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

[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; and

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, ora pharmaceutically acceptable salt thereof, to the pharmaceutically acceptable polymer is from 1:10 to 10:1.

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

the spray-dried solid dispersion as 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.

[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 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 examples, the pharmaceutically acceptable polymer has a high glass transition temperature (Tg). In some 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.

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 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; and

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.

2. The spray-dried solid dispersion of claim 1, 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 thereof, to the pharmaceutically acceptable polymer is from 1:1 to 1:10.

3. The spray-dried solid dispersion of claim 1, 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 thereof, to the pharmaceutically acceptable polymer is from 1:4 to 1:6.

4. The spray-dried solid dispersion of any one of claims 1-3 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 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride.

5. The spray-dried solid dispersion of claim 4, 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 thereof, to the pharmaceutically acceptable polymer is from 1:5 to 1:6.

6. The spray-dried solid dispersion of any one of claims 1-5, wherein the pharmaceutically acceptable polymer is HPMCAS.

7. The spray-dried solid dispersion of claim 6, wherein the HPMCAS comprises 7-11% by weight acetate, 10-14% by weight succinate, 21-25% by weight methoxy, and 5-9% by weight hydroxypropyloxy.

8. The spray-dried solid dispersion of any one of claims 1-5, wherein the pharmaceutically acceptable polymer is PVP/VA.

9. The spray-dried solid dispersion of claim 8, wherein the pharmaceutically acceptable polymer is polyvinylpyrrolidone polyvinyl acetate copolymers in a 6:4 ratio (PVP/VA 64).

10. The spray-dried solid dispersion of claim 9, 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 free base.

11. A tablet comprising:

the spray-dried solid dispersion of any one of claims 1-10;

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.

12. The tablet of claim 11, 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.

13. The tablet of claim 11 or claim 12, wherein:

the tablet comprises 2% by weight, 3% by weight, 4% by weight, 5% by weight, 6% by weight, 7% by weight, 8% by weight, 9% by weight, 10% by weight, 11% by weight, 12% by weight, 13% by weight, 14% by weight, or 15% by weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, wherein the % amounts are calculated based on the weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile free base.

14. The tablet of any one of claims 11 to 13, wherein the tablet comprises:

20% by weight to 40% of the spray dried dispersion of 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 a pharmaceutically acceptable polymer, wherein the % amounts are calculated based on the weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile free base;

60% by weight to 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 5% by weight of one or more film coating agents.

15. The tablet of claim 11, wherein the tablet comprises:

20% by weight to 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 dispersed in a polymer matrix formed from a pharmaceutically acceptable polymer, wherein the % amounts are calculated based on the weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile free base;

wherein the spray dried dispersion comprises a 15/85 to 35/65 weight ratio of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride 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;

60% by weight to 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 5% by weight of one or more film coating agents.

16. The tablet of any one of claims 11-15, wherein:

the tablet comprises 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, or 80 mg of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile monohydrochloride, wherein the amounts are calculated based on the weight of 3-[4-(4-amino-piperidin-1-yl)-3-(3,5-difluoro-phenyl)-quinolin-6-yl]-2-hydroxy-benzonitrile free base.

17. Use of the tablet of any one of claims 11-16 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.

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

19. Use of the spray-dried solid dispersion of any one of claims 1-10, in the manufacture of a medicament for the treatment of acromegaly or neuroendocrine tumors, or both, in a human.