~

~~3. The spray-dried solid dispersion of claim 1 or claim 2, wherein:~~

~~the pharmaceutically acceptable polymer comprises polymers of: cellulose optionally functionalized with any combination of alkyl ethers, alkyl esters, phthalate esters; vinyl alcohol; vinyl acetate; propylene glycol; pyrrolidone; vinylpyrrolidone, oxyethylene; oxypropylene; methacrylic acid; methyl methacrylate; ethylene glycol; ethylene glycol glycerides; ethylene oxide; propylene oxide; 2-ethyl-2-oxazoline; maleic acid; methyl vinyl ether; vinyl caprolactam; or combinations thereof.~~

~~4.~~2. The spray-dried solid dispersion of claim 1 ~~or claim 2~~, wherein:

the pharmaceutically acceptable polymer is hydroxypropyl methylcellulose (HPMC), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropyl cellulose (HPC), methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, hydroxyethyl ethyl cellulose, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone polyvinyl acetate copolymers (PVP/VA), polyethylene polyvinyl alcohol copolymers, polyoxyethylene-polyoxypropylene block copolymers, cellulose acetate phthalate (CAP), hydroxypropyl methyl-cellulose phthalate (HPMCP), co-polymers~~polymerc~~ of methacrylic acid and methyl methacrylate, polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol, hydroxypropylcellulose, copolymers of ethylene oxide and propylene oxide blocks, poly(2-ethyl-2-oxazoline), poly(maleic acid/methyl vinyl ether), polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, ethylene oxide/propylene oxide tetra functional

block copolymer, d-alpha tocopheryl polyethylene glycol 1000 succinate, or combinations thereof; and

the weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt thereof, to the pharmaceutically acceptable polymer is from 1:10 to 10:1, from 1:1 to 1:10, from 1:4 to 1:6, or from 1:1.5 to 1:6.

~~5.~~3. The spray-dried solid dispersion of claim 1 ~~or claim 2~~, wherein:

the pharmaceutically acceptable polymer is hydroxypropyl methyl cellulose acetate succinate (HPMCAS), or polyvinylpyrrolidone polyvinyl acetate copolymers (PVP/VA); and

the weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt thereof, to the pharmaceutically acceptable polymer is from 1:10 to 10:1, from 1:1 to 1:10, from 1:4 to 1:6, or from 1:1.5 to 1:6.

~~6.~~4. The spray-dried solid dispersion of claim 1 ~~or claim 2~~, wherein:

the pharmaceutically acceptable polymer is hydroxypropyl methyl cellulose acetate succinate grade M (HPMCAS-M); or

the pharmaceutically acceptable polymer is polyvinylpyrrolidone polyvinyl acetate copolymers in a 6:4 ratio (PVP/VA 64); and

the weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt thereof, to the pharmaceutically acceptable polymer is from 1:10 to 10:1, from 1:1 to 1:10, from 1:4 to 1:6, or from 1:1.5 to 1:6.

~~7. The spray-dried solid dispersion of claim 1 or claim 2, wherein:~~

~~the pharmaceutically acceptable polymer is polyvinylpyrrolidone polyvinyl acetate copolymers in a 6:4 ratio (PVP/VA 64).~~

~~8. The spray-dried solid dispersion of any one of claims 1-7, wherein:~~

~~the weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof, to the pharmaceutically acceptable polymer is from about 1:10 to about 10:1.~~

~~9. The spray-dried solid dispersion of any one of claims 1-7, wherein:~~

~~the weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof, to the pharmaceutically acceptable polymer is from about 1:1 to about 1:10.~~

10. The spray-dried solid dispersion of any one of claims 1-7, wherein:
the weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof, to the pharmaceutically acceptable polymer is from about 1:4 to about 1:6.

11. The spray-dried solid dispersion of any one of claims 1-7, wherein:
the weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof, to the pharmaceutically acceptable polymer is from about 1:1.5 to about 1:6.

12. The spray-dried solid dispersion of any one of claims 1-7, wherein:
the spray-dried solid dispersion comprises at least about 5% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof.

13. The spray-dried solid dispersion of any one of claims 1-7, wherein:
the spray-dried solid dispersion comprises at least about 10% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof.

14. The spray-dried solid dispersion of any one of claims 1-7, wherein:
the spray-dried solid dispersion comprises about 15% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof.

15. The spray-dried solid dispersion of any one of claims 1-7, wherein:
the spray-dried solid dispersion comprises about 35% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof.

16. The spray-dried solid dispersion of any one of claims 1-15, further comprising a non-aqueous solvent.

17. The spray-dried solid dispersion of claim 16, wherein the non-aqueous solvent is selected from the group consisting of tert-butanol, n-propanol, n-butanol, isopropanol, ethanol, methanol, acetone, ethyl acetate, acetonitrile, methyl ethyl ketone, methyl isobutyl ketone, methyl acetate, and mixtures thereof.

