[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 DISCLOSURE

[0011] The present disclosure resolves these longstanding problems with conventional delivery of biguanide compounds by delaying release of the compounds in the upper gastrointestinal tract and ensuring passage to and preferably through the duodenum before dissolution. As demonstrated herein, short-term fluctuations in stomach pH due to meals and other factors can lead to aberrant release patterns and produce spikes in systemic exposure to the biguanide compound, thereby increasing the risk of adverse events including gastrointestinal complications and, more dangerously, lactic acidosis in otherwise contraindicated patients.

[0012] In particular, the disclosure provides pharmaceutical compositions and formulations that deliver biguanide compounds to specific segments of the intestine while substantially

avoiding absorption of the biguanide in the stomach and duodenum. In preferred examples, the subject formulations are adapted to include both delayed release (DR) for delivery at a desired pH, *e.g.*, delivery at the pH of the distal small intestine, as well as a lag phase (LP) after contacting the desired pH during which drug release from the subject formulation is minimized in order to accommodate transient pH fluctuations in the stomach and ensure delayed release beyond the duodenum.

[0012a] In one aspect, provided herein is a delayed-release pharmaceutical composition for biguanide compound delivery, comprising an oral dosage form having a core comprising between 1 mg and 2000 mg of a biguanide compound and an enteric coating surrounding said core that delays release of said biguanide compound after ingestion until reaching one or more regions of the intestine downstream of the duodenum, wherein said oral dosage form is an enterically-coated tablet or capsule, wherein said enteric coating coats the core of said oral dosage at 3% to 8% (wt/wt) with respect to the core, and wherein said oral dosage form releases less than 15% of the biguanide *in vitro* after the composition contacts an aqueous medium of 0.1 N HCl for two hours, and wherein when the composition is subsequently transferred to an aqueous medium at a pH of 6.8, there is a lag phase of at least ten minutes, and at least 60% of the biguanide compound is released *in vitro* at pH 6.8 after the lag phase and within 60 minutes of the transfer, and at least 90% of the biguanide compound is released *in vitro* at pH 6.8 within 120 minutes of the transfer.

[0012b] In one aspect, provided herein is a use of the pharmaceutical composition as described herein in the manufacture of a medicament for reducing the risk of adverse events resulting from biguanide compound administration.

[0012c] In one aspect, provided herein is a use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating metabolic disorders in a patient in need thereof.

[0012d] In one aspect, provided herein is a use of the pharmaceutical composition as described herein in the manufacture of a medicament for reducing the onset of diabetes in a subject with pre-diabetes.

[0012e] In one aspect, provided herein is a use of the pharmaceutical composition as described herein in the manufacture of a medicament for inducing weight loss in a subject.

[0012f] In one aspect, provided herein is a use of the pharmaceutical composition as descrbied herein in the manufacture of a medicament for treating type I diabetes.

[0012g] In one aspect, provided herein is a use of the pharmaceutical composition as descrbied herein in the manufacture of a medicament for treating dyslipidemia.

[0012h] In one aspect, provided herein is a use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating obesity.

[0012i] In one aspect, provided herein is a pharmaceutical composition as described herein for use in therapy.

[0013] In one example, the formulation comprises an oral dosage form comprising a biguanide compound wherein the oral dosage form is adapted to minimize the release of the biguanide compound for a lag phase of at least about 5 or 10 minutes after contacting a pH of 6.0, 6.5, 6.8 or 7.0, more preferably for a lag phase of at least about 15 or 20 minutes after contacting the desired pH, still more preferably for a lag phase of at least about 25 or 30 minutes after contacting the desired pH in the distal small intestine. In a particularly preferred example, the formulation ensures passage of the biguanide through the stomach and release beyond the duodenum, with full release after a lag phase beginning at a pH of at least about 6.0, more preferably at least about 6.5, and still more preferably at 6.8 or 7.0.

[0014] In one example, an enteric coating is applied to the subject compositions at a weight gain of at least about 4.5 mg/cm^2, 5 mg/cm^2, 5.5 mg/cm^2, 6 mg/cm^2, 6.5 mg/cm^2, 7 mg/cm^2, 7.5 mg/cm^2, 8 mg/cm^2, 9 mg/cm^2, 10 mg/cm^2, 11 mg/cm^2, 12 mg/cm^2, or 15 mg/cm^2. In a further example, the enteric coating comprises an external layer on said formulation of at least about 5 mg/cm^2 to 7 mg/cm^2, more preferably at least about 5.5mg/cm^2 to at least about 6.5 mg/cm^2. As demonstrated herein, this ensures appropriate release at the desired intestinal location so as to avoid aberrant spikes in systemic biguanide compound exposure.

