GASTRIC RESIDENCE SYSTEMS FOR ADMINISTRATION OF RISPERIDONE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of U.S. Provisional Patent Application No. 63/139,299 filed on January 19, 2021 and U.S. Provisional Patent Application No. 63/174,497 filed on April 13, 2021. The entire contents of those applications are hereby incorporated by reference herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under R01 AI131416 awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD OF THE INVENTION

[0003] The invention relates to gastric residence systems for sustained gastric release of active agents, such as drugs, and methods of use thereof.

BACKGROUND OF THE INVENTION

[0004] Gastric residence systems are delivery systems for agents which remain in the stomach for days to weeks, or even over longer periods, during which time drugs or other agents can elute from the systems for absorption in the gastrointestinal tract. Examples of such systems are described in U.S. Patent No. 10,182,985, and in International Patent Application Nos. WO 2015/191920, WO 2015/191925, WO 2017/070612, WO 2017/100367, WO 2017/205844, and WO 2018/227147. Over the period of residence, the system releases an agent or agents, such as one or more drugs.

[0005] The current invention describes advancements in design, structure, and formulation of gastric residence systems, which provide improved control over residence time and release rate of agent.

SUMMARY

[0005a] In an aspect of the present disclosure, there is provided a gastric residence system comprising:

six arms affixed to a central elastomer, wherein at least one arm comprises a drug-eluting segment;

each arm comprising a proximal end, a distal end, and an outer surface therebetween; wherein the proximal end of each arm is attached to the central elastomer and projects radially from the central elastomer, each

arm having its distal end not attached to the central elastomer and located at a larger radial distance from the central elastomer than the proximal end;

wherein the at least one arm comprising a drug eluting segment comprises:

a first disintegrating matrix segment;

a first inert segment attached to the first disintegrating matrix segment;

a second disintegrating matrix segment attached to the first inert segment;

a second inert segment attached to the second disintegrating matrix segment;

the drug eluting segment attached to the second inert segment, wherein the drug eluting segment comprises a carrier polymer, and risperidone or a salt thereof, and wherein the drug eluting segment further comprises a coating comprising a release rate-modulating polymer film;

a third inert segment attached to the drug eluting segment;

and

a filament circumferentially connecting each arm.

[0005b] In another aspect of the present disclosure, there is provided a use of a gastric residence system disclosed herein, in the manufacture of a medicament for treating a psychiatric or neurological disorder in an individual.

[0005c] In a further aspect of the present disclosure, there is provided a gastric residence system disclosed herein, for use in therapy.

[0006] Risperidone dosage forms incorporating several features providing for more precise and consistent control of the desired residence time of gastric residence systems are disclosed.

The following features are included: a filament which is wrapped circumferentially around a gastric residence system and connecting the arms of the gastric residence system; use of timed linkers and enteric linkers which permit higher precision in retention and passage of the gastric residence system; and arms coated with release rate-modulating polymer films.

[0007] The features of any of the examples recited above and herein are combinable with any of the other examples recited above and herein where appropriate and practical.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] FIG. 1A shows a gastric residence system configuration.

[0009] FIG. 1B shows a detailed view of a gastric residence configuration.

[0010] FIG. 2A shows a configuration of a gastric residence system dosage form for risperidone.

[0011] FIG. 2B shows another configuration of a gastric residence system dosage form for risperidone.

[0012] FIG. 3 depicts a graph of the pharmacokinetics of the risperidone formulation of the gastric residence systems in Example 1 (upper curve: 28mg dosage form; lower curve: 14mg dosage form) in human subjects.

[0013] FIG. 4 depicts pharmacokinetics of risperidone in patients as they are transitioned from steady-state on immediate release (IR) risperidone to the extended release (ER) risperidone gastric residence systems. Concentrations of active moiety (risperidone and 9-hydroxyrisperidone combined) are plotted. The upper curve shows concentrations from administration of the 28 mg ER gastric residence systems, while the lower curve shows concentrations from administration of the 14 mg ER gastric residence systems. Bands showing C_{avg} and C_{min} for the corresponding matched IR groups are overlaid on the curves.

