

[00417] The specified tablet or capsule formulations of Table 1 may include co-formulation with an anti-psychotic drug. The combination used to treat the psychotic condition and to treat or prevent weight gain, dyslipidemia or impaired glucose tolerance in the treated subject. Drugs for treating various psychotic conditions that may be used include, but are not limited to, lithium or a salt thereof (250 to 2500 mg/unit), carbamazepine or a salt thereof (50 to 1200 mg/unit), valproate, valproic acid, or divalproex (125 to 2500 mg/unit), lamotrigine (12.5 to 200 mg/unit), olanzapine (5 to 20 mg/unit), clozapine (12.5 to 450 mg/unit), or risperidone (0.25 to 4 mg/unit). These coformulations are preferably intended for once per day administration. For a twice daily dosing, the amount of KATP channel opener selected from a salt of a compound of Formulae I–VIII is preferably half the amount included in the once daily formulation and the co-formulated anti-psychotic is half of the amount specified.

[00418] The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat or prevent ischemic or reperfusion injury. Drugs for treating or preventing ischemic or reperfusion injury that may be used include, but are not limited to: low molecular weight heparins (e.g., dalteparin, enoxaparin, nadroparin, tinzaparin or danaparoid), anecrod, pentoxifylline, nimodipine, flunarizine, ebselen, tirilazad, clomethiazole, an AMPA agonist (e.g., GYKI 52466, NBQX, YM90K, zonampanel, or MPQX), SYM 2081, selfotel, Cerestat, CP-101,606, dextrophan, dextromethorphan, MK-801, NPS 1502, remacemide, ACEA 1021, GV150526, eliprodil, ifenprodil, lubeluzole, naloxone, nalmefene citicoline, acetyl-L-carnitine, nifedipine, resveratrol, a nitro derivative, clopidogrel, dabigatram, prasugrel, troxoprodil, AGY-94806, or KAI-9803.

[00419] Provided are formulations administered once or twice daily to an obese or overweight subject continuously result in a circulating concentration of KATP channel opener selected from a salt of a compound of Formulae I – VIII sufficient to induce weight loss. Weight loss occurs by the preferential loss of body fat. Additional weight loss can occur when the formulation is administered in combination with a reduced caloric diet.

[00420] Provided are formulations of KATP channel openers selected from a salt of a compound of Formulae I – VIII administered as a single dose to an obese, overweight or

obesity-prone subject that result in the inhibition of fasting or glucose stimulated insulin secretion for about 24 hours or for about 18 hours.

[00421] Provided are formulations of KATP channel openers selected from a salt of a compound of Formulae I – VIII administered as a single dose to an obese, overweight or obesity-prone subject that result in the elevation of energy expenditure for about 24 hours or for about 18 hours.

[00422] Provided are formulations of KATP channel openers selected from a salt of a compound of Formulae I – VIII administered as a single dose to an obese, overweight or obesity-prone subject that result in the elevation of beta oxidation of fat for about 24 hours or for about 18 hours.

[00423] Provided are formulations of KATP channel openers selected from a salt of a compound of Formulae I – VIII administered as a single dose to an obese, overweight or obesity-prone hyperphagic subject that result in the inhibition of hyperphagia for about 24 hours or for about 18 hours.

[00424] Provided are formulations suitable for continuous administration once or twice daily (per 24 hours) to a subject, resulting in a circulating concentration of KATP channel openers selected from a salt of a compound of Formulae I – VIII sufficient to induce either beta-cell rest or improved insulin sensitivity or both. Such beta-cell rest and improvements in insulin sensitivity can contribute to effective treatment of type I diabetes, type II diabetes and prediabetes. Such beta-cell rest and improvements in insulin sensitivity can contribute to effective restoration of normal glucose tolerance in type II diabetic and prediabetic subjects.

[00425] The various pharmaceutical KATP channel opener formulations selected from a salt of a compound of Formulae I – VIII have a variety of applications, including, but not limited to: (1) treatment of obesity; (2) prevention of weight gain in subjects who are predisposed to obesity; (3) treatment of hyperinsulinemia or hyperinsulinism; (4) treatment of hypoglycemia; (5) treatment of hyperlipidemia, (6) treatment of type II diabetes, (7) preservation of pancreatic function in type I diabetics; (8) treatment of metabolic syndrome (or syndrome X); (9) prevention of the transition from prediabetes to diabetes, (10) correction of the defects in insulin secretion and insulin sensitivity

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contributing to prediabetes and type II diabetes, (11) treatment of polycystic ovary syndrome, (12) prevention of ischemic or reperfusion injury, (13) treat weight gain, dyslipidemia, or impairment of glucose tolerance in subjects treated with antipsychotics drugs, (14) prevent weight gain, dyslipidemia, or impairment of glucose tolerance in subjects treated with antipsychotics drugs and (15) treatment of any disease where hyperlipidemia, hyperinsulinemia, hyperinsulinism, hyperlipidemia, hyperphagia or obesity are contributing factors to the severity or progression of the disease, including but not limited to, Prader Willi Syndrome, Friesch's syndrome, Cohen syndrome, Summitt Syndrome, Alstrom Syndrome, Bjorjesen Syndrome, Bardet-Biedl Syndrome, or hyperlipoproteinemia type I, II, III, and IV.

[00426] In one embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an oral dosage once per 24 hours to induce weight loss. In further embodiments, the subject (a) is not a type I diabetic, (b) is not a type II diabetic, (c) is not experiencing chronic, recurrent or drug-induced hypoglycemia, (d) does not have metabolic syndrome, or (e) is not experiencing malignant hypertension.

[00427] In one embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an oral dosage twice per 24 hours to induce weight loss. This treatment can be the sole treatment to induce weight loss. In further embodiments, the overweight or obese subject (a) does not have an insulin secreting tumor, (b) is not suffering from Poly Cystic Ovary Syndrome, (c) is not a type I diabetic, (d) is not a type II diabetic, (e) does not have metabolic syndrome, (f) is not experiencing chronic recurrent or drug-induced hypoglycemia, (g) has not been treated for schizophrenia with haloperidol, or (h) is not experiencing malignant hypertension. In further embodiments, the overweight or obese adolescent (a) has not been diagnosed as being type I or type II diabetic, (b) is not experiencing chronic, recurrent or drug-induced hypoglycemia, or (c) has not been diagnosed as having metabolic syndrome.

[00428] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an oral dosage form three times per 24 hours to induce weight loss. This treatment can be

the sole treatment to induce weight loss. In further embodiments, the overweight or obese subject (a) does not have an insulin-secreting tumor, (b) is not suffering from Poly Cystic Ovary Syndrome, (c) is not a type I diabetic, (d) is not a type II diabetic, (e) does not have metabolic syndrome, or (f) is not experiencing chronic, recurrent or drug-induced hypoglycemia.

[00429] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese adolescent as an oral dosage form three times per 24 hours to induce weight loss. This treatment can be the sole treatment to induce weight loss. In further embodiments, the overweight or obese adolescent is (a) is not a type I or type II diabetic, (b) is not experiencing chronic, recurrent or drug-induced hypoglycemia or (c) does not have metabolic syndrome.

[00430] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered as an oral dosage form three times per 24 hours to induce weight loss to an overweight or obese adult who (a) is not simultaneously receiving glucagon injections, triiodothyroxin or furosemide, (b) is not being treated for schizophrenia with haloperidol, or (c) is not experiencing malignant hypertension.

[00431] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an oral dosage form four times per 24 hours to induce weight loss.

[00432] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an oral dosage form administered from one, two, three or four times per 24 hours to induce weight loss at a daily dose of 50 to 700 mg. In a further embodiment, the overweight or obese subject (a) is not type I diabetic, (b) is not type II diabetic, (c) is not suffering chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00433] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an oral dosage form administered from one, two, three or four times per 24 hours to induce weight loss at a daily dose of 130 to 400 mg. In a further embodiment, the overweight or

obese subject (a) is not type I diabetic, (b) is not type II diabetic, (c) is not suffering chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00434] In other embodiments, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obesity prone subject as an oral dosage form one, two, three or four times per 24 hours to maintain a weight loss, as it is preferable to maintain weight in an obese subject once some weight loss has occurred when the alternative is to regain weight. In a further embodiment, the administered daily dose of the KATP channel opener is 50 to 275 mg.

[00435] In other embodiments, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered as an oral dosage form to an overweight, obese, or obesity prone subject to (a) elevate energy expenditure, (b) elevate beta oxidation of fat, or (c) reduce circulating triglyceride concentrations.

[00436] In other embodiments, an oral dosage of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to a subject in need thereof to induce the loss of 25%, 50%, or 75% of initial body fat.

[00437] In another embodiment, an oral dosage of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to a subject in need thereof to induce (a) the preferential loss of body fat or (b) the preferential loss of visceral body fat.

[00438] In additional embodiments, an oral dosage of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered one, two or three times per 24 hours at daily doses of 50 to 700 mg to a subject to (a) induce the loss of 25%, 50% or 75% of initial body fat, (b) induce the preferential loss of body fat, or (c) induce the preferential loss of visceral fat.

[00439] In another embodiment, an oral dosage of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to a subject to induce the preferential loss of body fat and to induce reduction in circulating triglycerides.