[0015] In alternative examples, an enteric coating of at least about 2.5% or 3% (wt/wt) weight gain, still more preferably at least about 3.5% or 4% (wt/wt) weight gain is applied to the subject composition to produce the desired lag phase. For tablets and capsules, the enteric coating can be applied to achieve about a 2.5% to about a 5%, 6%, 7%, 8%, 9% or 10% (wt/wt) weight gain, more preferably about a 3% to at least about a 6% (wt/wt) weight gain. For

granules and other multi-particulate dosage forms up to 20 or 30% (wt/wt) weight gain or more can be applied, preferably from about 20% - 50% (wt/wt), more preferably from about 30% - 50% (wt/wt).

[0016] In another example, pharmaceutical compositions are provided comprising an enterically-coated oral dosage form comprising a biguanide compound, wherein the dosage form is adapted to minimize the release of the biguanide for a lag phase of at least about 5 or 10 minutes after contacting a pH of 6.0, 6.5, 6.8 or 7.0, more preferably for a lag phase of at least about 15 or 20 minutes after contacting the desired pH, still more preferably for a lag phase of at least about 25 or 30 minutes after contacting a pH of 6.0, 6.5, 6.8 or 7.0. In one example, an enteric coating is applied to the pharmaceutical composition at a weight gain of at least about 4.5 mg/cm^{2}5 mg/cm^2, 5.5 mg/cm^2, 6 mg/cm^2, 6.5 mg/cm^2, 7 mg/cm^2, 7.5 mg/cm^2, 8 mg/cm^2, 9 mg/cm^2, 10 mg/cm^2, 11 mg/cm^2, 12 mg/cm^2, or 15 mg/cm^2. In another example, the enteric coating is applied at a weight gain of at least about 5 mg/cm^2 to 9.5 mg/cm^2, more preferably at least about 5.5 mg/cm^2 to at least about 7.6 mg/cm^2. In alternative examples, an enteric coating is applied to the pharmaceutical composition to achieve at least about a 3.0% to at least about a 7.0% (wt/wt) weight gain, more preferably at least about a 4% to at least about a 6% (wt/wt) weight gain.

[0017] In particular examples, pharmaceutical compositions are provided comprising an enterically-coated oral dosage form comprising a biguanide compound, wherein the dosage form is adapted to release less than about 10% 5%, 4%, 3%, 2% and preferably less than 1% of the biguanide compound after contacting an aqueous medium (*e.g.*, submersion) at a pH of less than about 2 for about two hours followed by contacting an aqueous medium at a pH equal to or less than about 5.5 for at least 30 to 45 minutes. In a preferred example, the enterically-coated dosage form releases less than about 5%, 2 % or 1% of the biguanide compound in an aqueous medium of 0.1 N HCl for two hours and less than about 5%, 2% or 1% when transferred to an aqueous medium at pH 5.5 for at least 30 to 45 minutes.

[0018] In further examples, the enterically-coated dosage form releases less than 15%, 10%, 5%, 3%, 2% or less than 1% of the biguanide compound during the lag phase after the dosage form is contacted with an aqueous medium at a pH of about 6.5 or 6.8, wherein the lag phase is at least ten, fifteen or twenty minutes. In a preferred example, the enterically-coated dosage

form releases less than about 15% of the biguanide compound when the dosage form is contacted with an aqueous medium at a pH of about 6.5 or 6.8 for a lag phase of at least ten minutes and releases from about 75% to about 100%, and more preferably greater than 90%, 95%, 98%, or 99% of the biguanide compound after contacting with an aqueous medium at a pH of about 6.5 or 6.8 for a total of ninety to 120 minutes.

[0019] In two-stage dissolution examples, pharmaceutical compositions are provided comprising an enterically-coated oral dosage form comprising a biguanide compound, wherein the dosage form is adapted to release less than 5%, 2% or 1% of the biguanide compound in an aqueous medium of 0.1 N HCl for two hours. In these examples, less than 15%, 10%, 5%, 3%, 2%, or preferably 1% of the biguanide compound is released after contacting an aqueous medium of 0.1 N HCl for two hours and subsequently transferred to an aqueous medium at a pH of about 6.8 for a lag phase of at least ten, fifteen or twenty minutes. In preferred examples, less than 15% of the biguanide compound is released after two hours at acid pH and a lag phase of at least ten or fifteen minutes at pH 6.8, and at least 60% of the biguanide compound is released after the lag phase and within 60 minutes at pH 6.8, and at least 90% of the biguanide compound is released within 90 to 120 minutes at pH 6.8.