[0014] FIG. 5A depicts risperidone pharmacokinetics of gastric residence system (ER) doses. The mean concentration of active moiety (risperidone and 9-hydroxyrisperidone combined) is plotted, +/- standard deviation. The top graph shows 14 mg ER doses, while the bottom graph shows 28 mg ER doses. Bands showing C_{avg} and C_{min} for the final day of the IR lead-in are overlaid on the graphs.

CLAIMS

What is claimed is:

1. A gastric residence system comprising:

six arms affixed to a central elastomer, wherein at least one arm comprises a drug-eluting segment;

each arm comprising a proximal end, a distal end, and an outer surface therebetween; wherein the proximal end of each arm is attached to the central elastomer and projects radially from the central elastomer, each arm having its distal end not attached to the central elastomer and located at a larger radial distance from the central elastomer than the proximal end;

wherein the at least one arm comprising a drug eluting segment comprises:

a first disintegrating matrix segment;

a first inert segment attached to the first disintegrating matrix segment;

a second disintegrating matrix segment attached to the first inert segment;

a second inert segment attached to the second disintegrating matrix segment;

the drug eluting segment attached to the second inert segment, wherein the drug eluting segment comprises a carrier polymer, and risperidone or a salt thereof, and wherein the drug eluting segment further comprises a coating comprising a release rate-modulating polymer film;

a third inert segment attached to the drug eluting segment;

and

a filament circumferentially connecting each arm.

2. The gastric residence system of claim 1, wherein the segments are in the order listed from the proximal end to the distal end of the arm comprising a drug eluting segment, where the first disintegrating matrix segment is at the proximal end of the arm comprising the drug eluting segment, the first disintegrating matrix segment is attached to the central elastomer, and the third inert segment is at the distal end of the arm comprising a drug eluting segment.

3. The gastric residence system of claim 1 or claim 2, wherein at least one arm excludes a drug eluting segment.

4. The gastric residence system of claim 3, wherein the at least one arm excluding a drug eluting segment comprises:

a first disintegrating matrix segment;

a first inert segment attached to the first disintegrating matrix segment;

a second disintegrating matrix segment attached to the first inert segment;

a second inert segment attached to the second disintegrating matrix segment;

a third inert segment attached to the second inert segment;

and

a filament circumferentially connecting each arm.

5. The gastric residence system of claim 4, wherein the segments are in the order listed from the proximal end to the distal end of the arm excluding a drug eluting segment, where the first disintegrating matrix segment is at the proximal end of the arm excluding a drug eluting segment, the first disintegrating matrix segment is attached to the central elastomer, and the third inert segment is at the distal end of the arm excluding drug eluting segment.

6. The gastric residence system of any one of claims 1-5, wherein:
(a) one arm comprises the drug eluting segment and five arms exclude the drug eluting segment; or
(b) two arms comprise the drug eluting segment and four arms exclude the drug eluting segment; or
(c) three arms comprise the drug eluting segment and three arms exclude the drug eluting segment.

7. The gastric residence system of any one of claims 1-6, wherein the first disintegrating matrix segment comprises a time-dependent disintegrating matrix.

8. The gastric residence system of any one of claims 1-7, wherein the first inert segment comprises:
(a) polycaprolactone (PCL), optionally wherein the first inert segment comprises about 68 wt% to about 72 wt% PCL; and/or
(b) $(BiO)_2CO_3$, optionally wherein the first inert segment comprises about 28 wt% to about 32 wt% $(BiO)_2CO_3$.

9. The gastric residence system of any one of claims 1-8, wherein the second disintegrating matrix segment comprises an enteric disintegrating matrix.

