PHARMACEUTICAL COMPOSITION OF SEPIAPTERIN

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Provisional Application Number 63/250,167, filed September 29, 2021, the contents of which are incorporated by reference herein.

FIELD OF THE INVENTION

The invention generally relates to a pharmaceutical composition of sepiapterin, e.g., that has improved processibility and stability relative to alternative pharmaceutical compositions of sepiapterin, and methods of making and using the same.

BACKGROUND

Multiple disorders are associated with deficient or low tetrahydrobiopterin (BH_4) concentrations (e.g., Primary Tetrahydrobiopterin Deficiency, Phenylketonuria, and diabetic gastroparesis). These disorders may result in impaired hydroxylation of phenylalanine (Phe) to tyrosine (Tyr) resulting in hyperphenylalaninemia (HPA) or impaired hydroxylation of Tyr or tryptophan (Trp) or impaired synthesis of nitric oxide (NO) resulting in deficient neurotransmitter production (e.g., dopamine, serotonin, and NO).

Sepiapterin is a naturally occurring small molecule that serves as a substrate for de novo synthesis of BH_4 via the pterin salvage pathway making sepiapterin a naturally occurring precursor for BH_4. BH_4 is an essential cofactor for enzymes including PAH, tyrosine hydroxylase, tryptophan hydroxylase, fatty acid glyceryl ether oxygenase, and NO synthase.

Treatment with synthetic BH_4 (sapropterin dihydrochloride) is limited by poor bioavailability. Uptake of orally administered synthetic BH_4 has been shown to be hampered by rapid oxidation to 7,8-dihydrobiopterin (BH_2) and poor penetration into cells, resulting in a very low level of incorporation. In contrast, sepiapterin provides an exogenous source of sepiapterin that is stable in plasma, actively transported into cells, and converted to intracellular BH_4 by a simple, rapid unidirectional 2 step enzymatic reduction process as part of the pterin salvage pathway.

Sepiapterin is known to degrade in the presence of moisture, oxygen, and sunlight. Furthermore, known compositions of sepiapterin suffer from poor process efficiency, flow characteristics, and stability. Thus, a need exists for new pharmaceutical compositions of sepiapterin.

SUMMARY

In one aspect, the disclosure features a solid pharmaceutical composition comprising sepiapterin, a water-soluble diluent, a water-insoluble diluent, a disintegrant, a suspending agent, a glidant, a sweetener, and a lubricant.

In some examples, the sepiapterin is crystalline, e.g., crystalline Form F or Form D. In other examples, the crystalline sepiapterin is crystalline Form A, B, C, E, or G.

In some examples, the pharmaceutical composition is a powder.

In some examples, the pharmaceutical composition includes less than 60% humidity.

In some examples, the pharmaceutical composition is packaged in a sachet.

In some examples, the pharmaceutical composition includes about 20 to 50% sepiapterin by weight, e.g., about 20 to 30% sepiapterin by weight, about 22 to 28% sepiapterin by weight, about 24 to 26% by weight. In some examples, the pharmaceutical composition includes about 25% sepiapterin by weight.

In some examples, the diluents are selected from lactose, glucose, mannitol, xylitol, maltitol, sorbitol, isomalt, cellulose (e.g., crystalline or microcrystalline), sucrose, fructose, maltose, and trehalose. In some examples, the pharmaceutical composition includes two or more diluents, e.g., selected from lactose, glucose, mannitol, xylitol, maltitol, sorbitol, isomalt, cellulose (e.g., crystalline or microcrystalline), sucrose, fructose, maltose, and trehalose. In some examples, the diluents are soluble in water. In some examples, the diluents are insoluble in water.

In some examples, the pharmaceutical composition includes about 5 to 65% water-soluble diluent by weight, e.g., about 40 to 60% water soluble diluent by weight, about 45% to 55 % water-soluble diluent by weight. In some examples, the pharmaceutical composition includes about 50% water-soluble diluent by weight.

In some examples, one water-soluble diluent is isomalt. In some examples, the pharmaceutical composition includes about 5 to 45% isomalt by weight, e.g., about 35 to 45% isomalt by weight. In some examples, the composition includes about 40% isomalt by weight.

In some examples, one water-soluble diluent is mannitol. In some examples, the pharmaceutical composition includes about 5 to 20% mannitol by weight, e.g., about 5 to 15% mannitol by weight. In some examples, the pharmaceutical composition includes about 10% mannitol by weight.

In some examples, one water-insoluble diluent is microcrystalline cellulose. In some examples, the composition includes about 15 to 39% microcrystalline cellulose by weight, e.g., about 17 to 25% microcrystalline cellulose by weight, about 19 to 23% microcrystalline cellulose by weight. In some examples, the composition includes about 21% microcrystalline cellulose by weight.

In some examples, the composition includes isomalt, mannitol, and microcrystalline cellulose.

In some examples, the disintegrant is selected from sodium starch glycolate, crospovidone, cross-linked alginic acid, crosslinked starch, crosslinked alginate sodium, carmellose, carmellose calcium, croscarmellose sodium, glycerin fatty acid ester, low-substituted sodium carboxymethyl starch, and partially pregelatinized starch. In some examples, the composition includes about 0.5 to 1.5% disintegrant by weight. In some examples, the disintegrant is croscarmellose sodium. In some examples, the pharmaceutical composition includes about 0.5 to 1.5% croscarmellose sodium by weight. In some examples, the pharmaceutical composition includes about 1% croscarmellose sodium by weight.

