An immediate-release film-coated 10-mg tablet was developed for the phase 3 clinical trials and commercial launch of lorcaserin, but there remains a need for modified-release formulations to provide a delay in, and/or continuous drug-release over an extended period of time. Modified-release dosage forms elevate trough plasma levels and are suitable for use in once-a-day (q.d.) dosing regimens. Furthermore, modified-release dosage forms reduce the drug plasma concentration peak:trough ratio and can thereby decrease the incidence and severity of the adverse effects of intermittent dosing.

The choice of modified-release technology depends upon the plasma concentration profile desired and the active pharmaceutical ingredient (API) solubility. The drug molecule must have appropriate pharmacokinetics and sufficient solubility, permeability, and stability throughout the GI tract for a successful modified-release formulation. The salts and formulations described herein help meet these and other needs.

SUMMARY

The present disclosure pertains to modified-release dosage forms comprising a therapeutically effective amount of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

In one aspect, the present disclosure refers to a modified-release dosage form comprising a therapeutically effective amount of a salt selected from: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride and pharmaceutically acceptable solvates and hydrates thereof,

wherein said modified-release dosage form is a tablet;

wherein said modified-release dosage form comprises a rate-controlling polymer matrix;

wherein said matrix comprises:

(i) said salt; and

(ii) a rate-controlling polymer;

wherein said salt is dispersed in said rate-controlling polymer;

wherein the rate-controlling polymer is (hydroxypropyl)methylcellulose

wherein said tablet further comprises a film coating;

wherein said film coating comprises ethyl cellulose and (hydroxypropyl)methyl cellulose;

wherein the ratio of said ethyl celluslose to said (hydroxypropyl)methyl cellulose in said film coating is about 75:25, about 80:20, or about 85:15;

wherein said modified-release dosage form provides a release rate for which the time to achieve 80% cumulative release of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H-3*- benzazepine (T80%) is at least 3 hours, as determined using USP apparatus I (basket method) in 900 mL of 0.1 N HCI solution at 37 °C and 100 rpm.

In one aspect, the present disclosure refers to a modified-release dosage form as disclosed herein, for use in the treatment of the human or animal body by therapy.

In one aspect, the present disclosure refers to the use of the modified-release dosage form as disclosed herein in the manufacture of a medicament for a method of weight management.

One example of the present disclosure pertains to methods for weight management, comprising administering to an individual in need thereof, the modified-release dosage form of the present disclosure.

One example of the present disclosure pertains to a salt selected from: (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydroiodide salt; (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine maleate salt; (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine fumarate salt; and (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemifumarate salt; (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine orotate salt; (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine di-acetamidobenzoate salt-cocrystal; (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine *trans*-cinnamate salt; (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine heminapadisilate salt; (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (±)-mandelate salt; and (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemipamoate salt; and pharmaceutically acceptable solvates and hydrates thereof.

One example of the present disclosure pertains to a pharmaceutical composition comprising a salt of the present disclosure, and a pharmaceutically acceptable carrier.

One example of the present disclosure pertains to processes for preparing a pharmaceutical composition comprising admixing a salt of the present disclosure, and a pharmaceutically acceptable carrier.

One example of the present disclosure pertains to methods for weight management, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt or a pharmaceutical composition of the present disclosure.

One example of the present disclosure pertains to uses of salts or pharmaceutical compositions of the present disclosure, in the manufacture of a medicament for weight management in an individual.

One example of the present disclosure pertains to salts, and pharmaceutical compositions of the present disclosure, for use in a method of treatment of the human or animal body by therapy.

One example of the present disclosure pertains to modified-release dosage forms, salts, and pharmaceutical compositions of the present disclosure, for use in a method of weight management.

One example of the present disclosure pertains to modified-release dosage forms, salts, and pharmaceutical compositions of the present disclosure, for use in a method of weight management; wherein the weight management comprises one or more of: weight loss, and maintenance of weight loss.

One example of the present disclosure pertains to modified-release dosage forms, salts, and pharmaceutical compositions of the present disclosure, for use in a method of weight management; wherein the weight management comprises one or more of: weight loss, maintenance of weight loss, decreased food consumption, increasing meal-related satiety, reducing pre-meal hunger, and reducing intra-meal food intake.

One example of the present disclosure pertains to modified-release dosage forms, salts, and pharmaceutical compositions of the present disclosure, for use as an adjunct to diet and exercise for weight management.

One example of the present disclosure pertains to modified-release dosage forms, salts, and pharmaceutical compositions of the present disclosure, for use in a method of weight management; wherein the individual in need of weight management is selected from: an obese patient with an initial body mass index ≥ 30 kg/m^2; an overweight patient with an initial body mass index ≥ 27 kg/m^2 in the presence of at least one weight related comorbid condition; and an overweight patient with an initial body mass index ≥ 27 kg/m^2 in the presence of at least one weight related comorbid condition; wherein the weight related co-morbid condition is selected from: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

One example of the present disclosure pertains to modified-release dosage forms, salts, and pharmaceutical compositions of the present disclosure, for use in a method of weight management in combination with a second anti-obesity agent.