10. The gastric residence system of any one of claims 1-9, wherein the second disintegrating matrix comprises:
(a) polycaprolactone (PCL), optionally wherein the second disintegrating matrix comprises about 32 wt% to about 36 wt% PCL; and/or
(b) hydroxypropyl methylcellulose acetate succinate (HPMCAS); optionally wherein the second disintegrating matrix comprises about 62 wt% to about 66 wt% HPMCAS; and/or
(c) polyethylene glycol-polypropylene glycol-polyethylene glycol (PEG-PPG-PEG) block copolymer, optionally wherein the second disintegrating matrix comprises about 1 wt% to about 3 wt% of PEG-PPG-PEG block copolymer.

11. The gastric residence system of any one of claims 1-10, wherein the second inert segment comprises:
(a) polycaprolactone (PCL), optionally wherein the second inert segment comprises about 68 wt% to about 72 wt% PCL; and/or
(b) $(BiO)_2CO_3$, optionally wherein the second inert segment comprises about 28 wt% to about 32 wt% $(BiO)_2CO_3$.

12. The gastric residence system of any one of claims 1-11, wherein the third inert segment comprises:
(a) polycaprolactone (PCL), optionally wherein the third inert segment comprises about 64 wt% to about 69 wt% PCL; and/or
(b) copovidone; optionally wherein the third inert segment comprises about 30 wt% to about 34 wt% copovidone; and/or

(c) polyethylene glycol-polypropylene glycol-polyethylene glycol (PEG-PPG-PEG) block copolymer, optionally wherein the third inert segment comprises about 0.5 wt% to about 2.5 wt% of PEG-PPG-PEG block copolymer; and/or
(d) an optional coloring agent, optionally wherein the third inert segment comprises about 0.01 wt % to about 0.1 wt% of the coloring agent.

13. The gastric residence system of any one of claims 1-12, wherein the drug-eluting segment comprises:
(a) risperidone, optionally wherein the drug-eluting segments comprises about 33 wt% to about 37 wt% of risperidone; and/or
(b) polycaprolactone (PCL), optionally wherein the segment comprises about 54 wt% to about 58 wt% of PCL; and/or
(c) copovidone, optionally wherein the segment comprises about 4 wt% to about 6 wt% of copovidone; and/or
(d) polyethylene glycol-polypropylene glycol-polyethylene glycol (PEG-PPG-PEG) block copolymer, optionally wherein the segment comprises about 2 wt% to about 4 wt% of PEG-PPG-PEG block copolymer; and/or
(e) vitamin E succinate, optionally wherein the segment comprises about 0.2 wt% to about 0.8 wt% Vitamin E succinate; and/or
(f) colloidal silicon dioxide (SiO_2), optionally wherein the segment comprises about 0.2 wt% to about 0.8 wt% SiO_2; and/or
(g) an optional coloring agent, optionally wherein the segment comprises about 0.05 wt% to about 0.15 wt% of the coloring agent.

14. The gastric residence system of any one of claims 1-13, wherein the proximal end of the proximal segment of the arm is attached to the central elastomer via an inert polycaprolactone (PCL) linker; optionally wherein:
(a) the proximal segment of the arm is the first inert segment, or
(b) the proximal segment of the arm is the first disintegrating matrix.

15. The gastric residence system of any one of claims 1-14, wherein the central elastomer comprises silicone rubber, optionally wherein the central elastomer has a durometer of about 45A to about 55A.

16. The gastric residence system of any one of claims 1-15, wherein one or more segments of the arm is coated by a release-rate modulating polymer film.

17. The gastric residence system of claim 16, wherein the release-rate modulating polymer film comprises about 71 wt% to about 76 wt% PCL, about 22 wt% to about 27 wt% VA64, and about 1 wt% to about 3 wt% magnesium stearate.

18. Use of a gastric residence system of any one of claims 1-17, in the manufacture of a medicament for treating a psychiatric or neurological disorder in an individual.

19. The use of claim 18, wherein the psychiatric or neurological disorder is schizophrenia.

20. The use of claim 18, wherein the psychiatric or neurological disorder is bipolar disorder or irritability associated with autistic disorder.

21. A gastric residence system of any one of claims 1-17, for use in therapy.