[00440] In another embodiment, an oral dosage of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with sibutramine, orlistat, rimonabant, an appetite suppressant, an anti-depressant, an anti-epileptic, a diuretic, a drug that induces weight loss by a mechanism that is distinct from a KATP channel opener, or a drug that lowers blood pressure, to induce weight loss and/or treat obesity associated co-morbidities in an overweight, obese, or obesity prone subject. In further embodiments, the overweight, obese, or obesity prone subject (a) is a type I diabetic, (b) is not a type II diabetic, (c) is not suffering from chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00441] In another embodiment an oral dosage of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with an anti-depressant, a drug that lowers blood pressure, a drug that lowers cholesterol, a drug that raises HDL, an anti-inflammatory that is not a Cox-2 inhibitor, a drug that lowers circulating triglycerides, to an overweight, obese, or obesity prone subject to induce weight loss and/or treat obesity associated co-morbidities. In further embodiments, the overweight, obese, or obesity prone subject (a) is not a type I diabetic, (b) is not a type II diabetic, (c) is not suffering from chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00442] In another embodiment, an oral dosage of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with a drug that lowers blood pressure, a drug that lowers cholesterol, a drug that raises HDL, an anti-inflammatory that is not a Cox-2 inhibitor, a drug that lowers circulating triglycerides, to maintain weight and/or treat obesity associated co-morbidities in an overweight, obese, or obesity prone subject, as it is preferable to maintain weight in an obese subject once some weight loss has occurred when the alternative is to regain weight. In further embodiments, the overweight, obese, or obesity prone subject (a) is not a type I diabetic, (b) is not a type II diabetic, (c) is not suffering from chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00443] In additional embodiments, an oral dosage form of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is used to administer a therapeutically effective dose of a KATP channel opener to an obese, overweight or

obesity prone subject in need thereof to treat obesity, to (a) provide beta cell rest, (b) treat type I or type II diabetes, or (c) prevent the occurrence of diabetes.

[00444] In additional embodiments, an oral dosage form of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with Phentermine or a derivative thereof to an obese adult or adolescent to induce weight loss and/or treat obesity and obesity-associated co-morbidities. In further embodiments, a solid oral dosage form or tablet formulation of a KATP channel opener is co-administered with Phentermine or a derivative thereof to an obese adult or adolescent to treat metabolic syndrome in a patient in need thereof.

[00445] In further embodiments, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII at doses of 50 to 700 mg/day is co-administered with Phentermine or a derivative thereof at daily doses of 15 to 37.5 mg to an overweight or obese subject to induce weight loss, to treat metabolic syndrome, or to induce weight loss and treat obesity-associated co-morbidities.

[00446] In another embodiment, a quick dissolving formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is used to provide a therapeutically effective dose to a patient in need thereof.

[00447] In further embodiments, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered once per 24 hours at doses of 50 mg to 700 mg to an overweight or obese subject.

[00448] In further embodiments, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is formulated as a tablet or capsule for oral administration. The tablet or capsule may be co-formulated with metformin. In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is formulated as an oral suspension or solution, and the oral suspension or solution may be further encapsulated in another embodiment.

[00449] In another embodiment, a pharmaceutical salt of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is formulated as a tablet or

capsule for oral administration, or as an oral suspension or as an oral solution, or as an oral suspension or solution that is encapsulated.

[00450] In another embodiment a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-formulated with hydro-chlorothiazide, chlorothiazide, cyclothiazide, benzthiazide, metyclothiazide, bendro-flumethiazide, hydroflumethiazide, trichlormethiazide, or polythiazide in a pharmaceutical formulation suitable for oral administration.

[00451] Upon administration of formulations which include a salt of a compound of Formulae I – VIII provided herein to humans or animals, some or all of the following effects are observed: (1) the production of lipoprotein lipase by adipocytes is reduced; (2) enhanced lipolysis by adipocytes; (3) expression of fatty acid synthase by adipocytes is reduced; (4) glyceraldehydes phosphate dehydrogenase activity of adipocytes is reduced; (5) little or no new triglycerides are synthesized and stored by adipocytes; (6) enhanced expression of $\beta 3$ Adrenergic Receptor ($\beta 3AR$) an improvement in the adrenergic function in adipocytes; (7) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (8) decreased insulinemia; (9) enhanced blood glucose levels; (10) increased expression of Uncoupling Protein 1 in adipocytes; (11) enhanced thermogenesis in white and brown adipose tissue; (12) reduction of plasma triglyceride concentration; (13) decrease in circulating leptin concentrations; (14) up-regulation of insulin receptors; (15) enhanced glucose uptake; (16) reduced adipocyte hyperplasia; (17) reduced adipocyte hypertrophy; (18) reduced rates of conversion of preadipocytes to adipocytes; (19) reduced rates of hyperphagia; (20) increased protection of CNS, cardiac and other tissues from ischemic or reperfusion injury; (21) improved insulin sensitivity; (22) elevated CSF insulin concentrations; (23) elevated circulating adiponectin concentrations; (25) reduced circulating triglyceride concentrations; (26) enhancement of beta-cell rest.

[00452] Threshold concentrations of the current invention include those circulating concentrations of KATP channel openers resulting from the administration of salts of compounds of Formulae I – VIII as an i.v. formulation, an immediate release oral formulation, a controlled release formulation, a transdermal formulation, or an intranasal formulation to an overweight or obese subject which results in (1) measurable suppression of fasting insulin levels, (2) suppression of fasting insulin levels by at least

20% from the baseline measurement in the same subject prior to treatment with a K_{ATP} channel opener selected from a salt of a compound of Formulae I – VIII, (3) suppression of fasting insulin levels by at least 30% from the baseline measurement in the same subject prior to treatment with a K_{ATP} channel opener selected from a salt of a compound of Formulae I – VIII, (4) suppression of fasting insulin levels by at least 40% from the baseline measurement in the same subject prior to treatment with a K_{ATP} channel opener selected from a salt of a compound of Formulae I – VIII, (5) suppression of fasting insulin levels by at least 50% from the baseline measurement in the same subject prior to treatment with a K_{ATP} channel opener selected from a salt of a compound of Formulae I – VIII, (6) suppression of fasting insulin levels by at least 60% from the baseline measurement in the same subject prior to treatment with a K_{ATP} channel opener selected from a salt of a compound of Formulae I – VIII, (7) suppression of fasting insulin levels by at least 70% from the baseline measurement in the same subject prior to treatment with a K_{ATP} channel opener selected from a salt of a compound of Formulae I – VIII, (8) suppression of fasting insulin levels by at least 80% from the baseline measurement in the same subject prior to treatment with a K_{ATP} channel opener selected from a salt of a compound of Formulae I – VIII, (9) loss of weight, (10) elevation of resting energy expenditure, or (11) elevation of the oxidation of fat or fatty acids. Threshold effects of the current invention include those circulating concentrations of K_{ATP} channel openers selected from salts of compounds of Formulae I – VIII resulting from the administration of an i.v. formulation of the drug, or an immediate release oral formulation of the drug, or a controlled release formulation of the drug, or a sustained release formulation, or a transdermal formulation, or an intranasal formulation of the drug to an obesity prone subject which result in (1) the loss of weight, and (2) the maintenance of weight. Threshold effects of the current invention include those circulating concentrations of K_{ATP} channel openers selected from salts of compounds of Formulae I – VIII resulting from the administration of an i.v. formulation of the drug, or an immediate release oral formulation of the drug, or a controlled release formulation of the drug, or a sustained release formulation, or a transdermal formulation, or an intranasal formulation of the drug to a prediabetic subject which result in prevention of the transition to diabetes. Threshold effects of the current invention include those circulating concentrations of K_{ATP} channel openers resulting from the administration of salts of compounds of Formulae I – VIII as

an i.v. formulation, or an immediate release oral formulation, or a controlled release formulation, or a sustained release formulation, or a transdermal formulation, or an intranasal formulation to a subject with type 1 diabetes which result in beta cell rest.

[00453] The mode of action by which weight is maintained or lost resulting from the prolonged administration of K_{ATP} channel openers selected from salts of compounds of Formulae I – VIII to overweight, obese or obesity prone subjects as provided herein includes, but is not limited to, one or more of (1) enhanced energy expenditure, (2) enhanced oxidation of fat and fatty acids, (3) enhancement of lipolysis in adipose tissue, (4) enhanced glucose uptake by tissues and enhanced insulin sensitivity, and (5) improved beta adrenergic response. The mode of action by which weight is maintained or lost resulting from the prolonged administration of K_{ATP} channel openers selected from salts of compounds of Formulae I – VIII to obese or obesity prone subjects as provided herein may also include the suppression of appetite.