One example of the present disclosure pertains to modified-release dosage forms, salts, and pharmaceutical compositions of the present disclosure, for use in a method of weight

management in combination with a second anti-obesity agent selected from: chlorphentermine, clortermine, phenpentermine, and phentermine, and pharmaceutically acceptable salts, solvates, and hydrates thereof.

One example of the present disclosure pertains to modified-release dosage forms, salts, and pharmaceutical compositions of the present disclosure, for use in a method of weight management in combination with an anti-diabetes agent.

One example of the present disclosure pertains to modified-release dosage forms, salts, and pharmaceutical compositions of the present disclosure, for use in a method of weight management in combination with metformin.

One example of the present disclosure pertains to methods of manufacturing a pharmaceutical composition comprising: admixing a compound selected from: a salt of the present disclosure and pharmaceutically acceptable solvates and hydrates thereof, with a pharmaceutically acceptable excipient.

One example of the present disclosure pertains to methods of manufacturing a modified-release dosage form comprising: providing a compound selected from: (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine, and pharmaceutically acceptable salts, solvates, and hydrates thereof; and formulating the compound into a modified-release dosage form.

One example of the present disclosure pertains to methods for weight management, comprising administering to an individual in need thereof, a modified-release dosage form comprising a therapeutically effective dose of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate or hydrate thereof.

One example of the present disclosure pertains to modified-release dosage forms comprising a therapeutically effective dose of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine or a pharmaceutically acceptable salt, solvate or hydrate thereof.

One example of the present disclosure pertains modified-release dosage forms comprising a therapeutically effective dose of a salt selected from: (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine and pharmaceutically acceptable salts, solvates, and hydrates thereof, for use in a method of weight management in an individual.

One example of the present disclosure pertains to certain salts of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (Compound 1) and pharmaceutically acceptable solvates and hydrates thereof.

One example of the present disclosure pertains to certain salts of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (Compound 1).

One example of the present disclosure pertains to crystalline forms of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydroiodide salt.

One example of the present disclosure pertains to crystalline forms of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine maleate salt.

One example of the present disclosure pertains to crystalline forms of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine fumarate salt.

One example of the present disclosure pertains to crystalline forms of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemifumarate salt.

One example of the present disclosure pertains to crystalline forms of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine orotate salt.

One example of the present disclosure pertains to crystalline forms of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine orotate salt hydrate.

One example of the present disclosure pertains to crystalline forms of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine di-4-acetamidobenzoate salt-cocrystal methyl ethyl ketone solvate.

One example of the present disclosure pertains to crystalline forms of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine *trans*-cinnamate salt.

One example of the present disclosure pertains to crystalline forms of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine heminapadisilate salt.

One example of the present disclosure pertains to crystalline forms of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine heminapadisilate salt solvate 1.

One example of the present disclosure pertains to crystalline forms of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine heminapadisilate salt solvate 2.

One example of the present disclosure pertains to crystalline forms of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (±)-mandelate salt hydrate.

One example of the present disclosure pertains to crystalline forms of (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hemipamoate salt hydrate.

One example of the present disclosure pertains to pharmaceutical compositions comprising a salt of the present disclosure.

One example of the present disclosure pertains to processes for preparing pharmaceutical compositions comprising admixing a salt of the present disclosure, and a pharmaceutically acceptable carrier.

One example of the present disclosure pertains to bulk pharmaceutical compositions suitable for the manufacture of dosage forms for weight management, comprising a salt of the present disclosure, and a pharmaceutically acceptable carrier.

One example of the present disclosure pertains to processes for preparing a bulk pharmaceutical composition suitable for the manufacture of dosage forms for weight management, comprising admixing a salt of the present disclosure, and a pharmaceutically acceptable carrier.

One example of the present disclosure pertains to methods for weight management, comprising administering to an individual in need thereof, a therapeutically effective amount of a salt, or a pharmaceutical composition of the present disclosure.

One example of the present disclosure pertains to the use of a salt of the present disclosure in the manufacture of a medicament for weight management in an individual.

One example of the present disclosure pertains to salts and pharmaceutical compositions of the present disclosure, for use in a method of treatment of the human or animal body by therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: PXRD of Compound 1 Hydrochloride Salt, Hemihydrate Form III.

Figure 2: DSC of Compound 1 Hydrochloride Salt, Hemihydrate Form III.

Figure 3: TGA of Compound 1 Hydrochloride Salt, Hemihydrate Form III.

Figure 4: DMS of Compound 1 Hydrochloride Salt, Hemihydrate Form III.

Figure 5: PXRD of Compound 1 Hydroiodide Salt, Form I.

Figure 6: DSC and TGA of Compound 1 Hydroiodide Salt, Form I.

Figure 7: DMS of Compound 1 Hydroiodide Salt, Form I.

Figure 8: PXRD of Compound 1 Maleate Salt, Form I.

Figure 9: DSC and TGA of Compound 1 Maleate Salt, Form I.

Figure 10: DMS of Compound 1 Maleate Salt, Form I.

Figure 11: PXRD of Compound 1 Fumarate Salt, Form I.

Figure 12: DSC and TGA of Compound 1 Fumarate Salt, Form I.

