DELAYED RELEASE CYSTEAMINE BEAD FORMULATION, AND METHODS OF MAKING AND USING SAME

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application Serial No. 61/835,965 filed June 17, 2013, is hereby claimed, and the disclosure thereof is hereby incorporated by reference herein.

BACKGROUND

Field of the Disclosure

[0002] The disclosure relates generally to delayed release formulations of cysteamine and pharmaceutically acceptable salts thereof, and related methods of making and treatment, e.g. treatment of cystinosis and other metabolic and neurodegenerative diseases including non-alcoholic fatty liver disease (NAFLD), Huntingon's disease, Parkinson's disease, Rett Syndrome and others, use as free radical and radioprotectants, and as hepto-protectant agents. More particularly, the disclosure relates to enteric coated beads comprising cysteamine or a pharmaceutically acceptable salt thereof.

Brief Description of Related Technology

[0003] Cystinosis is a rare, autosomal recessive disease caused by intra-lysosomal accumulation of the amino acid cystine within various tissues, including the spleen, liver, lymph nodes, kidney, bone marrow, and eyes. Nephropathic cystinosis is associated with kidney failure that necessitates kidney transplantation. A specific treatment for nephropathic cystinosis is the sulfhydryl agent, cysteamine. Cysteamine has been shown to lower intracellular cystine levels, thereby reducing the rate of progression of kidney failure in children.

[0004] An enterically-coated cysteamine composition has been described, for increasing delivering of cysteamine to the small intestine and resulting in less frequent dosing compared to non enteric-coated cysteamine.

SUMMARY

[0005] The present disclosure provides a pharmaceutical dosage form including a plurality of cysteamine beads, the beads including a core particle including cysteamine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and an enteric membrane surrounding the core, wherein the plurality of beads is characterized by a distribution of particle sizes.

[0005a] In one aspect of the present disclosure, there is provided a pharmaceutical dosage form, comprising delayed-release cysteamine beads, the beads comprising

(i) a core particle comprising cysteamine or a pharmaceutically acceptable salt thereof and a binder, and

(ii) an enteric membrane surrounding the core particle, wherein the beads have a distribution of particle sizes in a range of about 0.7 mm to about 2.8 mm;

wherein the enteric membrane begins to dissolve within a pH range of about 4.5 to about 6.5;

wherein the enteric membrane is present in an amount in a range of about 25% to about 35% by weight, based on the weight of the core particles; and

wherein the pharmaceutical dosage form, upon administration in a capsule to fasted healthy normal subjects at 600 mg free cysteamine base, provides:

(a) a mean Cmax upon oral dosing in a range of 2.3±0.6 mg/L or in a range of 80% to 125% thereof; and

(b) a mean AUC (0-inf_D) upon oral dosing in a range of 0.84±0.19 min*mg/L/mg or in a range of 80% to 125% thereof.

[0006] The present disclosure also provides a pharmaceutical dosage form including a plurality of cysteamine beads, the beads including a core particle including cysteamine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and an enteric membrane surrounding the core, wherein the plurality of beads is characterized by irregular bead shapes.

[0007] The present disclosure further provides a pharmaceutical dosage form including a plurality of cysteamine beads, the beads including a core particle including cysteamine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and an enteric membrane surrounding the core, wherein the plurality of beads is characterized by a distribution of enteric membrane thicknesses.

[0008] The present disclosure also provides a method of making a pharmaceutical dosage form, including any embodiment described herein, by a method including coating a core particle including cysteamine or a pharmaceutically acceptable salt thereof and an excipient with an enteric polymer to form an enteric membrane. The method can include sorting core particles prior to enteric coating, to provide a selected core particle size distribution. The method can also include sorting enteric coated beads to provide a selected bead size distribution.

[0009] The present disclosure further provides a method for treating a patient in need of cysteamine comprising administering to the patient a dosage form described herein, including any embodiment described herein.

[0010] The present disclosure also provides dosage forms and related methods according the disclosure herein wherein the primary active component is cystamine rather than cysteamine or a pharmaceutically acceptable salt thereof.

[0011] For the compositions and methods described herein, optional features, including but not limited to components, compositional ranges thereof, substituents, conditions, and steps, are contemplated to be selected from the various aspects, embodiments, and examples provided herein.

[0012] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description. While the dosage form, method of making, and method of treatment are susceptible of embodiments in various forms, the description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the invention to the specific embodiments described herein.

