[0008] Unfortunately, however, systemic exposure of metformin still poses a serious risk of lactic acidosis for several patient populations. Lactic acidosis is a potentially fatal metabolic complication that occurs when lactic acid levels increase in the bloodstream. Accordingly, metformin is contraindicated in people with any condition that could increase the risk of lactic acidosis, including kidney disorders, lung disease, and liver disease. According to the prescribing information, heart failure, in particular, unstable or acute congestive heart failure, also increases risk of lactic acidosis with metformin. Thus, metformin remains unavailable to treat hyperglycemia in patients with these contraindications.

[0009] Moreover, conventional metformin formulations often produce dose-limiting adverse gastrointestinal (GI) complications including diarrhea, nausea, vomiting, dizziness, headaches and dyspepsia. Accordingly, patient administration is generally titrated upward over a period of time to a maximum tolerated dose based in not insignificant part on any resulting patient-specific adverse GI effects. Extended-release formulations have been developed in the hopes of addressing this, but have not adequately resolved these problems.

[0010] Clearly, there continues to be a need for better and safer compositions and methods for delivering biguanide compounds that address these tolerability and safety concerns. Ideally, these would also provide more effective treatment options for metabolic disorders in patients having contraindications for metformin and/or other biguanides.

SUMMARY OF THE ~~INVENTION~~DISCLOSURE

[0011] As demonstrated herein for the first time, the present ~~inventors~~ disclosure have surprisingly discovered that the systemic bioavailability of biguanides such as metformin can be minimized without compromising their therapeutic efficacy. Correspondingly, methods and compositions are provided for the treatment of metabolic disorders in patients, including otherwise contraindicated patient populations, by administering delayed-release (DR) formulations to minimize the systemic bioavailability of the biguanide compound in the patient.

[0012] Also demonstrated herein for the first time is the surprising finding that GI complications typically resulting from biguanide administration can be dramatically reduced using the subject compositions and methods. Accordingly, patient comfort and compliance is

delivery to the distal small intestine, and the formulation comprises an oral dosage form enterically coated at a pH at or above 6.0 or 6.5.

[0028] In the methods disclosed herein, the biguanide compound may be or comprise metformin, a metformin salt, solvate, polymorph, hydrate, N-oxide or prodrug. In preferred embodiments, the biguanide compound is a metformin salt selected from the group consisting of hydrochloride, phosphate, sulfate, hydrobromide, salicylate, maleate, benzoate, succinnate, ethanesulfonate, fumarate, glycolate, palmoate, oratate, acetate, isobutyrate, acetylsalicylate, nicotinic acid, adamantoate, zinc-chlorophylin, carboxylic acid, benzoic acid, dichloroacetic acid, theophylin-7-acetate, clofibrate, tartate, oxalate, tannate and hydroxyl acid. In a particularly preferred embodiment, the biguanide compound is metformin hydrochloride.

[0029] The methods disclosed herein may also further comprise the administration of an immediate-release, extended release or delayed-release formulation of one or more additional therapeutic agents, *e.g.*, a DPP-IV inhibitor (*e.g.*, sitagliptin, saxagliptin, berberine, vildagliptin, linagliptin, alogliptin, and the like), a chemosensory receptor ligand (e.g., a sweet receptor ligand, bitter receptor ligand, umami receptor ligand, sour receptor ligand, fat receptor ligand or bile acid receptor ligand), an anti-obesity or anti-diabetes agent, or a chemosensory receptor antagonist, *e.g.*, lactisole. Non-limiting examples include embodiments further comprising the administration of 100 mg sitagliptin OD, or 50 mg sitagliptin BID. The delayed-release formulation can be a bilayer tablet, or a capsule with the two components as encapsulated mini-tablets. The delayed-release formulation may also further comprise an immediate release component that has a pH 5.0 enteric coating for the additional therapeutic agent.

In another aspect, there is provided the use of a biguanide compound in the manufacture of a medicament for improving the gastrointestinal tolerability of, and/or reducing gastrointestinal complications resulting from, biguanide administration, in a patient, wherein the biguanide compound is in a delayed-release formulation.

In another aspect, there is provided the use of a biguanide compound in the manufacture of a medicament for treating metabolic disorders in a patient having a contraindication for the biguanide compound, wherein the biguanide compound is in a delayed-release formulation.