Figure 13: DMS of Compound 1 Fumarate Salt, Form I.

Figure 14: PXRD of Compound 1 Hemifumarate Salt, Form I.

Figure 15: DSC and TGA of Compound 1 Hemifumarate Salt, Form I.

Figure 16: DMS of Compound 1 Hemifumarate Salt, Form I.

Figure 17: PXRD of Compound 1 Orotate Salt, Form I.

Figure 18: DSC and TGA of Compound 1 Orotate Salt, Form I.

Figure 19: DMS of Compound 1 Orotate Salt, Form I.

Figure 20: PXRD of Compound 1 Orotate Salt Hydrate, Form I.

Figure 21: DSC and TGA of Compound 1 Orotate Salt Hydrate, Form I.

Figure 22: DMS of Compound 1 Orotate Salt Hydrate, Form I.

Figure 23: PXRD of Compound 1 Di-4-acetamidobenzoate Salt-Cocrystal Methyl Ethyl Ketone Solvate, Form I.

Figure 24: DSC and TGA of Compound 1 Di-4-acetamidobenzoate Salt-Cocrystal Methyl Ethyl Ketone Solvate, Form I.

Figure 25: DMS of Compound 1 Di-4-acetamidobenzoate Salt-Cocrystal Methyl Ethyl Ketone Solvate, Form I.

What is claimed is:

1. A modified-release dosage form comprising a therapeutically effective amount of a salt selected from: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride and pharmaceutically acceptable solvates and hydrates thereof,

wherein said modified-release dosage form is a tablet;

wherein said modified-release dosage form comprises a rate-controlling polymer matrix;

wherein said matrix comprises:

(i) said salt; and

(ii) a rate-controlling polymer;

wherein said salt is dispersed in said rate-controlling polymer;

wherein the rate-controlling polymer is (hydroxypropyl)methylcellulose

wherein said tablet further comprises a film coating;

wherein said film coating comprises ethyl cellulose and (hydroxypropyl)methyl cellulose;

wherein the ratio of said ethyl celluslose to said (hydroxypropyl)methyl cellulose in said film coating is about 75:25, about 80:20, or about 85:15;

wherein said modified-release dosage form provides a release rate for which the time to achieve 80% cumulative release of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3- benzazepine (T80%) is at least 3 hours, as determined using USP apparatus I (basket method) in 900 mL of 0.1 N HCI solution at 37 °C and 100 rpm.

2. A modified-release dosage form according to claim 1, wherein said salt is *(R)-8*-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride salt hemihydrate.

3. A modified-release dosage form according to claim 1 or 2, wherein said modified- release dosage form further comprises one or more ingredients

selected from: microcrystalline cellulose, mannitol, and magnesium stearate.

4. A modified-release dosage form according to any one of claims 1 to 3, for use in the treatment of the human or animal body by therapy.

5. Use of the modified-release dosage form according to any one of claims 1 to 3 in the manufacture of a medicament for a method of weight management.

6. The use according to claim 5, wherein the medicament is to be administered in combination with a second anti-obesity agent.

7. The use according to claim 6, wherein said second anti-obesity agent is selected from:

phentermine, chlorphentermine, clortermine, and phenpentermine, and pharmaceutically acceptable salts, solvates, and hydrates thereof.

8. The use according to claim 6 or 7, wherein said medicament and said second anti-obesity agent are to be administered simultaneously.

9. The use according to claim 5, wherein the medicament is to be administered in combination with an anti-diabetes agent.

10. The use according to claim 9, wherein said anti-diabetes agent is metformin.

11. The use according to claim 9 or 10, wherein said medicament and said anti-diabetes agent are to be administered simultaneously, separately, or sequentially.

12. The use according to claim 5, wherein said method comprises a plurality of administrations of said medicament to an individual, with a frequency wherein the average interval between any two sequential said administrations is 24 hours.

13. The use according to claim 12, wherein said method is more efficacious than an immediate- release method for weight management; wherein in said immediate-release method for weight management, an immediate-release dosage form comprising (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a pharmaceutically acceptable solvate or hydrate thereof is to be administered to an individual in need thereof; and wherein the total plasma exposure of said individual to (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a pharmaceutically acceptable solvate or hydrate thereof over the course of said immediate- release method is equal to or greater than the total plasma exposure of said individual to (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a pharmaceutically acceptable solvate or hydrate thereof over the course of said method.

14. The use according to claim 12 or 13, wherein the plasma concentration of said (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride or a pharmaceutically acceptable solvate or hydrate thereof in said individual has a C_{max} of less than 60 ng/ml.

15. The use according to claim 12 or 13, wherein the C_{max} divided by the therapeutically effective amount is less than 1×10^{-5} mL^{-1}.

16. The use according to any one of claims 12 to 15, wherein the C_{max} occurs more than 30 minutes after said administering.

17. The use according to any one of claims 12 to 16, wherein the average peak to trough ratio of the plasma concentration of said (*R*)-8-chloro-1-methyl-

2,3,4,5-tetrahydro-1*H-3*-benzazepine hydrochloride or a pharmaceutically acceptable solvate or hydrate thereof in said individual is less than 3:1.