In some examples, the glidant is selected from silicon dioxide (e.g., colloidal), hydrated sodium sulfoaluminate, and talc. In some examples, the pharmaceutical composition includes about 0.2% to 0.6% glidant by weight. In some examples, the glidant is colloidal silicon dioxide. In some examples, the pharmaceutical composition includes about 0.2% to 0.6% colloidal silicon dioxide by weight. In some examples, the pharmaceutical composition includes about 0.4% colloidal silicon dioxide by weight.

In some examples, the sweetener is selected from sucralose, sodium saccharin, aspartame, and neutrame (with aspartame contraindicated in the treatment of hyperphenylalaninemia). In some examples, the pharmaceutical composition includes about 0.5% to 2.0% sweetener by weight. In some examples, the sweetener is sucralose. In some examples, the pharmaceutical composition includes about 0.5% to 2.0% sucralose by weight. In some examples, the pharmaceutical composition includes about 1.0% sucralose by weight.

In some examples, the lubricant is selected from glyceryl behenate, glyceryl behaptate, sodium stearyl fumarate, stearic acid, magnesium stearate, calcium stearate, sodium stearate, hydrogenated vegetable oils, colloidal silica, talc, waxes, boric acid, sodium benzoate, sodium acetate, sodium fumarate, sodium chloride, DL-leucine, polyethylene glycol, sodium oleate, sodium lauryl sulfate, and magnesium lauryl sulfate. In some examples, the pharmaceutical composition includes about 0.4% to 0.8% lubricant by weight. In some examples, the lubricant is magnesium stearate. In some examples, the pharmaceutical composition includes about 0.4% to 0.8% magnesium stearate by weight. In some examples, the composition includes about 0.6% magnesium stearate by weight.

In some examples, the suspending agent is selected from xanthan gum and hydroxyethyl cellulose. In some examples, the pharmaceutical composition includes about 0.5% to 2.0% suspending agent by weight. In some examples, the suspending agent is xanthan gum. In some examples, the pharmaceutical composition includes about 0.5% to 2% xanthan gum by weight. In some examples, the pharmaceutical composition includes about 1% xanthan gum by weight.

In one example, the pharmaceutical composition includes about 25% sepiapterin, about 21% microcrystalline cellulose, about 40% isomalt, about 10% mannitol, about 1% croscarmellose sodium, about 1% xanthan gum, about 0.4% colloidal silicon dioxide, about 1.0% sucralose, and about 0.6% magnesium stearate by weight.

In another aspect, the present disclosure relates to a method of preparing any of the foregoing pharmaceutical compositions, comprising steps of (1) sieving sepiapterin and at least one water-soluble diluent, water-insoluble diluent, disintegrant, suspending agent, glidant, and sweetener, and blending, forming a pre-blended mixture, (2) sieving a lubricant, (3) mixing the lubricant with the preblended mixture to form a lubricated preblended mixture, (4) preparing ribbons of the lubricated preblended mixture using a roller compactor, (5) milling the ribbons to form a milled formulation, (6) blending the milled formulation with a blender, thereby forming the pharmaceutical composition as defined above. In some examples, the method further includes filling the pharmaceutical composition into sachets.

In another aspect, there is provided a method of preparing a liquid formulation comprising dispersing the pharmaceutical composition as defined above in a liquid, optionally wherein the liquid is water or fruit juice.

In another example, the present disclosure relates to a method of preparing a liquid formulation including dispersing any of the foregoing pharmaceutical compositions into a liquid. In some examples, the liquid is water or fruit juice. In some examples, the liquid formulation is a suspension.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing the dynamic vapor sorption curves for the sepiapterin drug substance.

FIG. 2 is a graph showing the dynamic vapor sorption curves for a formulation of the invention.

FIG. 3 is a graph showing the dissolution profiles of formulations of sepiapterin powder for oral use.

FIG. 4 is a schematic showing the design of a Phase 1, randomized, open-label, crossover study to evaluate the relative oral bioavailability of two formulations of sepiapterin.

FIG. 5A is a graph of mean concentration of BH_4 in ng/ml in human subjects after administration of 20 mg/kg of sepiapterin from Formula A (open squares) or from Formula B (solid triangles) over time.

FIG. 5B is a graph of mean concentration of BH_4 in ng/ml in human subjects after administration of 60 mg/kg of sepiapterin from Formula A (open circles) or from Formula B (solid squares) over time.

FIG. 6A is a graph of mean concentration of BH_4 in ng/ml in human subjects after administration of 20 mg/kg of sepiapterin from Formula A (open squares) or from Formula B (solid triangles) over time, where the data has been baseline adjusted.

FIG. 6B is a graph of mean concentration of BH_4 in ng/ml in human subjects after administration of 60 mg/kg of sepiapterin from Formula A (open circles) or from Formula B (solid squares) over time, where the data has been baseline adjusted.

DETAILED DESCRIPTION OF THE INVENTION

The present inventors have discovered pharmaceutical compositions of sepiapterin comprising a water-soluble diluent, a water-insoluble diluent, a disintegrant, a suspending agent, a glidant, a sweetener, and a

lubricant. The compositions disclosed herein provide improved processibility and stability relative to alternative compositions of sepiapterin.

Compositions of sepiapterin of the present invention preferably have at least one of the following characteristics: