e.g., as an adjunctive therapy for serotonin reuptake inhibitors. Further, such dosage forms could be used as an adjunctive therapy to other therapies that have only partial or no serotonin modulatory pharmacology.

SUMMARY

This summary lists several examples of the presently disclosed subject matter, and in many cases lists variations and permutations of these examples. This summary is merely exemplary of the numerous and varied examples. Mention of one or more representative features of a given example is likewise exemplary. Such an example can typically exist with or without the feature(s) mentioned; likewise, those features can be applied to other examples of the presently disclosed subject matter, whether listed in this summary or not. To avoid excessive repetition, this Summary does not list or suggest all possible combinations of such features.

The presently disclosed subject matter provides a gastroretentive dosage form comprising a tablet, wherein said tablet comprises two layers: (a) a swelling layer comprising one or more hydrophilic polymers, wherein each of said one or more hydrophilic polymers is swellable in the presence of gastric fluid; and (b) a modified release layer, wherein the modified release layer comprises 5-hydroxytryptophan (5-HTP) and carbidopa; and wherein a time period for 80% by weight of the 5-HTP to release from the dosage form in dissolution testing is within about 2 hours of a time period for release of 80% by weight percentage of the carbidopa. In some examples, the time period for 80% by weight of one or both of the 5-HTP and the carbidopa to release from the dosage form in dissolution testing is about 5 hours to about 12 hours.

In one aspect, the present disclosure provides a gastroretentive dosage form comprising a bilayer tablet, wherein said tablet comprises two layers:

(a) a swelling layer comprising one or more hydrophilic polymers, wherein each of said one or more hydrophilic polymers is swellable in the presence of gastric fluid; and

(b) a modified release layer, wherein the modified release layer comprises one or more hydrophilic polymers, 5-hydroxytryptophan (5-HTP) and carbidopa; and

(i) wherein the dosage form provides sustained release of both the 5-HTP and the carbidopa upon administration of the tablet to a mammalian subject;

(ii) wherein, in dissolution testing in a USP Apparatus III: (1) a time period over which 80% by weight of the 5-HTP releases from the dosage form ($T=80\%_{(5\text{-}HTP)}$) is 4 hours to 13.6 hours, and (2) $T=80\%_{(5\text{-}HTP)}$ and a time period over which 80% by weight of the carbidopa releases from the dosage form ($T=80\%_{(carbidopa)}$) differ by less than 2 hours; and

(iii) wherein the tablet comprises about 250 mg of 5-HTP and 0.3125 mg to 25 mg carbidopa.

In some examples, the modified release layer comprises one or more hydrophilic polymers selected from the group comprising a low viscosity hydroxypropyl methylcellulose (HPMC), medium viscosity HPMC, high viscosity HPMC, low molecular weight (MW) polyethylene oxide (PEO), medium MW PEO, high MW PEO, and high viscosity hydroxyethyl cellulose. In some examples, the modified release layer comprises about 14% (w/w) to about 37% (w/w) of the one or more hydrophilic polymers based on a total weight of the modified release layer. In some examples, the modified release layer comprises about 5% (w/w) of a medium MW PEO or a high MW PEO and about 13% (w/w) to about 32% (w/w) of a low viscosity HMPC, a medium viscosity HPMC, or a mixture of medium viscosity HPMC and high viscosity HPMC based on a total weight of the modified release layer.

In some examples, the modified release layer comprises, based on a total weight of the modified release layer: (i) about 50 % (w/w) 5-HTP; (ii) about 0.0625% (w/w) to about 5% (w/w) carbidopa; or (iii) about 50% (w/w) 5-HTP and about 0.0625% (w/w) to about 5% (w/w) carbidopa. In some examples, the modified release layer further comprises about 5% (w/w) to about 30% (w/w) of one or more ductile filler based on a total weight of the modified release layer, optionally wherein the ductile filler comprises or consists of microcrystalline cellulose (MCC). In some examples, the modified release layer further comprises about 0.5% (w/w) to about 3% (w/w) of a lubricant based on a total weight of the modified release layer, optionally wherein the lubricant is selected from the group comprising sodium stearyl fumarate (SSF), glyceryl behenate, stearic acid, magnesium stearate, and mixtures thereof. In some examples, the modified release layer further comprises about 0.01% (w/w) to about 1% (w/w) of an antioxidant based on a total weight of the modified release layer, optionally wherein the antioxidant is selected from the group comprising butylated hydroxytoluene (BHT), butylated hydroxyanisole, tocopherol, tocopherol acetate, ascorbic acid, sodium sulfite, sodium metabisulfite, and mixtures thereof.

In some examples, the swelling layer comprises high MW PEO and high viscosity HPMC, optionally wherein the swelling layer comprises a weight ratio of high MW PEO:high viscosity HPMC of about 1:1. In some examples, the swelling layer further comprises up to about 5 % (w/w) of a lubricant based on a total weight of the swelling layer, optionally wherein the lubricant comprises or consists of sodium stearyl fumarate (SSF).

In some examples, the swelling layer and the modified release layer have about the same weight. In some examples, the total weight of the tablet is between about 500 milligrams (mg) and about 2000 mg; optionally wherein the total weight of the tablet is about 1000 mg. In some examples, the tablet comprises about 250 mg of 5-HTP and about 0.3125 mg to about 25 mg of carbidopa.

In some examples, the modified release layer comprises, based on a total weight of the modified release layer: about 50% (w/w) 5-HTP; about 0.06% (w/w) to about 5.4% (w/w) carbidopa; about 5.7% (w/w) to about 25.1% (w/w) MCC, about 5% (w/w) medium or high MW PEO; about 7% (w/w) to about 18% (w/w) medium viscosity HPMC; about 0% (w/w) to about 25% (w/w) high viscosity HPMC; about 0.2% (w/w) BHT, about 0.1% (w/w) colloidal silica; and about 1.5% (w/w) SSF. In some examples, the modified release layer comprises, based on a total weight of the modified release layer: about 50% (w/w) 5-HTP; about 0.06% (w/w) to about 5.4% (w/w) carbidopa; about 19.8% (w/w) to about 25.1% (w/w) MCC; about 5% (w/w) medium

or high MW PEO; about 18% (w/w) medium viscosity HPMC; about 0.2% (w/w) BHT, about 0.1% (w/w) colloidal silica; and about 1. 5% (w/w) SSF.

In some examples, the swelling layer swells to at least about 150 % of the dry volume of the swelling layer in an aqueous solution. In some examples, tablet remains in the stomach for about 5 hours after oral administration to a human. In some examples, the modified release layer remains stable for at least 70 days when stored at 15°C to about 25°C protected from light. IN some examples, the modified release layer and the swelling layer remain attached to one another for at least 8 hours during disintegration testing according to USP <701> with use of a disk. In some examples, the modified release layer has an acceptance value (AV) of about 15 or less and a relative standard deviation (RSD) of about 3 or less in content uniformity testing according to USP <905>.

In some examples, administration of the tablet once or twice daily to a mammalian subject, optionally a human, provides a time to achieve a maximum plasma concentration (T_{Max}) of 5-HTP that is delayed about 4 hours on average compared to an immediate release dosage form of native 5-HTP. In some examples, administration of the tablet once or twice daily to a mammalian subject, optionally a human, provides about 1-fold to about 10-fold 5-HTP plasma exposure compared to an immediate release native 5-HTP dosage form comprising the same weight of 5-HTP and wherein said immediate release native 5-HTP dosage form does not comprise carbidopa.

In some examples, administration of the tablet once or twice daily to a mammalian subject, optionally a human, provides a steady state average 5-HTP plasma level of about 25 nanograms per milliliter (ng/ml) or more, optionally wherein the steady state average 5-HTP plasma level is about 50 ng/ml or more, optionally wherein the steady state average 5-HTP plasma level is about 100 ng/ml or more, optionally wherein the steady state average 5-HTP plasma level is between 100 ng/ml and 500 ng/ml. In some examples, administration of the tablet once or twice daily to a mammalian subject, optionally a human, provides a steady state average carbidopa plasma level of about 25 ng/ml or less, optionally about 20 ng/ml or less, further optionally about 10 ng/ml or less. In some examples, administration of the tablet once or twice daily to a mammalian subject, optionally a human, provides a steady state average maximum carbidopa plasma level (C_{Max}) of about 25 ng/ml or less, optionally about 20 ng/ml or less, further optionally about 10 ng/ml or less.

In some examples, administration of the tablet once or twice daily to a mammalian subject, optionally a human, provides an increased 5-HTP half-life compared to a 5-HTP half-life

when native 5-HTP is administered in an immediate release form, optionally wherein the 5-HTP half-life is increased by about 10% to about 200% compared to the 5-HTP half-life when the native 5-HTP is administered in an immediate release form. In some examples, the dosage form is configured to provide a same release rate for 5-HTP and/or a same release rate for carbidopa over a range of carbidopa content from 0.3125 mg to 25 mg when a total combined weight of carbidopa and microcrystalline cellulose is held constant.

Accordingly, it is an object of the presently disclosed subject matter to provide gastroretentive dosage forms or modified/sustained release of 5-HTP and carbidopa. An object of the presently disclosed subject matter having been stated hereinabove, and which is achieved in whole or in part by the presently disclosed subject matter, other objects will become evident as the description proceeds when taken in connection with the accompanying drawings and examples as best described herein below.

BRIEF DESCRIPTION OF THE DRAWINGS

In order that the disclosure may be readily understood and put into practical effect, reference will now be made to examples as illustrated with reference to the accompanying figures. The figures together with the description serve to further illustrate the embodiments of the invention and explain various principles and advantages.

Figures 1A-1D: Dissolution testing of 5-HTP/low-dose carbidopa gastroretentive tablets in vitro – 5-HTP release from “fast” vs “slow” tablets. 5-HTP release over 18h. (Figure 1A) “Fast” bilayer tablet, 250 mg 5-HTP, 0.3125 mg carbidopa. (Figure 1B) “Fast” bilayer tablet, 250 mg 5-HTP, 25 mg carbidopa. (Figure 1C) “Slow” bilayer tablet, 250 mg 5-HTP, 0.3125 mg carbidopa. (Figure 1D) Slow bilayer tablet, 250 mg 5-HTP, 25 mg carbidopa. Conditions: USP III (Reciprocating Cylinder) Dissolution Bath. 250 mL of 0.1 M HCl + 0.02% disodium EDTA. 37°C ± 0.5.

Figure 2: Dissolution testing of “fast” 5-HTP/low-dose carbidopa gastroretentive tablets in vitro – Effect of carbidopa levels on 5-HTP release. Conditions: USP III (Reciprocating Cylinder) Dissolution Bath. 250 mL of 0.1 M HCl + 0.02% disodium EDTA. 37°C ± 0.5.

Figures 3A-3C: Dissolution testing of “fast” 5-HTP/low-dose carbidopa gastroretentive tablets in vitro – Parallel release of 5-HTP and carbidopa across formulations. (Figure 3A) “Fast” bilayer tablet 250 mg 5-HTP 25 mg carbidopa. (Figure 3B) “Slow” bilayer tablet 250 mg 5-HTP 25 mg carbidopa. (Figure 3C) “Intermediate” bilayer tablet 250 mg 5-HTP 5 mg carbidopa.

Claims

What is claimed is:

1. A gastroretentive dosage form comprising a bilayer tablet, wherein said tablet comprises two layers:

(a) a swelling layer comprising one or more hydrophilic polymers, wherein each of said one or more hydrophilic polymers is swellable in the presence of gastric fluid; and

(b) a modified release layer, wherein the modified release layer comprises one or more hydrophilic polymers, 5-hydroxytryptophan (5-HTP) and carbidopa; and

(i) wherein the dosage form provides sustained release of both the 5-HTP and the carbidopa upon administration of the tablet to a mammalian subject;

(ii) wherein, in dissolution testing in a USP Apparatus III: (1) a time period over which 80% by weight of the 5-HTP releases from the dosage form ($T=80\%_{(5\text{-}HTP)}$) is 4 hours to 13.6 hours, and (2) $T=80\%_{(5\text{-}HTP)}$ and a time period over which 80% by weight of the carbidopa releases from the dosage form ($T=80\%_{(carbidopa)}$) differ by less than 2 hours; and

(iii) wherein the tablet comprises about 250 mg of 5-HTP and 0.3125 mg to 25 mg carbidopa.

2. The gastroretentive dosage form of claim 1, wherein one or both of $T=80\%_{(5\text{-}HTP)}$ and $T=80\%_{(carbidopa)}$ in dissolution testing in a USP Apparatus III are 5 hours to 12 hours.

3. The gastroretentive dosage form of claim 1 or claim 2, wherein the one or more hydrophilic polymers of the modified release layer are each selected from the group consisting of a low viscosity hydroxypropyl methylcellulose (HPMC), medium viscosity HPMC, high viscosity HPMC, low molecular weight (MW) polyethylene oxide (PEO), medium MW PEO, high MW PEO, and high viscosity hydroxyethyl cellulose.

4. The gastroretentive dosage form of claim 3, wherein the modified release layer comprises 14% (w/w) to 37% (w/w) of the one or more hydrophilic polymers based on a total weight of the modified release layer.

5. The gastroretentive dosage form of claim 3 or claim 4, wherein the modified release layer comprises about 5% (w/w) of a medium MW PEO or a high MW PEO and 13% (w/w) to 32% (w/w) of a low viscosity HMPC, a medium viscosity HPMC, or a mixture of medium viscosity HPMC and high viscosity HPMC based on a total weight of the modified release layer.

6. The gastroretentive dosage form of any one of claims 1-5, wherein the modified release layer further comprises 5% (w/w) to 30% (w/w) of one or more ductile filler based on a total weight of the modified release layer.

7. The gastroretentive dosage form of any one of claims 1-6, wherein the modified release layer further comprises 0.5% (w/w) to 3% (w/w) of a lubricant based on a total weight of the modified release layer.

8. The gastroretentive dosage form of any one of claims 1-7, wherein the modified release layer further comprises 0.01% (w/w) to 1% (w/w) of an antioxidant based on a total weight of the modified release layer.

9. The gastroretentive dosage form of any one of claims 1-8, wherein the swelling layer comprises high MW PEO and high viscosity HPMC.

10. The gastroretentive dosage form of any one of claims 1-9, wherein the swelling layer further comprises up to 5 % (w/w) of a lubricant based on a total weight of the swelling layer.

11. The gastroretentive dosage form of any one of claims 1-10, wherein the swelling layer and the modified release layer have about the same weight.

12. The gastroretentive dosage form of any one of claims 1-11, wherein a total weight of the tablet is 500 milligrams (mg) to 2000 mg.

13. The gastroretentive dosage form of any one of claims 1-12, wherein the modified release layer comprises, based on a total weight of the modified release layer: about 50%

(w/w) 5-HTP; 0.06% (w/w) to 5.4% (w/w) carbidopa; 5.7% (w/w) to 25.1% (w/w) microcrystalline cellulose (MCC); about 5% (w/w) medium or high MW PEO; 7% (w/w) to 18% (w/w) medium viscosity HPMC; 0% (w/w) to 25% (w/w) high viscosity HPMC; about 0.2% (w/w) butylated hydroxytoluene (BHT), about 0.1% (w/w) colloidal silica; and about 1.5% (w/w) sodium stearyl fumarate (SSF).

14. The gastroretentive dosage form of claim 13, wherein the modified release layer comprises, based on a total weight of the modified release layer: about 50% (w/w) 5-HTP; 0.06% (w/w) to 5.4% (w/w) carbidopa; 19.8% (w/w) to 25.1% (w/w) MCC; about 5% (w/w) medium or high MW PEO; about 18% (w/w) medium viscosity HPMC; about 0.2% (w/w) BHT, about 0.1% (w/w) colloidal silica; and about 1. 5% (w/w) SSF.

15. The gastroretentive dosage form of any one of claims 1-14, wherein the swelling layer swells to at least 150 % of the dry volume of the swelling layer in an aqueous solution.

16. The gastroretentive dosage form of any one of claims 1-15, wherein the tablet remains in the stomach for about 5 hours after oral administration to a human.

17. The gastroretentive dosage form of any one of claims 1-16, wherein the modified release layer remains chemically stable for at least 70 days when stored at 15°C to 25°C protected from light.

18. The gastroretentive dosage form of any one of claims 1-17, wherein the modified release layer and the swelling layer remain attached to one another for at least 8 hours during disintegration testing according to USP <701> with use of a disk.

19. The gastroretentive dosage form of any one of claims 1-18, wherein the modified release layer has an acceptance value (AV) of 15 or less and a relative standard deviation (RSD) of 3 or less in content uniformity testing according to USP <905>.

20. The gastroretentive dosage form of any one of claims 1-19, wherein administration of the tablet once or twice daily to a mammalian subject provides a time to achieve a

maximum plasma concentration (T_{Max}) of 5-HTP that is delayed about 4 hours on average compared to an immediate release dosage form of native 5-HTP.

21. The gastroretentive dosage form of any one of claims 1-20, wherein administration of the tablet once or twice daily to a mammalian subject provides 1-fold to 10-fold 5-HTP plasma exposure compared to an immediate release dosage form of native 5-HTP comprising the same weight of 5-HTP as said tablet and wherein said immediate release dosage form of native 5-HTP does not comprise carbidopa.

22. The gastroretentive dosage form of any one of claims 1-21, wherein administration of the tablet once or twice daily to a mammalian subject provides a steady state average 5-HTP plasma level of 25 nanograms per milliliter (ng/ml) or more.

23. The gastroretentive dosage form of any one of claims 1-22, wherein administration of the tablet once or twice daily to a mammalian subject provides a steady state average carbidopa plasma level of 25 ng/ml or less.

24. The gastroretentive dosage form of any one of claims 1-23, wherein administration of the tablet once or twice daily to a mammalian subject provides a steady state average maximum carbidopa plasma level (C_{Max}) of 25 ng/ml or less.

25. The gastroretentive dosage form of any one of claims 1-24, wherein administration of the tablet once or twice daily to a mammalian subject provides an increased 5-HTP half-life compared to a 5-HTP half-life when native 5-HTP is administered in an immediate release form.

26. The gastroretentive dosage form of any one of claims 1-25, wherein the dosage form is configured to provide a same release rate for 5-HTP and/or a same release rate for carbidopa over a range of carbidopa content from 0.3125 mg to 25 mg when a total combined weight of carbidopa and microcrystalline cellulose is held constant.

27. The gastroretentive dosage form of any one of claims 1-26, wherein administration of the dosage form to a human subject provides an average time to achieve maximum plasma concentration (T_{Max}) for 5-HTP of 4 hours to 8 hours.

28. The gastroretentive dosage form of any one of claims 1-27, wherein administration of the dosage form to a human subject provides an average time to achieve maximum plasma concentration (T_{Max}) for both 5-HTP and carbidopa of about 5 hours.