[00454] Prolonged administration of pharmaceutical formulations of K_{ATP} channel openers selected from salts of compounds of Formulae I – VIII to overweight or obese humans or animals results in substantial and sustained weight loss including some or all of the following effects: (1) preferential loss of body fat; (2) loss of greater than 25% of initial body fat mass; (3) loss of greater than 50% of initial body fat mass; (4) loss of greater than 75% of initial body fat mass; (5) significant increase in resting energy expenditure; (6) increase in the oxidation of fat and fatty acids; (7) reduction in blood pressure; (8) production of lipoprotein lipase by adipocytes is reduced; (9) enhanced lipolysis by adipocytes; (10) expression of fatty acid synthase by adipocytes is reduced; (11) glyceraldehydes phosphate dehydrogenase activity of adipocytes is reduced; (12) little or no new triglycerides are synthesized and stored by adipocytes; (13) enhanced expression of β_3 Adrenergic Receptor (β_3AR) and an improvement in the adrenergic function in adipocytes; (14) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (15) decreased insulinemia; (16) enhanced blood glucose levels; (17) increased expression of Uncoupling Protein 1 in adipocytes; (18) enhanced thermogenesis in white and brown adipose tissue; (19) reduction of plasma triglyceride concentration; (20) decrease in circulating leptin concentrations; (21) up-regulation of insulin receptors; (22) enhanced glucose uptake; (23) reduced adipocyte hyperplasia; (24) reduced adipocyte

hypertrophy; (25) reduced rates of conversion of preadipocytes to adipocytes; (26) reduced rates of hyperphagia; (27) the sequential loss first of the metabolically most active adipose tissue (visceral), followed by the loss of less metabolically active adipose tissue; (28) elevation of circulating adiponectin concentrations; (29) elevation of cerebrospinal fluid insulin levels; (30) enhanced islet insulin mRNA and insulin content; or (31) enhanced metabolic efficiency of insulin.

[00455] Prolonged administration of formulations of KATP channel openers selected from salts of compounds of Formulae I – VIII to obesity prone humans or animals, including subjects who have undergone various types of bariatric surgery, results in sustained maintenance of weight including some or all of the following effects: (1) increased resting energy expenditure; (2) increase in the oxidation of fat and fatty acids; (3) reduction in blood pressure; (4) production of lipoprotein lipase by adipocytes is reduced; (5) enhanced lipolysis by adipocytes; (6) expression of fatty acid synthase by adipocytes is reduced; (7) glyceraldehyde phosphate dehydrogenase activity of adipocytes is reduced; (8) little or no new triglycerides are synthesized and stored by adipocytes; (9) enhanced expression of $\beta 3$ Adrenergic Receptor ($\beta 3$ AR) and improvement in the adrenergic function in adipocytes; (10) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (11) decreased insulinemia; (12) enhanced blood glucose levels; (13) increased expression of Uncoupling Protein 1 in adipocytes; (14) enhanced thermogenesis in white and brown adipose tissue; (15) reduction of plasma triglyceride concentration; (16) decreased circulating leptin concentration; (17) up-regulation of insulin receptors; (18) enhanced glucose uptake; (19) reduced adipocyte hyperplasia; (20) reduced adipocyte hypertrophy; (21) reduced rates of conversion of preadipocytes to adipocytes; (22) reduced rates of hyperphagia; (23) elevated circulating adiponectin concentration; (24) elevated cerebrospinal fluid insulin levels; (25) enhanced islet insulin mRNA and insulin content; or (26) enhanced metabolic efficiency of insulin.

[00456] Immediate or prolonged administration of formulations of KATP channel openers selected from salts of compounds of Formulae I – VIII to prediabetic or type I diabetic humans or animals results in the prevention of beta cell failure, improved glycemic control, and prevention of the transition from prediabetes to diabetes including some or all of the following effects: (1) increase in resting energy expenditure; (2)

increase in the oxidation of fat and fatty acids; (3) reduction in blood pressure; (4) production of lipoprotein lipase by adipocytes is reduced; (5) enhanced lipolysis by adipocytes; (6) expression of fatty acid synthase by adipocytes is reduced; (7) glyceraldehyde phosphate dehydrogenase activity of adipocytes is reduced; (8) little or no new triglycerides are synthesized and stored by adipocytes; (9) enhanced expression of $\beta 3$ Adrenergic Receptor ($\beta 3$ AR) and an improvement in the adrenergic function in adipocytes; (10) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (11) decreased insulinemia; (12) enhanced blood glucose levels; (13) increased expression of Uncoupling Protein 1 in adipocytes; (14) enhanced thermogenesis in white and brown adipose tissue; (15) reduction of plasma triglyceride concentration; (16) decreased circulating leptin concentrations; (17) up-regulation of insulin receptors; (18) enhanced glucose uptake; (19) reduced adipocyte hyperplasia; (20) reduced adipocyte hypertrophy; (21) reduced rates of conversion of preadipocytes to adipocytes; (22) reduced rates of hyperphagia; (23) elevated circulating adiponectin concentrations; (24) elevated cerebrospinal fluid insulin levels; (25) enhanced islet insulin mRNA and insulin content; or (26) enhanced metabolic efficiency of insulin.

[00457] Immediate or prolonged administration of formulations of KATP channel openers selected from salts of compounds of Formulae I – VIII to humans or animals that are at risk for myocardial infarct, or stroke, or undergoing surgical procedure that restores blood flow to heart or brain results in improved therapeutic outcomes post-surgically, or following the occurrence of myocardial infarct or stroke by improving the survival of tissue after blood flow is restored, reduced stunning of tissue, and altering the nature of the inflammatory responses.

[00458] Pharmaceutical formulations as provided herein are designed to be used in the treatment of obesity, hyperlipidemia, hypertension, weight maintenance, type I diabetes, prediabetes, type II diabetes, metabolic syndrome or any condition where weight loss, reduction in circulating triglycerides or beta cell rest contributes to therapeutic outcomes provide for a range of critical changes in pharmacodynamic and pharmacokinetic responses to administered doses of KATP channel openers selected from salts of compounds of Formulae I – VIII which changes include one or more of the following: (1) extending the pharmacodynamic effect of an administered dose to 24 hours or longer

as measured by the suppression of insulin secretion; (2) providing for substantial uptake of the active pharmaceutical ingredient in the small intestine; (3) providing for substantial uptake of the active pharmaceutical ingredient in the large intestine; (4) result in lowered C_{max} versus current oral suspension or capsule products for the same administered dose of active pharmaceutical ingredient; (5) provide for circulating concentrations of unbound active pharmaceutical ingredient above threshold concentrations for 24 or more hours from a single administered dose; and (6) provide for more consistent drug absorption by treated subjects as compared to existing capsule formulations.

[00459] Pharmaceutical co-formulations of the current invention designed to treat a range of conditions in humans and animals include the combination of KATP channel openers selected from salts of compounds of Formulae I – VIII with: (1) a diuretic, (2) a drug that lowers blood pressure, (3) a drug that suppresses appetite, (4) a cannabinoid receptor antagonist, (5) a drug that suppresses that action of gastric lipases, (6) any drug that is used to induce weight loss, (7) a drug that lowers cholesterol, (8) a drug that lowers LDL bound cholesterol, (9) a drug that improves insulin sensitivity, (10) a drug that improves glucose utilization or uptake, (11) a drug that reduces incidence of atherosclerotic plaque, (12) a drug that reduces inflammation, (13) a drug that is antidepressant, (14) a drug that is an anti-epileptic, or (15) a drug that is an anti-psychotic.

[00460] Treatment of humans or animals using pharmaceutical formulations (which include KATP channel openers selected from salts of compounds of Formulae I – VIII) result in reduced incidence of adverse side effects including but not limited to edema, fluid retention, reduced rates of excretion of sodium, chloride, and uric acid, hyperglycemia, ketoacidosis, nausea, vomiting, dyspepsia, ileus and headaches. These reductions in frequency of adverse side effects are achieved by: (1) initiating dosing of subjects at subtherapeutic doses and in a step wise manner increasing the dose daily until the therapeutic dose is achieved where the number of days over which the step up in dose is effected is 2 to 10, (2) use of the lowest effective dose to achieve the desired therapeutic effect, (3) use of a pharmaceutical formulation that delays release of active until gastric transit is complete, (4) use of a pharmaceutical formulation that results in lower circulating peak drug levels as compared to an immediate release oral suspension

or capsule formulation for the same administered dose, and (5) optimizing the timing of administration of dose within the day and relative to meals.

[00461] Treatment of patients suffering from Prader Willi Syndrome, Froelich's Syndrome, Cohen Syndrome, Summit Syndrome, Alstrom Syndrome, Borjesen Syndrome, Bardet-Biedl Syndrome, and hyperlipoproteinemia type I, II, III, and IV with the current invention using pharmaceutical formulations of KATP channel openers selected from salts of compounds of Formulae I – VIII result in some or all of the following therapeutic outcomes: (1) weight loss, (2) reduced rates of weight gain, (3) inhibition of hyperphagia, (4) reduced incidence of impaired glucose tolerance, prediabetes or diabetes, (5) reduced incidence of congestive heart failure, (6) reduced hypertension, and (7) reduced rates of all cause mortality.

[00462] Treatment of prediabetic subjects using invention pharmaceutical formulations of KATP channel openers selected from salts of compounds of Formulae I – VIII result in some or all of the following therapeutic outcomes: (1) weight loss, (2) restoration of normal glucose tolerance, (3) delayed rates of progression to diabetes, (4) reduced hypertension, and (5) reduced rates of all cause mortality.

[00463] Treatment of diabetic subjects using invention pharmaceutical formulations of KATP channel openers selected from salts of compounds of Formulae I – VIII result in some or all of the following therapeutic outcomes: (1) weight loss, (2) restoration of normal glucose tolerance, (3) delayed rates of progression of diabetes, (4) improvements in glucose tolerance, (5) reduced hypertension, and (6) reduced rates of all cause mortality.