18. The spray-dried solid dispersion of claim 16 or claim 17, wherein the non-aqueous solvent is selected from the group consisting of methanol, acetone, and mixtures thereof.

19. The spray-dried solid dispersion of any one of claims 16-18, wherein the non-aqueous solvent is methanol.

~~20. The spray-dried solid dispersion of any one of claims 1-19, wherein 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt or solvate thereof, is substantially amorphous.~~

~~21.~~5. The spray-dried solid dispersion of any one of claims 1-~~20~~ 5 wherein 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile, or a pharmaceutically acceptable salt ~~or solvate~~ thereof, is 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride~~, or solvate thereof~~.

6. The spray-dried solid dispersion of claim 1, wherein the spray dried dispersion comprises 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride dispersed in a polymer matrix formed from polyvinylpyrrolidone polyvinyl acetate copolymers in a 6:4 ratio (PVP/VA 64); and wherein the spray dried dispersion comprises a 15/85 weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride to PVP/VA 64. wherein the 15/85 weight ratio is based on the weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile.

~~22.~~7. A tablet comprising:

the spray-dried solid dispersion of any one of claims 1-~~21~~5;

one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more lubricants, one or more glidants; and

optionally one or more film coating agents.

~~23.~~8. A tablet comprising:

the spray-dried solid dispersion of claim 6~~3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer~~;

one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more disintegrant aid, one or more lubricants, one or more glidants; and

optionally one or more film coating agents.

~~24. The tablet of claim 23, wherein the 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof,~~

~~dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer is a spray-dried solid dispersion.~~

~~25.~~9. The tablet of any one of claims 7-8~~22-24~~, wherein:

the one or more pharmaceutical acceptable ingredients comprise microcrystalline cellulose, mannitol, pregelatinized starch croscarmellose sodium crospovidone, sodium chloride, 1:1 sodium chloride:potassium chloride, colloidal silicon dioxide, and magnesium stearate.

~~26. The tablet of any one of claims 22-25, wherein the tablet comprises:~~

~~about 2% by weight to about 20% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof.~~

~~27.~~10. The tablet of any one of claims ~~22~~7-~~25~~9, wherein ~~the tablet comprises~~:

the tablet comprises about 2% by weight, about 3% by weight, about 4% by weight, about 5% by weight, about 6% by weight, about 7% by weight, about 8% by weight, about 9% by weight, about 10% by weight, about 11% by weight, about 12% by weight, about 13% by weight, about 14% by weight, or about 15% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride~~, or solvate thereof~~.

~~28. The tablet of any one of claims 23-27, wherein the tablet comprises about 10% by weight to about 35% by weight of the polymer matrix formed from the pharmaceutically acceptable polymer.~~

~~29. The tablet of any one of claims 23-28, wherein the tablet comprises:~~

~~about 2% by weight to about 15% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer, wherein the dispersed 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, in the polymer matrix is about about 20% by weight to about 35% by weight of the tablet;~~

~~about 40% by weight to about 80% by weight of one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more lubricants, one or more glidants; and~~

~~optionally less than about 5% by weight of one or more film coating agents.~~

~~30.~~11. The tablet of any one of claims ~~23~~7-~~24~~8, wherein the tablet comprises:

about 20% by weight to about 40% of ~~a~~ the spray dried dispersion of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride~~, or solvate thereof,~~ dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer;

about 60% by weight to about 80% by weight of one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more disintegrant aids, one or more lubricants, one or more glidants; and

optionally less than about 5% by weight of one or more film coating agents.

~~31. The tablet of claim 30, wherein:~~

~~the spray dried dispersion comprises an about 15/85 to about 35/65 ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof to a polymer matrix of hydroxypropyl methyl cellulose acetate succinate (HPMCAS), or polyvinylpyrrolidone polyvinyl acetate copolymers (PVP/VA).~~

~~32.~~12. The tablet of claim ~~23~~7, wherein the tablet comprises:

~~about~~ 20% by weight to ~~about~~ 35% of by weight a spray dried dispersion of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride~~, or solvate thereof,~~ dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer;

wherein the spray dried dispersion comprises a~~an about~~ 15/85 to ~~about~~ 35/65 weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride~~, or solvate thereof~~ to a polymer matrix of hydroxypropyl methyl cellulose acetate succinate (HPMCAS), or polyvinylpyrrolidone polyvinyl acetate copolymers (PVP/VA); wherein the 15/85 to 35/65 weight ratio is based on the weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile;

about 60% by weight to about 80% by weight of one or more pharmaceutical acceptable ingredients selected from the group consisting of microcrystalline cellulose, mannitol, pregelatinized starch, croscarmellose sodium, crospovidone, sodium chloride, 1:1 sodium chloride:potassium chloride, silicon dioxide, and magnesium stearate;

optionally less than about 5% by weight of one or more film coating agents.