In another aspect, there is provided the use of a biguanide compound in the manufacture of a medicament for treating a renally impaired patient having diabetes, wherein the biguanide compound is in a delayed-release formulation.

In another aspect, there is provided the use of a biguanide compound in the manufacture of a medicament for treating a diabetic patient having congestive heart failure, a hypoxic state and/or advanced liver disease, wherein the biguanide compound is in a delayed-release formulation.

In another aspect, there is provided the use of a biguanide compound in the manufacture of a medicament for reducing the onset of diabetes in a patient with pre-diabetes, wherein the biguanide compound is in a delayed-release formulation.

In another aspect, there is provided the use of a biguanide compound in the manufacture of a medicament for inducing weight loss in a patient, wherein the biguanide compound is in a delayed-release formulation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] FIG. 1 shows the design of the study described in Example 1.

[0031] FIG. 2 shows the events during the treatment period of the study described in Example 1.

[0032] FIG. 3 shows the plasma concentration of metformin immediate-release (Metformin IR) (●) and metformin delayed-release (Metformin DR) (■) (x-axis; ng/mL) as a function of time (y-axis; min) after ingestion at t = -240 and after a meal at t = 0 min.

What is claimed is:

1. A method of improving the gastrointestinal tolerability of and/or reducing gastrointestinal complications resulting from biguanide administration, comprising administering a therapeutically effective amount of a biguanide compound in a delayed-release formulation to a patient in need thereof.

2. A method of treating metabolic disorders in a patient in need thereof, comprising administering a therapeutically effective amount of a biguanide compound to said patient in a delayed-release formulation, wherein said patient has a contraindication for the biguanide compound.

3. The method according to claim 2, wherein the patient has a contraindication selected from the group consisting of a hypoxic condition, impaired lactate clearance, and impaired clearance of the biguanide compound.

4. The method according to claim 3, wherein the patient has a hypoxic condition.

5. The method according to claim 3, wherein the patient has impaired lactate clearance.

6. The method according to claim 3, wherein the patient has impaired clearance of the biguanide compound.

7. The method according to claim 3, wherein the patient has moderate renal impairment, severe renal impairment, or endstage renal disease which results in impaired clearance of the biguanide compound.

8. The method according to claim 3, wherein the patient has chronic kidney disease.

9. The method according to any one of the preceding claims, wherein the patient in need thereof has hyperglycemia.

10. The method according to claim 9, wherein the hyperglycemia is chronic.

11. The method according to claim 9 or claim 10, wherein the hyperglycemia is caused by type II diabetes.

12. A method of treating a renally impaired subject having diabetes, comprising administering a therapeutically effective amount of a biguanide compound to said subject in a delayed-release formulation.

13. A method of treating a diabetic subject having congestive heart failure, a hypoxic state and/or advanced liver disease, comprising administering a therapeutically effective amount of a biguanide compound to said subject in a delayed-release formulation.

14. A method of reducing the onset of diabetes in a subject with pre-diabetes, comprising administering a therapeutically effective amount of a biguanide compound to said subject in a delayed-release formulation.

15. A method of inducing weight loss in a subject, comprising administering a therapeutically effetive amount of a biguanide compound to said subject in a delayed release formulation.

16. The method acording to any one of claims 1-15, wherein the biguanide compound has a reduced relative bioavailability of about 40, 50 or 60% in said delayed-release formulation in comparison with an immedicate-release formulation havig the same amount of said biguanide compound.

17. The method according to any one of claims 1-15, wherein the administration produces a mean plasma AUC_{0-36} less than about 14,000, 13,000 or 12,000 ng*h/mL when said formulation is administered at 500 mg twice daily.

18. The method according to any one of claims 1-15, wherein the administration produces a mean C_{max} less than about 800, 700 or 600 ng/mL when said formulation is administered at 500 mg twice daily.

19. The method according to any one of the preceding claims, wherein the biguanide compound is targeted for delivery to the small intestine, and the formulation comprises an oral dosage form enterically coated at a pH at or above 5.0 or 5.5.

20. The method according to claim 19, wherein the biguanide compound is targeted for delivery to the distal small intestine, and the formulation comprises an oral dosage form enterically coated at a pH at or above 6.0 or 6.5.

21. The method according to claim 19 or 20, wherein said oral dosage form further comprises a modified release component for at least a portion of said biguanide compound.