[00464] Co-administration of drugs with formulations of KATP channel openers selected from salts of compounds of Formulae I – VIII in the treatment of diseases of overweight, obese or obesity prone human and animal subjects involves the co-administration of a pharmaceutically acceptable formulation of KATP channel openers with an acceptable formulation of: (1) sibutramine, (2) orlistat, (3) rimonabant, (4) a drug that is an appetite suppressant, (5) any drug used to induce weight loss in an obese or overweight subject, (6) a non-thiazide diuretic, (7) a drug that lowers cholesterol, (8) a drug that raises HDL cholesterol, (9) a drug that lowers LDL cholesterol, (10) a drug that

lowers blood pressure, (11) a drug that is an anti-depressant, (12) a drug that improves insulin sensitivity, (13) a drug that improves glucose utilization and uptake (14) a drug that is an anti-epileptic, (15) a drug that is an anti-inflammatory, or (16) a drug that lowers circulating triglycerides.

[00465] Co-administration of drugs with formulations of KATP channel openers selected from salts of compounds of Formulae I – VIII in the treatment or prevention of weight gain, dyslipidemia, impaired glucose tolerance or diabetes in subjects treated with antipsychotics drugs involve the co-administration of a pharmaceutically acceptable formulation of KATP channel openers with an acceptable formulation of: lithium, carbamazepine, valproic acid and divalproex, and lamotrigine; antidepressants generally classified as monoamine oxidase inhibitors including isocarboxazid, phenelzine sulfate and tranylepromine sulfate; tricyclic antidepressants including doxepin, clomipramine, amitriptyline, maprotiline, desipramine, nortriptyline, desipramine, doxepin, trimipramine, imipramine and protriptyline; tetracyclic antidepressants including mianserin, mirtazapine, maprotiline, oxaprotiline, desipramine, levoprotidine, trifluorcarbine, setipiline, azipramine, aptazapine maleate and pirlindole; and major tranquilizers and atypical antipsychotics including perphenazine, thioridazine, risperidone, clozapine, olanzapine and chlorpromazine.

[00466] In one embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an oral, transdermal or intranasal formulation to reach and maintain the threshold concentration required to measurably reduce fasting insulin levels for a prolonged period. Preferably the KATP channel opener formulation reduces fasting insulin levels by at least 20%, more preferably by at least 30%, more preferably by at least by 40%, more preferably by at least 50%, more preferably by at least by 60%, more preferably by at least by 70%, and more preferably by at least 80%. Fasting insulin levels are commonly measured using the glucose tolerance test (OGTT). After an overnight fast, a patient ingests a known amount of glucose. Initial glucose levels are determined by measuring pre-test glucose levels in blood and urine. Blood insulin levels are measured by a blood is draw every hour after the glucose is consumed for up to three hours. In a fasting

glucose assay, subjects with plasma glucose values greater than 200 mg/dl at 2 hours post-glucose load indicate an impaired glucose tolerance.

[00467] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an oral, transdermal or intranasal formulation to reach and maintain the threshold concentration required to induce weight loss for a prolonged period.

[00468] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an oral, transdermal or intranasal formulation to reach and maintain the threshold concentration required to elevate resting energy expenditure for a prolonged period.

[00469] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an oral, transdermal or intranasal formulation to reach and maintain the threshold concentration required to elevate fat and fatty acid oxidation for a prolonged period.

[00470] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an obesity prone subject as an oral, transdermal or intranasal formulation to reach and maintain the threshold concentration required to induce weight loss for a prolonged period.

[00471] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an obesity prone subject as an oral, transdermal or intranasal formulation to reach and maintain the threshold concentration required to maintain weight for a prolonged period.

[00472] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an oral, transdermal or intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to induce weight loss for a prolonged period.

[00473] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an

oral, transdermal or intranasal formulation for a prolonged period of time to reduce body fat by more than 25%, more preferably by at least 50%, and more preferably by at least 75%.

[00474] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an oral, transdermal or intranasal formulation for a prolonged period of time to preferentially reduce visceral fat deposits.

[00475] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an overweight or obese subject as an oral, transdermal or intranasal formulation for a prolonged period of time to reduce visceral fat depots and other fat deposits.

[00476] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to a normoinsulinemic overweight or obese subject as an oral, transdermal or intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to induce weight loss for a prolonged period.

[00477] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to a prediabetic subject as an oral, transdermal or intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to prevent the transition to diabetes for a prolonged period.

[00478] In another embodiment, a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to a type 1 diabetic subject as an oral, transdermal or intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to induce beta cell rest for a prolonged period.

[00479] In another embodiment, a single dose of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an subject in need thereof that results in circulating

concentration of active drug sufficient to diminish the secretion of insulin for 24 or more hours.

[00480] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered over a prolonged basis to an subject in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to diminish the secretion of insulin on a continuous basis.

[00481] In another embodiment, a single dose of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an subject in need thereof that results in circulating concentration of active drug sufficient to elevate non-esterified fatty acids in circulation for 24 or more hours.

[00482] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered over a prolonged basis to an subject in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to elevate non-esterified fatty acids in circulation on a continuous basis.

[00483] In another embodiment, a single dose of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an subject in need thereof that results in circulating concentration of active drug sufficient to treat hypoglycemia in circulation for 24 or more hours.

[00484] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered over a prolonged basis to an subject in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to treat hypoglycemia on a continuous basis.

[00485] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered

over a prolonged basis to an subject in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to induce weight loss on a continuous basis.

[00486] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered over a prolonged basis to an subject in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to maintain weight on a continuous basis, as it is preferable to maintain weight in an obese subject once some weight loss has occurred when the alternative is to regain weight.

[00487] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered over a prolonged basis to an subject in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to reduce circulating triglyceride levels on a continuous basis.

[00488] In another embodiment, a single dose of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered to an subject in need thereof that results in circulating concentration of active drug sufficient to reduce or prevent ischemic or reperfusion injury in circulation for 24 or more hours.

[00489] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is administered over a prolonged basis to an subject in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient reduce or prevent ischemic or reperfusion injury on a continuous basis.

[00490] In another embodiment, the frequency of adverse effects caused by treatment with a KATP channel opener selected from a salt of a compound of Formulae I – VIII is reduced using a pharmaceutically acceptable formulation of diazoxide or its derivatives that is administered to an subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached.

[00491] In another embodiment, the frequency of adverse effects caused by treatment with a KATP channel opener selected from a salt of a compound of Formulae I – VIII is reduced using a pharmaceutically acceptable formulation that is administered to an subject in need thereof on a daily basis in which the active ingredient is not released from the formulation until gastric transit is complete.

[00492] In another embodiment, the frequency of adverse effects caused by treatment with a KATP channel opener selected from a salt of a compound of Formulae I – VIII is reduced using a pharmaceutically acceptable formulation that is administered to an subject in need thereof on a daily basis in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation of Proglycem®.

[00493] In another embodiment, the frequency of adverse effects caused by treatment with a KATP channel opener selected from a salt of a compound of Formulae I – VIII is reduced using a pharmaceutically acceptable formulation that is administered to an subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not release from the formulation until gastric transit is complete and in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation of Proglycem®.

[00494] In another embodiment, the frequency of adverse effects caused by treatment with a KATP channel opener selected from a salt of a compound of Formulae I – VIII is reduced using a pharmaceutically acceptable formulation that is administered to an overweight or obese subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not release from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation of Proglycem®, and in which the maximum dose is less than 5 mg/kg/day.

[00495] In another embodiment, the frequency of adverse effects caused by treatment with a KATP channel opener selected from a salt of a compound of Formulae I – VIII is reduced using a pharmaceutically acceptable formulation that is administered to an overweight or obese subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not release from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 2.5 mg/kg/day.

[00496] In another embodiment, the treatment of an overweight or obese subject is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide continuous release for at least 6 hours.

[00497] In another embodiment, the treatment of an overweight or obese subject is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide continuous release for at least 12 hours.

[00498] In another embodiment, the treatment of an overweight or obese subject is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 8 hours.

[00499] In another embodiment, the treatment of an overweight or obese subject is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 12 hours.

[00500] In another embodiment, the treatment of an overweight or obese subject is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII once per 24 hours in which the release of the active ingredient from the formulation has been modified to match the pattern of basal insulin secretion.

[00501] In another embodiment, the frequency of adverse effects caused by treatment with a KATP channel opener selected from a salt of a compound of Formulae I – VIII is reduced using a pharmaceutically acceptable formulation that is administered to an obesity prone subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not release from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 5 mg/kg/day.

[00502] In another embodiment, the frequency of adverse effects caused by treatment with a KATP channel opener selected from a salt of a compound of Formulae I – VIII is reduced using a pharmaceutically acceptable formulation that is administered to an obesity prone subject in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not release from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 2.5 mg/kg/day.

[00503] In another embodiment, the treatment of an obesity prone subject is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide continuous release for at least 6 hours.

[00504] In another embodiment, the treatment of an obesity prone subject is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide continuous release for at least 12 hours.

[00505] In another embodiment, the treatment of an obesity prone subject is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 8 hours.

[00506] In another embodiment, the treatment of an obesity prone subject is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 12 hours.

[00507] In another embodiment, the treatment of an obesity prone subject is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII once per 24 hours in which the release of the active ingredient from the formulation has been modified to match the pattern of basal insulin secretion.

[00508] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with sibutramine to an overweight or obese subject to induce weight loss.

[00509] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with orlistat to an overweight or obese subject to induce weight loss.

[00510] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with rimonabant to an overweight or obese subject to induce weight loss.

[00511] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with an appetite suppressant to an overweight or obese subject to induce weight loss.