~~33. The tablet of any one of claims 23-32, wherein the tablet comprises:~~

~~about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, or about 35% by weight of a spray dried dispersion of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer;~~

~~wherein the spray dried dispersion comprises an about 15/85 or about 35/65 ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof to a polymer matrix of hydroxypropyl methyl cellulose acetate succinate (HPMCAS), or polyvinylpyrrolidone polyvinyl acetate copolymers (PVP/VA);~~

~~about 60% by weight to about 80% by weight of one or more pharmaceutical acceptable ingredients selected from the group consisting of one or more diluents, one or more disintegrants, one or more disintegrant aids, one or more lubricants, one or more glidants; and~~

~~optionally less than about 5% by weight of one or more film coating agents.~~

~~34. The tablet of any one of claims 23-32, wherein the tablet comprises:~~

~~about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, or about 35% by weight of a spray dried dispersion of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer;~~

~~wherein the spray dried dispersion comprises an about 15/85 or about 35/65 ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof to a polymer matrix of hydroxypropyl methyl cellulose acetate succinate (HPMCAS), or polyvinylpyrrolidone polyvinyl acetate copolymers (PVP/VA);~~

~~about 60% by weight to about 80% by weight of one or more pharmaceutical acceptable ingredients selected from the group consisting of microcrystalline cellulose, mannitol, pregelatinized starch, croscarmellose sodium, crospovidone, sodium chloride, 1:1 sodium chloride:potassium chloride, silicon dioxide, and magnesium stearate;~~

~~optionally less than about 5% by weight of one or more film coating agents.~~

~~35.~~13. The tablet of any one of claims ~~22~~7-~~34~~12, wherein:

the tablet comprises about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, or about 80 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride~~, or solvate thereof~~.

~~36. The tablet of any one of claims 22-35, wherein:~~

~~the tablet comprises about 10 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof.~~

~~37. The tablet of any one of claims 22-35, wherein:~~

~~the tablet comprises about 20 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof.~~

~~38. The tablet of any one of claims 22-35, wherein:~~

~~the tablet comprises about 30 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof.~~

~~39. The tablet of any one of claims 22-35, wherein:~~

~~the tablet comprises about 40 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof.~~

~~40. The tablet of any one of claims 22-35, wherein:~~

~~the tablet comprises about 50 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof.~~

~~41. The tablet of any one of claims 22-35, wherein:~~

~~the tablet comprises about 60 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof.~~

14. The tablet of claim 8, wherein the tablet comprises:

20% by weight to 35% of the spray-dried solid dispersion of claim 6;

between 50% and 65% by weight of one or more diluents;

between 10% and 20% by weight of one or more disintegrants;

between 0.1% and 1% by weight of one or more lubricants;

one or more glidants; and

optionally less than about 5% by weight of one or more film coating agents;

wherein the amount of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride in the tablet is between 10 mg and 40 mg.

15. The tablet of claim 14, wherein the tablet comprises:

between 50% and 65% by weight of diluents, wherein the diluents are microcrystalline cellulose and mannitol;

between 10% and 20% by weight of crospovidone as a disintegrant;
between 0.1% and 1% by weight of magnesium stearate as a lubricant;
colloidal silicon dioxide as a glidant; and
less than about 5% by weight of one or more film coating agents.

~~42.~~16. Use of the tablet of any one of claims 7-15 in the manufacture of a medicament for ~~A method of~~ treating acromegaly or neuroendocrine tumors, or both, in a human, wherein one or more of the tablets are to be orally administered once daily ~~comprising orally administering~~ to the human with acromegaly or neuroendocrine tumors ~~the tablet of any one of claims 22-41~~.

17. The use of claim 16, wherein the one or more tablets are to be administered at least 30 minutes or at least 60 minutes before a meal.

18. Use of the spray-dried solid dispersion of any one of claims 1-6, in the manufacture of a medicament for the treatment of acromegaly or neuroendocrine tumors, or both, in a human.

19. A tablet of any one of claims 7-15, or a spray-dried solid dispersion of any one of claims 1-6, for use in therapy.

~~43. The method of claim 42, wherein: the tablet is administered once daily.~~

~~44. The method of claim 42 or claim 43, wherein: the tablet is administered at least 30 minutes before a meal.~~

~~45. The method of claim 43 or claim 44, wherein: the tablet is administered at least 60 minutes before a meal.~~

~~46. The method of any one of claims 42-45, wherein: the tablet is administered with a glass of water on an empty stomach at least 30 minutes before a meal.~~

~~47. The method of any one of claims 42-46, wherein: the bioavailability of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, or solvate thereof, is not substatntially affected by the coadministration of proton pump inhibitors, histamine H2-receptor antagonists, or antacids.~~

~~48. The method of any one of claims 42-47, wherein: the tablet is coadministered with a proton pump inhibitor, histamine H2-receptor antagonist, or antacid.~~