22. The method according to claim 19 or 20, wherein the oral dosage form comprises less than 500 mg of the biguanide compound.

23. The method according to any one of the preceding claims, wherein said biguanide compound is selected from the group consisting of metformin, phenformin, buformin and imeglimin.

24. A method according to any one of the previous claims, further comprising administration of a DPP-IV inhibitor.

25. A method according to any one of the previous claims, further comprising administration of an anti-obesity or anti-diabetes agent.

1. Use of a biguanide compound in the manufacture of a medicament for improving the gastrointestinal tolerability of, and/or reducing gastrointestinal complications resulting from, biguanide administration, in a patient, wherein the biguanide compound is in a delayed-release formulation.

2. Use of a biguanide compound in the manufacture of a medicament for treating metabolic disorders in a patient having a contraindication for the biguanide compound, wherein the biguanide compound is in a delayed-release formulation.

3. The use according to claim 2, wherein the patient has a contraindication selected from the group consisting of a hypoxic condition, impaired lactate clearance, and impaired clearance of the biguanide compound.

4. The use according to claim 3, wherein the patient has a hypoxic condition.

5. The use according to claim 3, wherein the patient has impaired lactate clearance.

6. The use according to claim 3, wherein the patient has impaired clearance of the biguanide compound.

7. The use according to claim 3, wherein the patient has moderate renal impairment, severe renal impairment, or endstage renal disease which results in impaired clearance of the biguanide compound.

8. The use according to claim 3, wherein the patient has chronic kidney disease.

9. The use according to claim 1, wherein the patient has hyperglycemia.

10. The use according to claim 9, wherein the hyperglycemia is chronic.

11. The use according to claim 9 or claim 10, wherein the hyperglycemia is caused by type II diabetes.

12. Use of a biguanide compound in the manufacture of a medicament for treating a renally impaired patient having diabetes, wherein the biguanide compound is in a delayed-release formulation.

13. Use of a biguanide compound in the manufacture of a medicament for treating a diabetic patient having congestive heart failure, a hypoxic state and/or advanced liver disease, wherein the biguanide compound is in a delayed-release formulation.

14. Use of a biguanide compound in the manufacture of a medicament for reducing the onset of diabetes in a patient with pre-diabetes, wherein the biguanide compound is in a delayed-release formulation.

15. Use of a biguanide compound in the manufacture of a medicament for inducing weight loss in a patient, wherein the biguanide compound is in a delayed-release formulation.

16. The use according to any one of claims 1 to 15, wherein the biguanide compound has a reduced relative bioavailability of about 40, 50 or 60% in the delayed-release formulation in comparison with an immediate-release formulation having the same amount of the biguanide compound.

17. The use according to any one of claims 1 to 15, which produces a mean plasma AUC_{0-36} of the biguanide compound of less than about 14,000, 13,000 or 12,000 ng*h/mL when the delayed-release formulation is administered to the patient at 500 mg twice daily.

18. The use according to any one of claims 1 to 15, which produces a mean plasma C_{max} of the biguanide compound of less than about 800, 700 or 600 ng/mL when the delayed-release formulation is administered to the patient at 500 mg twice daily.

19. The use according to any one of claims 1 to 18, wherein the biguanide compound is targeted for delivery to the small intestine, and the delayed-release formulation comprises an oral dosage form enterically coated to release the biguanide compound at a pH at or above 5.0 or 5.5.

20. The use according to claim 19, wherein the biguanide compound is targeted for delivery to the distal small intestine, and the delayed-release formulation comprises an oral dosage form enterically coated to release the biguanide compound at a pH at or above 6.0 or 6.5.

21. The use according to claim 19 or 20, for use in combination with a modified release formulation of the biguanide compound.

22. The use according to claim 19 or 20, wherein the oral dosage form comprises less than 500 mg of the biguanide compound.

23. The use according to any one of claims 1 to 22, wherein the biguanide compound is selected from the group consisting of metformin, phenformin, buformin and imeglimin.

24. The use according to any one of claims 1 to 22, wherein the biguanide compound is metformin hydrochloride.

25. The use according to any one of claims 1 to 24, for use in combination with a DPP-IV inhibitor.

26. The use according to any one of claims 1 to 24, for use in combination with an anti-obesity or anti-diabetes agent.