[00512] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with an anti-depressant to an overweight or obese subject to induce weight loss.

[00513] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with anti-epileptic to an overweight or obese subject to induce weight loss.

[00514] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener is selected from a salt of a compound of Formulae I – VIII is co-administered with a non-thiazide diuretic to an overweight or obese subject to induce weight loss.

[00515] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with a drug that induces weight loss by a mechanism that is distinct from diazoxide to an overweight or obese subject to induce weight loss.

[00516] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with a drug that lowers blood pressure to an overweight, obesity prone or obese subject to induce weight loss and treat obesity associated co-morbidities.

[00517] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with a drug that lowers cholesterol to an overweight, obesity prone or obese subject to induce weight loss and treat obesity associated co-morbidities.

[00518] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with a drug that raises HDL associated cholesterol to an overweight, obesity prone or obese subject to induce weight loss and treat obesity associated co-morbidities.

[00519] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with a drug that improves insulin sensitivity to an overweight, obesity prone or obese subject to induce weight loss and treat obesity associated co-morbidities.

[00520] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with a an anti-inflammatory to an overweight, obesity prone or obese subject to induce weight loss and treat obesity associated co-morbidities.

[00521] In another embodiment, a pharmaceutically acceptable formulation of a KATP channel opener selected from a salt of a compound of Formulae I – VIII is co-administered with a drug that lowers circulating triglycerides to an overweight, obesity prone or obese subject to induce weight loss and treat obesity associated co-morbidities.

[00522] In another embodiment, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with sibutramine in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese subject to induce weight loss and treat obesity-associated co-morbidities.

[00523] In another embodiment, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with orlistat or other active that suppresses the action of gastric lipases in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese subject to induce weight loss and treat obesity-associated co-morbidities.

[00524] In another embodiment, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with a non-thiazide diuretic in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese subject to induce weight loss and treat obesity-associated co-morbidities.

[00525] In another embodiment, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with an appetite suppressant in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese subject to induce weight loss and treat obesity-associated co-morbidities.

[00526] In another embodiment, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with a cannabinoid receptor antagonist in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese subject to induce weight loss and treat obesity-associated co-morbidities.

[00527] In another embodiment, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with an anti-cholesteremic active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese subject to induce weight loss and treat obesity-associated co-morbidities.

[00528] In another embodiment, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with an antihypertensive active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese subject to induce weight loss and treat obesity-associated co-morbidities.

[00529] In another embodiment, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with an insulin sensitizing active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese subject to induce weight loss and treat obesity-associated co-morbidities.

[00530] In another embodiment, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with an anti-inflammatory active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese subject to induce weight loss and treat obesity-associated co-morbidities.

[00531] In another embodiment, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with an anti-depressant active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese subject to induce weight loss and treat obesity-associated co-morbidities.

[00532] In another embodiment, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with an anti-epileptic active in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese subject to induce weight loss and treat obesity-associated co-morbidities.

[00533] In another embodiment, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with an active that reduces the incidence of atherosclerotic plaque in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese subject to induce weight loss and treat obesity-associated co-morbidities.

[00534] In another embodiment, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with an active that lowers circulating concentrations of triglycerides in a pharmaceutically acceptable formulation that is administered to an overweight, obesity prone or obese subject to induce weight loss and treat obesity-associated co-morbidities.

[00535] The reduction of circulating triglycerides in an overweight, obese or obesity prone subject is achieved by the administration of an effective amount of an oral dosage form of a KATP channel opener, selected from a salt of a compound of Formulae I – VIII.

[00536] An oral dosage form of KATP channel opener selected from a salt of a compound of Formulae I – VIII can be used to administer a therapeutically effective dose of KATP channel opener to an overweight or obesity prone subject in need thereof to maintain weight, as it is preferable to maintain weight in an obese subject once some weight loss has occurred when the alternative is to regain weight.

[00537] In another embodiment of the invention, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with a drug to treat obesity. Such co-formulations can be formulated for oral administration once per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of the active over a period of 2 to 24 hours. Such obesity treatment drugs include, but are not limited to: sibutramine hydrochloride (5-30 mg), orlistat (50-360 mg), phentermine

hydrochloride or resin complex (15 to 40 mg), zonisamide (100 to 600 mg), topiramate (64 to 400 mg), naltrexone hydrochloride (50 to 600 mg), or rimonabant (5 to 20 mg).

[00538] A further embodiment of the co-formulation contains KATP channel openers selected from salts of compounds of Formulae I – VIII and a drug to treat obesity. Such co-formulations can be formulated for oral administration twice per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of the active over a period of 2 to 12 hours. Such obesity treatment drugs include, but are not limited to: sibutramine hydrochloride (2.5 to 15 mg), orlistat (25 to 180 mg), phentermine hydrochloride or resin complex (7.5 to 20 mg), zonisamide (50 to 300 mg), topiramate (32 to 200 mg), naltrexone hydrochloride (25 to 300 mg), or rimonabant (2.5 to 10 mg).

[00539] In another embodiment of the invention KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with a drug to treat obesity, diabetes, metabolic syndrome or an obesity related comorbidity. Such drugs to treat these conditions include drugs that: agonizes the $\alpha 1$ -noradrenergic receptor; agonizes the $\beta 2$ noradrenergic receptor; stimulates noradrenalin release; blocks noradrenalin uptake; stimulates 5-HT release; blocks 5-HT uptake; is a serotonin (5-hydroxytryptamine) 2C receptor agonist; antagonizes acetyl-CoA carboxylase 2; agonizes the D1-receptor; antagonizes the H3-receptor; is a leptin analogue; agonizes the leptin receptor, sensitizes CNS tissue to the action of leptin; agonizes the MC4 receptor; agonizes NPY-Y1; agonizes NPY-Y2; agonizes NPY-Y4; agonizes NPY-Y5; antagonizes the MCH receptor; blocks CRH-BP; agonizes the CRH receptor; agonizes the urocortin receptor; antagonizes the galanin receptor; antagonizes the orexin receptor; agonizes the CART receptor; agonizes the Amylin receptor; agonizes the Apo(AIV) receptor; antagonizes the CB-1 receptor; is an α MSH analogue; inhibits FTF-1B; antagonizes PPAR γ receptor; is a short acting bromocriptine; agonizes somatostatin; increases adiponectin; increases CCK activity; increases PYY activity; increases GLP-1 activity; decreases ghrelin activity; is a selective B3 stimulator or agonist; agonizes thyroid receptor; inhibits gastrointestinal lipases or other digestive enzymes; blocks absorption of dietary fat; or block de-novo fatty acid synthesis. Additionally, such drugs to treat obesity may include, but are not limited to those that antagonize or agonize the function or expression of 11B hydroxysteroid dehydrogenase type 1; acetyl-CoA carboxylase 1; ADAM 12, member

12 of a disintegrin and metalloprotease family or its shorter secreted form; agouti related protein; angiotensinogen; adipocyte lipid binding protein; adipocyte fatty acid binding protein; adrenergic receptors; acylation-stimulating protein; bombesin receptor subtype-3; C/EBP, CCAAT/enhancer binding protein; cocaine- and amphetamine-regulated transcript; cholecystokinin; cholecystokinin A receptor; CD36, fatty acid translocase; corticotropin-releasing hormone; diacylglycerol acyltransferases; E2F transcription factor; eukaryotic translation initiation factor 4e binding protein 1; estrogen receptor; fatty acid synthase; fibroblast growth factor; forkhead box C2; glucose-dependent insulinotropic peptide; GIP receptor; inhibitory G protein alpha-subunit; glucagon-like peptide-1; GLP-1 receptor; glycerol-3-phosphate acyltransferase; glycerol 3-phosphate dehydrogenase; stimulatory G protein alpha-subunit; high-mobility group phosphoprotein isoform I-C; hormone sensitive lipase; inducible nitric oxide synthase; Janus kinases; lipoprotein lipase; melanocortin-3 receptor; melanocortin-4 receptor; mitochondrial GPAT; metallothionein-I and -II; nescient helix-loop-helix 2; neuropeptide Y; neuropeptide Y-1 receptor; neuropeptide Y-2 receptor; neuropeptide Y-4 receptor; neuropeptide Y-5 receptor; plasminogen activator inhibitor-1; PPARgamma co-activator 1; pro-opiomelanocortin; peroxisome proliferator-activated receptor; protein tyrosine phosphatase 1B; regulatory subunit IIbeta of protein kinase A; retinoid X receptor; steroidogenic factor 1; single-minded 1; sterol regulatory element binding protein; tyrosine hydroxylase; thyroid hormone receptor $\alpha 2$; uncoupling protein; nerve growth factor induced protein; leucine zipper transcription factor; α -melanocyte-stimulating hormone.

[00540] In another embodiment of the invention, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with a drug to treat diabetes. Such co-formulations can be formulated for oral administration once per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of the active over a period of 2 to 24 hours. Such diabetes treatment drugs include, but are not limited to: acarbose (50 to 300 mg), miglitol (25 to 300 mg), metformin hydrochloride (300 to 2000 mg), repaglinide (1-16 mg), nateglinide (200 to 400 mg), or rosiglitazone (5 to 50 mg).