[0020] In three-stage dissolution examples, pharmaceutical compositions are provided comprising an enterically-coated oral dosage form comprising a biguanide compound, wherein the dosage form is adapted to release less than 5%, 2% or 1% of the biguanide compound in an aqueous medium of 0.1 N HCl for two hours and less than 5%, 2% or 1% when transferred to an aqueous medium at pH 5.5 for at least one hour. In these examples, less than 25%, 20%, 15%, 10%, or 5% of the biguanide compound is released after two hours in aqueous medium of 0.1 N HCl, 30 minutes in an aqueous medium at pH 5.5, and during a lag phase of at least ten or fifteen minutes at pH 6.8. In preferred examples, less than 15%, 10% or 5% of the biguanide compound is released after two hours at acid pH, 30 minutes at pH 5.5 and a lag phase of at least ten or fifteen minutes at pH 6.8, and at least 60% of the biguanide compound is released after the lag phase and within 60 minutes at pH 6.8, and at least 90% of the biguanide compound is released within 90 to 120 minutes at pH 6.8.

[0021] In some examples, the enteric coating comprises a first polymer which minimizes the release of the biguanide compound for at least about 5 or 10 minutes after contacting a pH of 6.0,

6.5, 6.8 or 7.0, more preferably for at least about 15 or 20 minutes, still more preferably for at least about 25 or 30 minutes after contacting a pH of 6.0, 6.5, 6.8 or 7.0. In preferred examples the polymer is insoluble in acidic media, but dissolves by salt formation or the like above pH 7.0. In an exemplary preferred example the polymer is selected from the group consisting of Eudragit FS, Eugragit S, shellac, and/or combinations thereof.

[0022] In further examples, the enteric coating further comprises a second polymer that dissolves at a lower pH than the first polymer. In preferred examples, the second polymer is insoluble at pH 5.5 and below, but dissolves by salt formation or the like above pH 5.5. In an exemplary preferred example the second polymer is selected from the group consisting of Eudragit L, cellulose acetate succinate, hydroxy propyl methyl cellulose phthalate, hydroxy propyl methyl cellulose acetate succinate (hypromellose acetate succinate), polyvinyl acetate phthalate (PVAP) and sodium alginate, stearic acid, and/or combinations thereof.

[0023] In some examples the enteric coating comprises about 90% Eudragit FS and about 10% Eudragit L, about 80% Eudragit FS and about 20% Eudragit L, about 70% Eudragit FS and about 30% Eudragit L, about 60% Eudragit FS and about 40% Eudragit L, about 50% Eudragit FS and about 50% Eudragit L, about 40% Eudragit FS and about 60% Eudragit L, about 30% Eudragit FS and about 70% Eudragit L, about 20% Eudragit FS and about 80% Eudragit L, or about 10% Eudragit FS and about 90% Eudragit L. In preferred examples, Eudragit FS and said Eudragit L are present in about a 7:5 to about a 5:7 ratio, and more preferably about a 6:4 to about a 4:6 ratio. In an exemplary preferred example, the enteric coating comprises about 60% Eudragit FS and about 40% Eudragit L.

[0024] In some examples, a seal coating may be added between the core comprising the biguanide compound and the enteric coating. The seal coating material may be selected so as to have no effect on the drug release. Suitable materials include, *e.g.*, hydroxypropylmethyl cellulose (HPMC). In other examples, the seal coating material may be selected to extend the lag phase so as to further slow drug release after the enteric coating is breached. Suitable materials include, *e.g*. Eudragit E which dissolves in acid but swells at higher pH, and may be used to extend the lag phase after the enteric coating has been breached.

[0025] In one exemplary and preferred example, the seal coating comprises a mixture of hypromellose, titanium dioxide, polyethylene glycol 400 (macrogol), and polysorbate 80, *e.g.*

Opadry® White YS-1-7003 available from Colorcon Inc. In an alternative exemplary and preferred example, the seal coating comprises hypromellose, triacetin, and talc, *e.g.*Opadry® 03K19229 Clear also available from Colorcon Inc.

[0026] Accordingly, the subject formulations and compositions may further comprise a seal coating between the biguanide compound and the enteric coating, providing a total coating thickness corresponding to at least about 4% to 8% (wt./wt.) weight gain, more preferably at least about 4.5% to 6.0% (wt./wt.) weight gain. In some examples, the combination of the outer enteric coating and inner seal coat comprises at least about 6.9 mg/cm^2 to 13.3 mg/cm^2, more preferably at least about 7.8 mg/cm^2 to at least about 11.4 mg/cm^2.

[0027] In alternative examples, the subject formulations and compositions further comprise one or more disintegrants to accelerate the dissolution of the core upon breaching of the enteric coating. In preferred examples, the disintegrant comprises croscarmellose sodium, sodium starch glycolate, or combinations thereof.

[0028] In one example, the biguanide compound is selected from the group consisting of metformin, phenformin, buformin and imeglimin. In a preferred example, the biguanide compound comprises metforming or a salt thereof, preferably metformin hydrochloride.

[0029] In additional examples, the oral dosage forms disclosed herein further comprise a DPP-IV inhibitor. In another example, the oral dosage forms disclosed herein further comprise an additional anti-obesity and/or or anti-diabetes agent.

[0030] The oral dosage forms disclosed herein may preferably take the form of a tablet, capsule, or microsphere, which is preferably enterically coated. Preferably, the tablet, capsule or microsphere is smooth and does not comprise an embossed surface. However, tablets, capsules or microspheres comprising an embossed surface are alternative examples encompassed, wherein the coating thickness of the enteric coating and/or seal coating are adjusted accordingly to provide the delayed release and lag phase release profiles described herein.

[0031] Correspondingly, methods and compositions are provided for the treatment of metabolic disorders in patients, including otherwise contraindicated patient populations, by administering the lag phase-enhanced delayed-release formulations having the requisite coating to ensure targeted delivery of the biguanide compound to the small intestine of the patient, and

preferably the distal small intestine, and thereby minimize systemic bioavailability. The biguanide compounds of the disclosure may be administered to a subject in need thereof to treat various metabolic disorders, including obesity, dislipidemia or other disorders of lipid metabolism as well as hyperglycemic conditions and histopathological diseases associated with hyperglycemia, including type II diabetes, prediabetes, gestational diabetes and polycystic ovary syndrome. The effective use of biguanide compounds for prophylaxis and prevention of such diseases and disorders, as well as for more general weight loss purposes in overweight or mildly to severely obese individuals, is also explicitly contemplated.

[0032] In one example, methods of reducing the risk of an adverse event from biguanide administration are provided, comprising administering a therapeutically effective amount of a biguanide compound to a subject in need thereof in a delayed-release formulation that minimizes the release of the biguanide compound for a lag phase of at least about 5 or 10 minutes after contacting a pH of 6.0, 6.5, 6.8 or 7.0, more preferably for a lag phase of at least about 15 or 20 minutes, still more preferably for a lag phase of at least about 25 or 30 minutes after contacting a pH of 6.0, 6.5, 6.8 or 7.0. In one example, the adverse event is lactic acidosis. In another event, the adverse event is a gastrointesinal complication selected from the group comprising nausea, diarrhea, dyspepsia, and vomiting.

[0033] In another example, methods of reducing the risk of an adverse event from biguanide administration are provided, comprising administering an enterically-coated oral dosage form comprising a biguanide compound to a patient in need thereof, wherein the dosage form is adapted to release less than about 10% 5%, 4%, 3%, 2% and preferably less than 1% of the biguanide compound after contacting an aqueous medium at a pH of less than about 2 for about two hours followed by contacting an aqueous medium at a pH equal to or less than about 5.5 for at least 30 to 45 minutes. In a preferred example, the enterically-coated dosage form releases less than about 5%, 2 % or 1% of the biguanide compound in an aqueous medium of 0.1 N HCl for two hours and less than about 5%, 2% or 1% when transferred to an aqueous medium at pH 5.5 for at least 30 to 45 minutes.

[0034] In additional examples, the enterically-coated dosage form releases less than 15%, 10%, or 5% of the biguanide compound during the lag phase after the dosage form is contacted with an aqueous medium at a pH of about 6.5 or 6.8, wherein the lag phase is at least ten, fifteen

or twenty minutes. In a preferred example, the enterically-coated dosage form releases less than about 15% of the biguanide compound when the dosage form is contacted with an aqueous medium at a pH of about 6.5 or 6.8 for a lag phase of at least ten minutes and releases from about 75% to about 100%, and more preferably greater than 90%, 95%, 98%, or 99% of the biguanide compound after contacting with an aqueous medium at a pH of about 6.5 or 6.8 for a total of ninety to 120 minutes.

[0035] Also provided herein are methods 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 which minimizes the release of the biguanide compound for a lag phase of at least about 5 or 10 minutes after contacting a pH of 6.0, 6.5, 6.8 or 7.0, more preferably for a lag phase of at least about 15 or 20 minutes, still more preferably for a lag phase of at least about 25 or 30 minutes after contacting a pH of 6.0, 6.5, 6.8 or 7.0. In some examples, the subject methods comprise administering an enterically-coated oral dosage form comprising a biguanide compound to a patient in need thereof, where the dosage form is adapted to release less than about 10%, 5%, 4%, 3%, 2% or 1% of the biguanide compound at a pH of less than 2 for at least two hours, followed by a pH equal to or less than about 5.5 for at least 30 to 45 minutes. In further examples, the dosage form is adapted to release less than 15%, 10%, or 5% of the biguanide compound when the dosage form is contacted with an aqueous medium at a pH of about 6.8 or less for at least about ten or fifteen minutes.

[0036] Also provided herein are methods of reducing the onset of diabetes in a subject with pre-diabetes, comprising administering a therapeutically effective amount of a biguanide compound to said patient in a delayed-release formulation which minimizes the release of the biguanide compound for a lag phase of at least about 5 or 10 minutes after contacting a pH of 6.0, 6.5, 6.8 or 7.0, more preferably for a lag phase of at least about 15 or 20 minutes, still more preferably for a lag phase of at least about 25 or 30 minutes after contacting a pH of 6.0, 6.5, 6.8 or 7.0. In some examples, the subject methods comprise administering an enterically-coated oral dosage form comprising a biguanide compound to a patient in need thereof, where the dosage form is adapted to release less than about 10%, 5%, 4%, 3%, 2% or 1% of the biguanide compound at a pH of less than 2 for at least two hours, followed by a pH equal to or less than about 5.5 for at least 30 to 45 minutes. In further examples, the dosage form is adapted to release

less than 15%, 10%, or 5% of the biguanide compound when the dosage form is contacted with an aqueous medium at a pH of about 6.8 or less for at least about ten or fifteen minutes.

[0037] Also provided herein are methods of inducing weight loss in a subject, comprising administering a therapeutically effective amount of a biguanide compound to said patient in a delayed-release formulation which minimizes the release of the biguanide compound for a lag phase of at least about 5 or 10 minutes after contacting a pH of 6.0, 6.5, 6.8 or 7.0, more preferably for a lag phase of at least about 15 or 20 minutes, still more preferably for a lag phase of at least about 25 or 30 minutes after contacting a pH of 6.0, 6.5, 6.8 or 7.0. In some examples, the subject methods comprise administering an enterically-coated oral dosage form comprising a biguanide compound to a patient in need thereof, where the dosage form is adapted to release less than about 10%, 5%, 4%, 3%, 2% or 1% of the biguanide compound at a pH of less than 2 for at least two hours, followed by a pH equal to or less than about 5.5 for at least 30 to 45 minutes. In preferred examples, the dosage form is adapted to release less than 15%, 10%, or 5% of the biguanide compound when the dosage form is contacted with an aqueous medium at a pH of about 6.8 or less for at least about ten or fifteen minutes.

[0038] In some examples, the weight loss induced clinically results in over 5 pounds lost in the subject, e.g., over 10 pounds lost, preferably over 25 pounds lost, and even more preferably over 50 pounds lost. In other examples, the induced weight loss results in the subject having a body mass index between 18.5 and 24.9. In another example, the weight loss induced results in at least a loss of at least 0.5 inches in the waist circumference.

[0039] The methods and compositions disclosed herein are also suitable for patients having a contraindication for the biguanide compound, *e.g*, metformin, phenformin or buformin. Such contraindication may be a hypoxic condition, impaired lactate clearance, and/or impaired clearance of the biguanide compound, e.g., impaired metformin clearance.

[0040] For example, in one example, the methods disclosed herein may be used to treat a patient who may have a hypoxic condition, such as but not limited to respiratory failure and heart failure. In another example, the patient may have impaired lactate clearance. In another example, the patient may suffer from liver failure, which may result in impaired lactate clearance. In another example, the patient may have impaired clearance of the biguanide compound, which may be caused, *e.g.*, by renal impairment and/or kidney disease. Accordingly,

in one example the patient may have renal impairment. Such renal impairment may be moderate or severe renal impairment, or endstage renal disease. In another example, the patient may have kidney disease, which may be chronic. In another example, the patient may have hyperglycemia, which may be chronic, and which may be caused by type II diabetes.

[0041] Suitable biguanide compounds for use in the subject disclosure include, *e.g.*, metformin, phenformin, buformin or imeglimin, including analogs, salts, solvates, polymorphs, hydrates, N-oxides, and prodrugs of such compounds.

[0042] In preferred examples, the biguanide compound has a reduced relative bioavailability of 70%, 60%, 50%, 40%, 30%, 20% or 10% in the subject formulations compared to a conventional immediate-release (IR) or extended-release (XR) composition having the same amount of the biguanide compound. Accordingly, in specific examples, administration of the subject delayed-release formulation minimizes the mean plasma AUC, the mean plasma C_{max} and/or the circulating plasma concentration of the biguanide compound in said patient compared to an identical protocol administering an IR or XR formulation having the same amount of the biguanide compound. In preferred examples, the biguanide compound is metformin, the IR composition is Glucophage® and the XR composition is Glucophage® XR.

[0043] In one example, the mean plasma AUC_{0-36} of the biguanide compound is less than about 15,000 ng*h/mL or 14,000 ng*h/mL, preferably less than about 12,000 ng*h/mL, more preferably less than about 11,000 ng*h/mL, and most preferably less than about 10,000 ng*h/mL when administered at 2000 mg total daily dose (TDD) or 1000 mg twice a day (*bis in die*; abbreviated as "b.i.d" or "BID"). In another example, the mean plasma AUC_{0-36} of the biguanide compound is less than about 10,000 ng*h/mL, preferably less than about 9,000 ng*h/mL, more preferably less than about 8,000 ng*h/mL or 7,000 ng*h/mL, and most preferably less than about 6,000 ng*h/mL or 5,000 ng*h/mL when administered at 1000 mg TDD, 500 mg BID, or lower effective doses.

[0044] In one example, the mean plasma C_{max} of the biguanide compound is less than about 1100 ng/mL, preferably less than about 1000 ng/mL, more preferably less than about 950 ng/mL, and most preferably less than about 900 ng/mL when administered at 2000 mg TDD or 1000 mg BID. In another example, the mean plasma C_{max} of the biguanide compound is less than about 800 ng/mL, preferably less than about 700 ng/mL, more preferably less than about 600 ng/mL,

and most preferably less than about 600 ng/mL or 500 ng/mL when administered at 1000 mg TDD, 500 mg BID, or lower effective doses.

[0045] In one example, the resulting circulating plasma concentration of the biguanide compound is below about 5 μg/ml or 4 μg/ml, preferably below about 3 μg/ml or 2.5 μg/ml, more preferably below about 2 μg/ml, 1 μg/ml, 0.5 μg/ml, or 0.25 μg/ml in the patient.

[0046] Administration of the subject formulations may be twice daily in the morning and evening, or once daily (*omni in die*, abbreviated "OD"). In certain preferred examples, administration may be once daily in the morning, *e.g.*, before 1 pm, preferably before 12 noon or 11 am, more preferably before 10 or 9 am, or with the morning meal. In other preferred examples, administration may be once daily in the evening, *e.g.*, after 5 pm, more preferably after 6 pm or 7 pm, or with the evening meal. In another preferred example, administration may be once daily at bedtime.

[0047] The subject methods administer therapeutically effective amounts of the biguanide compound(s). Notably, however, the inventive methods provided herein advantageously allow for lower therapeutic doses than prior art formulations, both on a per unit basis and/or on a daily dose basis. In certain examples of the methods disclosed herein, the biguanide compound is administered twice daily in an oral dosage form at a per unit dose greater than 500 mg BID, *e.g.* 600 or 800 mg BID. In certain preferred examples of the methods

disclosed herein, the twice daily oral dosage is less than 500 mg BID, *e.g.*, less than 400 mg BID, *e.g.*, less than 300 mg BID, *e.g.*, about 150, 200 or 250 mg BID. In alternative preferred examples, the biguanide compound is administered once a day at a per unit dose of 75 mg OD, 125 mg OD, 250 mg OD, 300 mg OD, 500 mg OD, 600 mg OD, 750 mg OD, 800 mg OD or 1000 mg OD. In additional examples, the total daily dose of the biguanide compound is less than 2000 mg/day, preferably less than 1500 mg/day, more preferably less than 1000 or 750 mg/day, most preferably less than 500, 400, 300, or 200 mg/day.

[0048] In another example, the oral dosage form may further comprise an extended-release formulation for the biguanide compound. In preferred examples, the biguanide compound is targeted for delivery to the distal small intestine.

[0049] 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 examples, the biguanide compound is a metformin salt selected from the group consisting of hydrochloride, phosphate, sulfate, hydrobromide, salicylate, maleate, hemi-maleate, benzoate, succinnate, hemi- succinnate, ethanesulfonate, fumarate, hemi-fumarate, glycolate, palmoate, oratate, acetate, isobutyrate, acetylsalicylate, nicotinateic acid, adamantoate, chlorophylin including zinc-chlorophylin, carboxylateic acid, benzoateic acid, dichloroacetateic acid, theophylin-7-acetate, clofibrate, tartrate, oxalate, hemi-oxalate, tannate and hydroxyl acid. In a particularly preferred example, the biguanide compound is metformin hydrochloride.

[0050] 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 such as, *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 examples 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0051] FIG. 1 shows the design of the study described in Example 1.

[0052] FIG. 2 shows the events during the treatment period of the study described in Example 1.

[0053] 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.

[0054] FIG. 4A shows the plasma concentration of PYY (x-axis; pg/mL) as a function of time (y-axis; min) in subjects at baseline (□,○) or after ingestion of either Metformin IR (●) or Metformin DR (■) and after a meal at t = 0 min. FIG.4B shows the plasma concentration of active GLP-1(x-axis; GLP-1A pmol/L) as a function of time (y-axis; min) in subjects at baseline (□,○) or after ingestion of either Metformin IR (●) or Metformin DR (■) and after a meal at t = 0 min. FIG. 4C shows the plasma concentration of total GLP-1 (x-axis; GLP-1T pmol/L) as a

What is claimed is:

1. A delayed-release pharmaceutical composition for biguanide compound delivery, comprising an oral dosage form having a core comprising between 1 mg and 2000 mg of a biguanide compound and an enteric coating surrounding said core that delays release of said biguanide compound after ingestion until reaching one or more regions of the intestine downstream of the duodenum, wherein said oral dosage form is an enterically-coated tablet or capsule, wherein said enteric coating coats the core of said oral dosage at 3% to 8% (wt/wt) with respect to the core, and wherein said oral dosage form releases less than 15% of the biguanide *in vitro* after the composition contacts an aqueous medium of 0.1 N HCl for two hours, and wherein when the composition is subsequently transferred to an aqueous medium at a pH of 6.8, there is a lag phase of at least ten minutes, and at least 60% of the biguanide compound is released *in vitro* at pH 6.8 after the lag phase and within 60 minutes of the transfer, and at least 90% of the biguanide compound is released *in vitro* at pH 6.8 within 120 minutes of the transfer.

2. The pharmaceutical composition according to claim 1, wherein said enteric coating has a coating weight of at least 4.5 mg/cm^2.

3. The pharmaceutical composition according to claim 1 or claim 2, wherein said enteric coating has a coating weight of at least 5.0 mg/cm^2.

4. The pharmaceutical composition according to any one of claims 1 to 3, wherein said enteric coating coats the core of said oral dosage form at 3% to 7% (wt/wt) with respect to the core.

5. The pharmaceutical composition according to any one of claims 1 to 4, wherein said enteric coating coats the core of said oral dosage form at 3% to 6% (wt/wt) with respect to the core.

6. The pharmaceutical composition according to any one of claims 1 to 4, wherein said enteric coating coats the core of said oral dosage form at 3% to 5% (wt/wt) with respect to the core.

7. The pharmaceutical composition according to any one of claims 1 to 4, wherein said enteric coating coats the core of said oral dosage form at 3.8% (wt/wt) with respect to the core.

8. The pharmaceutical composition according to any one of claims 1 to 7, further comprising a seal coating between the core and the enteric coating, providing a total coating of 4% to 8% (wt./wt.) with respect to the core.

9. The pharmaceutical composition according to any one of claims 1 to 7, further comprising a seal coating between the core and the enteric coating, providing a total coating of 4.5% to 6% (wt./wt.) with respect to the core.

10. The pharmaceutical composition according to any one of claims 1 to 7, further comprising a seal coating between the core and the enteric coating, providing a total coating of 21 mg/cm^2 to 41 mg/cm^2.

11. The pharmaceutical composition according to any one of claims 1 to 7, further comprising a seal coating between the core and the enteric coating, providing a total coating of 23 mg/cm^2 to 35 mg/cm^2.

12. The pharmaceutical composition according to any one of claims 1 to 11, wherein said oral dosage form releases less than about 15%, 10%, or 5% of said biguanide compound during said lag phase.

13. The pharmaceutical composition according to any one of claims 1 to 12, wherein said oral dosage form releases between about 75% to about 100% of said biguanide compound within about 90 minutes after contacting a pH of about 6.8.

14. The pharmaceutical composition according to any one of claims 1 to 13, wherein said enteric coating comprises a polymer that is insoluble in acidic media, but dissolves above pH 7.0.

15. The pharmaceutical composition according to claim 14, wherein said polymer is Eudragit FS.

16. The pharmaceutical composition according to any one of claims 1 to 15, wherein said enteric coating further comprises a polymer that is insoluble at pH 5.5 and below, but dissolves above pH 5.5.