What is claimed is:

1. A pharmaceutical dosage form, comprising delayed-release cysteamine beads, the beads comprising

(i) a core particle comprising cysteamine or a pharmaceutically acceptable salt thereof and a binder, and

(ii) an enteric membrane surrounding the core particle, wherein the beads have a distribution of particle sizes in a range of about 0.7 mm to about 2.8 mm;
wherein the enteric membrane begins to dissolve within a pH range of about 4.5 to about 6.5;
wherein the enteric membrane is present in an amount in a range of about 25% to about 35% by weight, based on the weight of the core particles; and
wherein the pharmaceutical dosage form, upon administration in a capsule to fasted healthy normal subjects at 600 mg free cysteamine base, provides:

(a) a mean Cmax upon oral dosing in a range of 2.3±0.6 mg/L or in a range of 80% to 125% thereof; and

(b) a mean AUC (0-inf_D) upon oral dosing in a range of 0.84±0.19 min*mg/L/mg or in a range of 80% to 125% thereof.

2. The pharmaceutical composition of claim 1, wherein the particle sizes of the beads are in a range of about 0.7 mm to about 2.5 mm.

3. The pharmaceutical dosage form of claim 1, wherein the distribution of bead sizes is characterized by at least 80% by weight of the beads having a particle size in a range of about 850 μm to about 1180 μm.

4. The pharmaceutical composition of claim 1, wherein 5% or less of the beads by weight are retained on a #12 mesh (1.68mm) screen and 10% or less by weight pass through a #20 mesh (0.84mm) screen.

5. The pharmaceutical composition of claim 1, wherein the distribution of bead sizes is characterized by less than 5% by weight of the beads being retained on a 1400 μm sieve.

6. The pharmaceutical dosage form of claim 1, wherein the distribution of bead sizes is characterized by less than 30% by weight of the beads being retained on a 1180 μm sieve.

7. The pharmaceutical dosage form of claim 1, wherein the distribution of bead sizes is characterized by less than 70% by weight of the beads being retained on a 1000 μm sieve.

8. The pharmaceutical dosage form of claim 1, wherein the distribution of bead sizes is characterized by less than 20% by weight of the beads being retained on a 850 μm sieve.

9. The pharmaceutical dosage form of claim 1, wherein the distribution of bead sizes is characterized by at least 15% by weight of the beads being retained on a 1180 μm sieve.

10. The pharmaceutical dosage form of claim 1, wherein the distribution of bead sizes is characterized by at least 50% by weight of the beads being retained on a 1000 μm sieve.

11. The pharmaceutical dosage form of claim 1, wherein the distribution of bead sizes is characterized by at least 10% by weight of the beads being retained on a 850 μm sieve.

12. The pharmaceutical dosage form of claim 1, wherein the distribution of bead sizes is characterized by a median particle size in a range of about 850 μm to about 1180 μm.

13. The pharmaceutical dosage form of claim 1, wherein the bead core particle particle further comprises a filler.

14. The pharmaceutical dosage form of claim 1, wherein the cysteamine (as free base) is present in the bead core particle in an amount of at least 10 wt.%.

15. The pharmaceutical dosage form of claim 1, wherein the cysteamine or pharmaceutically acceptable salt thereof is a pharmaceutically acceptable salt of cysteamine.

16. The pharmaceutical dosage form of claim 1, wherein 5% or less of the bead core particles by weight are retained on a #12 mesh (1.68mm) screen and 10% or less by weight pass through a #20 mesh (0.84mm) screen.

17. The pharmaceutical dosage form of claim 1, wherein the enteric-coated beads are characterized by acid resistance such that not more than 10% of the cysteamine in the beads is dissolved after a period of two hours in a 0.1N HCl solution.

18. The pharmaceutical dosage form of claim 1, wherein the enteric-coated beads are characterized by dissolution such that 80% of the cysteamine or pharmaceutically acceptable salt thereof is released within 20 minutes in a solution buffered at pH 6.8.

19. The pharmaceutical dosage form of claim 1, further comprising a capsule shell enclosing the plurality of beads.

20. The pharmaceutical dosage form of claim 1, wherein the beads provide a mean Cmax and mean AUC (0-inf_D) upon oral dosing, fasted, when administered inside a capsule shell that are bioequivalent to the mean Cmax and mean AUC (0-inf_D) upon oral dosing, fasted, when administered without a capsule shell.

21. The pharmaceutical dosage form of claim 1, wherein the enteric membrane comprises an enteric material that begins to dissolve at pH of about 5.5 in an aqueous solution.

22. The pharmaceutical dosage form of claim 1, wherein the pharmaceutical dosage form, upon administration in a capsule to fasted healthy normal subjects at 600 mg free cysteamine base, provides:

(a) a mean Cmax upon oral dosing in a range of 2.3±0.6 mg/L; and

(b) a mean AUC (0-inf_D) upon oral dosing in a range of 0.84±0.19 min*mg/L/mg.

23. The pharmaceutical dosage form of claim 1, wherein the pharmaceutical dosage form, upon administration in a capsule to fasted healthy normal subjects at 600 mg free cysteamine base, provides:

(a) a mean Cmax upon oral dosing of 2.3 mg/L or in a range of 80% to 125% thereof; and

(b) a mean AUC (0-inf_D) upon oral dosing of 0.84 min*mg/L/mg or in a range of 80% to 125% thereof.