[00541] In a further embodiment, the co-formulation can be formulated for oral administration twice per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of the active over a period of 2 to 12 hours. Such drugs to treat diabetes include, but are not limited to: acarbose (25 to 150 mg), miglitol (12.5 to 150 mg), metformin hydrochloride (150 to 1000 mg), repaglinide (0.5 to 8 mg), nateglinide (100 to 200 mg), or rosiglitazone (2.5 to 25 mg).

[00542] In another embodiment of the invention, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with a drug to treat elevated cholesterol. Such co-formulations can be formulated for oral administration once per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of the active over a period of 2 to 24 hours. Such drugs to treat elevated cholesterol include, but are not limited to: pravastatin, simvastatin, atorvastatin, fluvastatin, rosuvastatin or lovastatin (10 to 80 mg).

[00543] In a further embodiment, the co-formulation can be formulated for oral administration twice per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of the active over a period of 2 to 12 hours. Such drugs to treat elevated cholesterol include, but are not limited to: pravastatin, simvastatin, atorvastatin, fluvastatin, rosuvastatin or lovastatin (5 to 40 mg).

[00544] In another embodiment of the invention, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with a drug to treat depression. Such co-formulations can be formulated for oral administration once per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of the active over a period of 2 to 24 hours. Such drugs to treat depression include, but are not limited to: citalopram hydrobromide (10 to 80 mg), escitalopram hydrobromide (5 to 40 mg), fluvoxamine maleate (25 to 300 mg), paroxetine hydrochloride (12.5 to 75 mg), fluoxetine hydrochloride (30 to 100 mg), setraline hydrochloride (25 to 200 mg), amitriptyline hydrochloride (10 to 200 mg), desipramine hydrochloride (10 to 300 mg), nortriptyline hydrochloride (10 to 150 mg), duloxetine hydrochloride (20 to 210 mg), venlafaxine hydrochloride (37.5 to 150 mg), phenelzine sulfate (10 to 30 mg), bupropion hydrochloride (200 to 400 mg), or mirtazapine (7.5 to 90 mg).

[00545] In a further embodiment, the co-formulation can be formulated for oral administration twice per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of the active for 2 to 12 hours. Such drugs to treat depression include, but are not limited to: citalopram hydrobromide (5 to 40 mg), escitalopram hydrobromide (2.5 to 20 mg), fluvoxamine maleate (12.5 to 150 mg), paroxetine hydrochloride (6.25 to 37.5 mg), fluoxetine hydrochloride (15 to 50 mg), setraline hydrochloride (12.5 to 100 mg), amitriptyline hydrochloride (5 to 100 mg), desipramine hydrochloride (5 to 150 mg), nortriptyline hydrochloride (5 to 75 mg), duloxetine hydrochloride (10 to 100 mg), venlafaxine hydrochloride (18 to 75 mg), phenelzine sulfate (5 to 15 mg), bupropion hydrochloride (100 to 200 mg), or mirtazapine (4 to 45 mg).

[00546] In another embodiment of the invention, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with a drug to treat hypertension. Such co-formulations can be formulated for oral administration once per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of the active over a period of 2 to 24 hours. Such drugs to treat hypertension include, but are not limited to: enalapril maleate (2.5 to 40 mg), captopril (2.5 to 150 mg), lisinopril (10 to 40 mg), benazepril hydrochloride (10 to 80 mg), quinapril hydrochloride (10 to 80 mg), perindopril erbumine (4 to 8 mg), ramipril (1.25 to 20 mg),trandolapril (1 to 8 mg), fosinopril sodium (10 to 80 mg), moexipril hydrochloride (5 to 20 mg), losartan potassium (25 to 200 mg), irbesartan (75 to 600 mg), valsartan (40 to 600 mg), candesartan cilexetil (4 to 64 mg), olmesartan medoxamil (5 to 80 mg), telmisartan (20 to 160 mg), eprosartan mesylate (75 to 600 mg), atenolol (25 to 200 mg), propranolol hydrochloride (10 to 180 mg), metoprolol tartrate, succinate or fumarate (25 to 400 mg), nadolol (20 to 160 mg), betaxolol hydrochloride (10 to 40 mg), acebutolol hydrochloride (200 to 800 mg), pindolol (5 to 20 mg), bisoprolol fumarate (5 to 20 mg), nifedipine (15 to 100 mg), felodipine (2.5 to 20 mg), amlodipine besylate (2.5 to 20 mg), nicardipine (10 to 40 mg), nisoldipine (10 to 80 mg), terazosin hydrochloride (1 to 20 mg), doxazosin mesylate (4 to 16 mg), prazosin hydrochloride (2.5 to 10 mg), or alfuzosin hydrochloride (10 to 20 mg).

[00547] In a further embodiment, the co-formulation can be formulated for oral administration twice per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of active over a period of 2 to 12 hours. Such drugs to treat hypertension include, but are not limited to: enalapril maleate (1.25 to 20 mg), captopril (2 to 75 mg), lisinopril (5 to 20 mg), benazepril hydrochloride (5 to 40 mg), quinapril hydrochloride (5 to 40 mg), perindopril erbumine (2 to 4 mg), ramipril (1 to 10 mg), trandolapril (1 to 4 mg), fosinopril sodium (5 to 40 mg), moexipril hydrochloride (2.5 to 10 mg), losartan potassium (12.5 to 100 mg), irbesartan (37.5 to 300 mg), valsartan (20 to 300 mg), candesartan cilexetil (2 to 32 mg), olmesartan medoxamil (2.5 to 40 mg), telmisartan (10 to 80 mg), eprosartan mesylate (37.5 to 300 mg), atenolol (12.5 to 100 mg), propranolol hydrochloride (5 to 90 mg), metoprolol tartrate, succinate or fumarate (12.5 to 200 mg), nadolol (10 to 80 mg), betaxolol hydrochloride (5 to 20 mg), acebutolol hydrochloride (100 to 400 mg), pindolol (2.5 to 10 mg), bisoprolol fumarate (2.5 to 10 mg), nifedipine (7.5 to 50 mg), felodipine (1 to 10 mg), amlodipine besylate (1 to 10 mg), nicardipine (5 to 20 mg), nisoldipine (5 to 40 mg), terazosin hydrochloride (1 to 10 mg), doxazosin mesylate (2 to 8 mg), prazosin hydrochloride (1 to 5 mg), or alfuzosin hydrochloride (5 to 10 mg).

[00548] In another embodiment of the invention, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with a diuretic. Such co-formulations can be formulated for oral administration once per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of the active over a period of 2 to 24 hours. Such diuretics can include, but are not limited to: amiloride hydrochloride (1 to 10 mg), spironolactone (10 to 100 mg), triamterene (25 to 200 mg), bumetanide (0.5 to 4 mg), furosemide (10 to 160 mg), ethacrynic acid or ethacrynate sodium (10 to 50 mg), torsemide (5 to 100 mg), chlorthalidone (10 to 200 mg), indapamide (1 to 5 mg), hydrochlorothiazide (10 to 100 mg), chlorothiazide (50 to 500 mg), bendroflumethiazide (5 to 25 mg), hydroflumethiazide (10 to 50 mg), mythclothiazide (1 to 5 mg), and polythiazide (1 to 10 mg).

[00549] In a further embodiment, the co-formulation can be formulated for oral administration twice per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of the active over a period of 2 to 12 hours. Such

diuretics include, but are not limited to: amiloride hydrochloride (0.5 to 5 mg), spironolactone (5 to 50 mg), triamterene (12 to 100 mg), bumetanide (0.2 to 2 mg), furosemide (5 to 80 mg), ethacrynic acid or ethacrynate sodium (5 to 25 mg), torsemide (2 to 50 mg), chlorthalidone (5 to 100 mg), indapamide (0.5 to 2.5 mg), hydrochlorothiazide (5 to 50 mg), chlorothiazide (25 to 250 mg), bendroflumethiazide (2 to 12.5 mg), hydroflumethiazide (5 to 25 mg), mythyclothiazide (0.5 to 2.5 mg), and polythiazide (0.5 to 5 mg).

[00550] In another embodiment of the invention, KATP channel openers selected from salts of compounds of Formulae I – VIII are co-formulated with a drug to treat inflammation or pain. Such co-formulations can be formulated for oral administration once per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of the active over a period of 2 to 24 hours. Such drugs to treat inflammation or pain include, but are not limited to: aspirin (100 to 1000mg), tramadol hydrochloride (25 to 150 mg), gabapentin (100 to 800 mg), acetaminophen (100 to 1000 mg), carbamazepine (100 to 400 mg), ibuprofen (100 to 1600 mg), ketoprofen (12 to 200 mg), fenpropfen sodium (100 to 600 mg), flurbiprofen sodium or flurbiprofen (50 to 200 mg), or combinations of these with a steroid or aspirin.

[00551] In a further embodiment, the co-formulation can be formulated for oral administration twice per 24 hours, for delayed release of the active until gastric transit is complete, and for sustained release of the active over a period of 2 to 12 hours. Such drugs to treat inflammation or pain include, but are not limited to: aspirin (100 to 650 mg), tramadol hydrochloride (12 to 75 mg), gabapentin (50 to 400 mg), acetaminophen (50 to 500 mg), carbamazepine (50 to 200 mg), ibuprofen (50 to 800 mg), ketoprofen (6 to 100 mg), fenpropfen sodium (50 to 300 mg), flurbiprofen sodium or flurbiprofen (25 to 100 mg), or combinations of these with a steroid or aspirin.