17. The pharmaceutical composition according to claim 16, wherein said polymer is Eudragit L.

18. The pharmaceutical composition according to any one of claims 1 to 13, wherein said enteric coating comprises Eudragit FS and Eudragit L present in about a 7:5 to about a 5:7 (wt/wt) ratio.

19. The pharmaceutical composition according to claim 18, wherein said Eudragit FS and said Eudragit L are present in about a 6:4 to about a 4:6 (wt/wt) ratio.

20. The pharmaceutical composition according to claim 18, wherein said enteric coating comprises (wt/wt) about 60% Eudragit FS and about 40% Eudragit L.

21. The pharmaceutical composition according to any one of claims 8 to 11, wherein the seal coating comprises hypromellose, titanium dioxide, polyethylene glycol 400, polysorbate 80, triacetin, talc, or a combination thereof.

22. The pharmaceutical composition according to any one of claims 1 to 21, wherein said biguanide compound is selected from the group consisting of metformin, phenformin, buformin, imeglimin, and a salt thereof.

23. The pharmaceutical composition according to claim 22 wherein said biguanide compound comprises metformin or a salt thereof.

24. The pharmaceutical composition according to claim 23, wherein said biguanide comprises metformin hydrochloride.

25. The pharmaceutical composition according to any one of claims 1 to 24, wherein said lag phase is at least 15 minutes after contacting a pH of at least 6.8.

26. The pharmaceutical composition according to any one of claims 1 to 24, wherein said lag phase is at least 20 minutes after contacting a pH of at least 6.8.

27. The pharmaceutical composition according to any one of claims 1 to 24, wherein said lag phase is at least t 25 minutes after contacting a pH of at least 6.8.

28. The pharmaceutical composition according to any one of claims 1 to 24, wherein said lag phase is at least 30 minutes after contacting a pH of at least 6.8.

29. The pharmaceutical composition according to any one of claims 1 to 28, wherein said dosage form releases greater than 95% of said biguanide compound after contacting a pH of about 6.8 for a total of 90 to 120 minutes.

30. The pharmaceutical composition according to any one of claims 1 to 28, wherein said dosage form releases greater than 99% of said biguanide compound after contacting a pH of about 6.8 for a total of 90 to 120 minutes.

31. The pharmaceutical composition according to any one of claims 1 to 28, wherein said dosage form releases 100% of said biguanide compound after contacting a pH of about 6.8 for a total of 90 to 120 minutes.

32. The pharmaceutical composition according to any one of claims 1 to 31, wherein said enteric coating delays release of said biguanide compound after ingestion until reaching one or more regions of the intestine downstream of the jejunum.

33. The pharmaceutical composition according to any one of claims 1 to 31, wherein said enteric coating delays release of said biguanide compound after ingestion until reaching one or more regions of the intestine downstream of the ileum.

34. Use of the pharmaceutical composition according to any one of claims 1 to 33 in the manufacture of a medicament for reducing the risk of adverse events resulting from biguanide compound administration.

35. The use according to claim 34, wherein the adverse event is lactic acidosis.

36. The use according to claim 34, wherein said adverse event is a gastrointestinal complication selected from the group consisting of nausea, diarrhea, dyspepsia, and vomiting.

37. Use of the pharmaceutical composition according to any one of claims 1 to 33 in the manufacture of a medicament for treating metabolic disorders in a patient in need thereof.

38. The use according to claim 37, wherein said patient has a contraindication for the biguanide compound.

39. The use according to claim 38, 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.

40. The use according to claim 39, wherein the patient has moderate renal impairment, severe renal impairment, or end stage renal disease which results in impaired clearance of the biguanide compound.

41. The use according to any one of claims 37 to 40, wherein the patient in need thereof has hyperglycemia.

42. The use according to claim 41, wherein the hyperglycemia is chronic.

43. The use according to claim 41 or 42, wherein the hyperglycemia is caused by type II diabetes.

44. Use of the pharmaceutical composition according to any one of claims 1 to 33 in the manufacture of a medicament for reducing the onset of diabetes in a subject with pre-diabetes.

45. Use of the pharmaceutical composition according to any one of claims 1 to 33 in the manufacture of a medicament for inducing weight loss in a subject.

46. Use of the pharmaceutical composition according to any one of claims 1 to 33 in the manufacture of a medicament for treating type I diabetes.

47. Use of the pharmaceutical composition according to any one of claims 1 to 33 in the manufacture of a medicament for treating dyslipidemia.

48. Use of the pharmaceutical composition according to any one of claims 1 to 33 in the manufacture of a medicament for treating obesity.

49. The pharmaceutical composition according to any one of claims 1 to 33 for use in therapy.