[00552] A method of inducing loss of greater than 25% of initial body fat in an overweight or obese subject can be achieved by the prolonged administration of an oral dosage form of a KATP channel opener, selected from a salt of a compound of Formulae I – VIII.

[00553] A method of inducing loss of greater than 50% of initial body fat in an overweight or obese subject can be achieved by the prolonged administration of an oral dosage form of a KATP channel opener selected from a salt of a compound of Formulae I – VIII.

[00554] A method of inducing loss of greater than 75% of initial body fat in an overweight or obese subject can be achieved by the prolonged administration of an oral dosage form of a KATP channel opener, selected from a salt of a compound of Formulae I – VIII.

[00555] A method of inducing preferential loss of visceral fat in an overweight or obese subject can be achieved by the prolonged administration of an oral dosage form of a KATP channel opener, selected from a salt of a compound of Formulae I – VIII.

[00556] A method of inducing loss of body fat and reductions in circulating triglycerides in an overweight or obese subject can be achieved by the prolonged administration of an oral dosage form of a KATP channel opener, selected from a salt of a compound of Formulae I – VIII.

[00557] In some embodiments, the invention provides a polymorph of a salt, which salt includes diazoxide and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or quaternary ammonium group. In some embodiments, the cation is choline.

[00558] In some embodiments, the polymorph of diazoxide choline salt is of Form A having characteristic peaks in the XRPD pattern at values of two-theta (Cu K α , 40 kV, 40 mA) at approximately 9.8, 10.5, 14.9, 17.8, 17.9, 18.5, 19.5, 22.1, 22.6, 26.2, 29.6, and 31.2 degrees.

[00559] In some embodiments, the polymorph of diazoxide choline salt is of Form B having characteristic peaks in the XRPD pattern at values of two-theta (Cu K α , 40 kV, 40 mA) at approximately 8.9, 10.3, 12.0, 18.3, 20.6, 24.1, 24.5, 26.3, 27.1, and 28.9 degrees.

[00560] In some embodiments, the polymorph of diazoxide choline salt is of Form A having characteristic infrared absorbances at 2926, 2654, 1592, 1449, and 1248 cm^{-1} .

[00561] In some embodiments, the polymorph of diazoxide choline salt is of Form B having characteristic infrared absorbances at 3256, 2174, 2890, 1605, 1463, and 1235 cm^{-1} .

[00562] In some embodiments, the polymorph of diazoxide includes potassium as the cation.

[00563] In some embodiments, the polymorph of diazoxide potassium salt is of Form A having characteristic peaks in the XRPD pattern at values of two-theta ($\text{Cu K}\alpha$, 40 kV, 40 mA) at approximately 6.0, 8.1, 16.3, 17.7, 18.6, 19.1, 22.9, 23.3, 23.7, 24.7, 25.4, 26.1, 28.2, 29.6, and 30.2 degrees.

[00564] In some embodiments, the polymorph of diazoxide potassium salt is of Form B having characteristic peaks in the XRPD pattern at values of two-theta ($\text{Cu K}\alpha$, 40 kV, 40 mA) at approximately 8.5, 10.8, 16.9, 18.2, 21.6, 25.5, 26.1, and 28.9 degrees.

[00565] In some embodiments, the polymorph of diazoxide potassium salt is of Form C having characteristic peaks in the XRPD pattern at values of two-theta ($\text{Cu K}\alpha$, 40 kV, 40 mA) at approximately 5.7, 6.1, 17.9, 23.9, 25.1, and 37.3 degrees.

[00566] In some embodiments, the polymorph of diazoxide potassium salt is of Form D having characteristic peaks in the XRPD pattern at values of two-theta ($\text{Cu K}\alpha$, 40 kV, 40 mA) at approximately 5.7, 6.2, 8.1, 8.5, 8.8, 16.9, 18.6, 23.2, 24.5, 25.8, and 26.1 degrees.

[00567] In some embodiments, the polymorph of diazoxide potassium salt is of Form E having characteristic peaks in the XRPD pattern at values of two-theta ($\text{Cu K}\alpha$, 40 kV, 40 mA) at approximately 6.7, 7.1, 14.1, and 21.2 degrees.

[00568] In some embodiments, the polymorph of diazoxide potassium salt is of Form F having characteristic peaks in the XRPD pattern at values of two-theta ($\text{Cu K}\alpha$, 40 kV, 40 mA) at approximately 8.5, 9.0, 18.7, 20.6, 23.5, 27.5, and 36.3 degrees.

[00569] In some embodiments, the polymorph of diazoxide potassium salt is of Form G having characteristic peaks in the XRPD pattern at values of two-theta (Cu K α , 40 kV, 40 mA) at approximately 5.2, 5.5, 13.1, 16.5, 19.3, 22.8, 24.8, 26.4, 28.7, and 34.1 degrees.

[00570] In some embodiments, the polymorph of diazoxide potassium salt is of Form A having characteristic infrared absorbances at 1503, 1374, 1339, 1207, 1131, 1056, and 771 cm⁻¹.

[00571] In some embodiments, the polymorph of diazoxide potassium salt is of Form B having characteristic infrared absorbances at 1509, 1464, 1378, and 1347 cm⁻¹.

[00572] In some embodiments, the polymorph of diazoxide potassium salt is of Form C having characteristic infrared absorbances at 1706, 1208, 1146, and 746 cm⁻¹.

[00573] In some embodiments, the polymorph of diazoxide potassium salt is of Form D having characteristic infrared absorbances at 1595, 1258, 1219, and 890 cm⁻¹.

[00574] In some embodiments, the polymorph of diazoxide potassium salt is of Form E having characteristic infrared absorbances at 1550, 1508, 1268, 1101, and 1006 cm⁻¹.

[00575] In some embodiments, the polymorph of diazoxide potassium salt is of Form F having characteristic infrared absorbances at 1643, 1595, 1234, 1145, and 810 cm⁻¹.

[00576] In some embodiments, the polymorph of diazoxide potassium salt is of Form G having characteristic infrared absorbances at 1675, 1591, 1504, 1458, 1432, 1266, 999, 958, 905, and 872 cm⁻¹.

[00577] In some embodiments, the polymorph of diazoxide choline salt is of Form A having characteristic peaks in the XRPD pattern substantially as shown in FIG. 16(a), and an NMR spectrum substantially as shown in FIG. 17(a).

[00578] In some embodiments, the polymorph of diazoxide choline salt is of Form B having characteristic peaks in the XRPD pattern substantially as shown in FIG. 16(c) and an NMR spectrum substantially as shown in FIG. 17(b).

[00579] In some embodiments, the polymorph of diazoxide potassium salt includes one or more of Forms A-G, wherein each of the Forms A-G has characteristic peaks in the XRPD pattern substantially as shown in FIG. 18-19.

[00580] In some embodiments of the invention there are provided methods for producing a diazoxide choline salt, which methods include suspending diazoxide in a solvent (e.g., alcohols such as methanol, i-BuOH, i-AmOH, t-BuOH, and the like, ketones, tetrahydrofuran, dimethylformamide, n-methyl pyrrolidinone, and the like) and mixing with a choline salt (e.g., choline hydroxide), adding a co-solvent (e.g., MTBE, EtOA, IPA, c-Hexane, heptane, toluene, CH₂Cl₂, dioxane, and the like) to the suspension under conditions sufficient to cause formation and precipitation of said diazoxide choline salt, and harvesting the precipitate to provide the diazoxide choline salt.

[00581] In some embodiments, the solvent is tetrahydrofuran. In some embodiments, the solvent is 2-methyltetrahydrofuran (2-MeTHF).

[00582] In some embodiments, the diazoxide and the solvent are present at a ratio of about 1 g diazoxide per 1 mL solvent to about 1 g diazoxide per 5 mL solvent. In some embodiments, the diazoxide and the solvent are present at a ratio of about 1 g diazoxide per 3 mL solvent.

[00583] In some embodiments, the choline salt is a solution in MeOH. In some embodiments, the choline salt is choline hydroxide in about a 45% solution (e.g., 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%) in MeOH.

[00584] In some embodiments, the choline salt is added as 1 equivalent of diazoxide.

[00585] In some embodiments, the co-solvent is MTBE.

[00586] In some embodiments, the amount of co-solvent added is in a ratio to the amount of the solvent of about 3:14 (solvent:co-solvent) (e.g., 3:12, 3:13, 3:14, 3:15, 3:16).

[00587] In some embodiments, the process of making polymorphs of diazoxide choline salt includes the step of seeding with crystals of diazoxide choline salt polymorph Form B prior to the harvesting step.

[00588] In some embodiments for the method for producing a diazoxide choline salt the salt includes polymorph Form B substantially free of polymorph Form A, the polymorph Form B having characteristic peaks in the XRPD pattern at values of two-theta (Cu K α , 40 kV, 40 mA) at approximately 8.9, 10.3, 12.0, 18.3, 20.6, 24.1, 24.5, 26.3, 27.1, and 28.9 degrees.

[00589] In some embodiments for the method of treating obesity or obesity-related morbidity in an obese subject, the compound is a compound of Formula V.

[00590] In some embodiments for the method of treating obesity or obesity-related morbidity in an obese subject, the compound is a compound of Formula VI.

[00591] In some embodiments for the method of treating obesity or obesity-related morbidity in an obese subject, the compound is a compound of Formula VII.

[00592] In some embodiments for the method of treating obesity or obesity-related morbidity in an obese subject, the compound is a compound of Formula VIII.

[00593] In some embodiments for the method of treating obesity or obesity-related morbidity in an obese subject, the method further comprises administering a drug selected from the group consisting of Sibutramine, Orlistat, Rimonabant, an appetite suppressant, a non-thiazide diuretic, a drug that lowers cholesterol, a drug that raises HDL cholesterol, a drug that lowers LDL cholesterol, a drug that lowers blood pressure, a drug that is an anti-depressant, a drug that is an anti-epileptic, a drug that is an anti-inflammatory, a drug that is an appetite suppressant, a drug that lowers circulating triglycerides, and a drug that is used to induce weight loss in an overweight or obese individual.

[00594] In some embodiments for the method of treating obesity or obesity-related morbidity in an obese subject, the method further comprises administering a pharmaceutically active agent other than the KATP channel opener. In some embodiments, the other pharmaceutically active agent is an agent useful for the treatment of a condition selected from the group consisting of obesity, prediabetes, diabetes, hypertension, depression, elevated cholesterol, fluid retention, obesity associated co-morbidities, ischemic and reperfusion injury, epilepsy, cognitive impairment, schizophrenia, mania, and other psychotic condition.

[00595] In some embodiments for the method for treating a subject suffering from or at risk for Alzheimer's disease (AD), the method includes administration to a subject a therapeutically effective amount of a salt of diazoxide including salts provided herein. In some embodiments for the method for treating a subject suffering from or at risk for AD, the method includes administration to a subject a therapeutically effective amount of a compound according to any of Formulae I-VIII. In some embodiments, the compound is diazoxide or a salt thereof.

[00596] AD is a neurodegenerative disorder neuropathologically characterized by abnormal accumulations of intracellular neurofibrillary tangles and extracellular amyloid plaques throughout cortical and limbic brain regions and the loss of synapses and neurons. AD is further characterized by significant cognitive and memory impairment. β amyloid plaques form from the β amyloid peptide, either 1-40 or 1-42 peptide, which is released from amyloid precursor protein following cleavage by gamma secretase. In addition to forming plaques, the β amyloid peptides are cytotoxic either as the monomer or as a short-lived oligomeric intermediate. β amyloid peptides (monomers, dimers or oligomers) can be identified both in CSF (cerebrospinal fluid) and in serum. Amyloid angiopathy is characterized by A β deposition and may contribute to the cerebrovascular abnormalities that precede the onset of AD.

[00597] In one embodiment, a therapeutically effective amount of a KATP channel opener, or pharmaceutical salt thereof, is formulated for once, twice or thrice per day administration for the treatment of patients diagnosed with hypercholesterolemia, combined hyperlipidemia, endogenous hyperlipidemia, or hypertriglyceridemia. These conditions include Fredrickson class IIa, IIb, IV and V (Fredrickson, DS, Lees, LS, Circulation 1965 31:321-327; Beaumont, JL et al. Bull World Health Org 1970 43(6):891-915).

[00598] Also provided are pharmaceutical coformulations comprising a therapeutically effective amount of a KATP channel opener, or pharmaceutical salt thereof, and one or more of the following:

a) an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase or pharmaceutical salt thereof;

- b) a statin or pharmaceutical salt thereof;
- c) 10 to 100 mg equivalent of atorvastatin, or a pharmaceutical salt thereof;
- d) 10 mg to 100 mg of fluvastatin, or a pharmaceutical salt thereof;
- e) 10 to 80 mg equivalent of lovastatin, or a pharmaceutical salt thereof;
- f) 10 to 100 mg equivalent of mevastatin, or a pharmaceutical salt thereof;
- g) pitavastatin, or a pharmaceutical salt thereof;
- h) 10 to 100 mg equivalent of pravastatin, or a pharmaceutical salt thereof;
- i) rosuvastatin, or a pharmaceutical salt thereof;
- j) 5 to 100 mg equivalent of simvastatin, or a pharmaceutical salt thereof;
- k) 5 to 20 mg equivalent of ezetimibe, or a pharmaceutical salt thereof;
- l) a fibrate, or a pharmaceutical salt thereof;
- m) 25 mg to 250 mg equivalent of fenofibrate, or a pharmaceutical salt thereof;
- n) 200 mg to 600 mg equivalent of clofibrate, or a pharmaceutical salt thereof;
- o) 200 mg to 700 mg equivalent of gemfibrozil, or a pharmaceutical salt thereof;
- p) 100 mg to 800 mg equivalent of benzaifibrate, or a pharmaceutical salt thereof;
- q) 50 mg to 400 mg equivalent of ciprofibrate, or a pharmaceutical salt thereof;
- r) 50 mg to 400 mg equivalent of ciprofibrate, or a pharmaceutical salt thereof;
- s) histamine H3 antagonist, or a pharmaceutical salt thereof;
- t) histamine H3 inverse agonist, or a pharmaceutical salt thereof;
- u) absorbable or non-absorbable MTP inhibitor, or a pharmaceutical salt thereof;
- v) a thyroid receptor activator, or a pharmaceutical salt thereof; or

w) a squalene synthase inhibitor, or a pharmaceutical salt thereof,

[00599] Any of the above pharmaceutical coformulations may be administered either once per day, twice per day or three times per day for the treatment of patients diagnosed with hypercholesterolemia, combined hyperlipidemia, endogenous hyperlipidemia, or hypertriglyceridemia. These conditions include Fredrickson class IIa, IIb, IV and V.

Treatment of hypertriglyceridemic patients with omega-3 fatty acids and Diazoxide

[00600] Prescription omega-3 fatty acids (p-OM3) are often used to treat patients with elevated triglycerides, however fatty acid compositions differ among products, which can lead to different effects on levels of LDL-C in these patients. Some products contain very high levels of eicosapentaenoic acid (EPA) and are substantially free of docosahexaenoic acid (DHA). Exemplary products include AMR-101 (1 gram gel cap that contains at least 950 mg of ethyl EPA and is substantially free of the ethyl ester of DHA) and Epadel® (highly pure ethyl EPA packaged in gel caps dosages of 300 mg, 600 mg or 900 mg). Other products are not substantially free of DHA, such as Lovaza® or Omacor® (1 capsule contains about 465 mg of EPA and 375 mg of DHA).

[00601] Treatment of hypertriglyceridemic patients with a p-OM3 formulation high in EPA and substantially free of DHA generally results in a more modest improvement in triglycerides while causing a limited increase in LDL-C concentrations. In contrast, treatment with a p-OM3 formulation with EPA and higher amounts of DHA generally results in greater improvements in triglyceride levels but also can result in up to a nearly 50% increase in LDL-C. The increase in LDL-C results from the mode of action of omega 3 fatty acid products which include DHA, namely increasing clearance of triglycerides, while decreasing the size of secreted VLDL particles. Triglycerides synthesized by the liver circulate primarily as a component of apolipoprotein B-containing particles. These particles, which are atherogenic, contain both cholesterol and triglycerides, and are secreted as very low density lipoprotein particles. Triglycerides are removed from these particles by the action of lipoprotein lipase. As triglycerides are removed, the density of these particles gradually increases from very low density (VLDL) to intermediate density (IDL) and ultimately to low density (LDL). Drugs that reduce triglycerides by removal of triglycerides from Apo B-containing lipoprotein particles will

cause the transition of VLDL to IDL and ultimately to LDL, thereby raising the concentration of LDL-C in treated patients.

[00602] Thus, a very high triglyceride patient being treated with p-OM3 that contains DHA may be at increased risk for myocardial infarction or stroke because of elevated LDL-C. Treatment with p-OM3 that is substantially free of DHA can reduce this problem. Nevertheless, patients treated with a p-OM3 that is substantially free of DHA may fail to reach their triglyceride goal due to their moderate effects on reducing triglyceride levels. In these instances, such patients may benefit from co-administration of another triglyceride-lowering drug.

[00603] A preferred combination of drugs to treat dyslipidemia is one in which the mode of action of the drugs differs, and which offer substantial opportunity for complementary effects. However, some drug combinations do not provide an additive improvement in triglyceride levels.

[00604] For example, a clinical study has been conducted evaluating the value of co-administering the p-OM3 product (Lovaza®) with fenofibrate in the treatment of patients with very high triglycerides (Roth et al., J Cardiovasc Pharmacol. 2009 Sep;54(3):196-203). The net result of addition of Lovaza® treatment for patients undergoing fenofibrate treatment for very high triglycerides was little further improvement in triglyceride levels compared to treatment with fenofibrate alone (see section 15.4 and Figure 29). This lack of additional improvement is likely because both of drugs have similar modes of action, namely clearance of triglycerides from circulation. Furthermore, the combined use of Lovaza® with fenofibrate in the treatment of patients with very high triglycerides results in very marked increases in LDL cholesterol (see Example 15.4 and Figure 29), which contributes to increased risk of major cardiovascular events.

[00605] For a patient with very high triglycerides who has elevated risk for major cardiovascular events attributable to elevated LDL-C, a more preferable drug combination for lowering triglycerides is a K_{ATP} channel agonist, e.g. diazoxide or a salt thereof, co-administered with a p-OM3 product (such as AMR-101 or Epadel®) that includes a high concentration of EPA and is substantially free of DHA. Treatment of very high triglyceride patients by co-administering a K_{ATP} channel agonist, e.g. diazoxide

or a salt thereof, and a high EPA / low DHA p-OM3 product will result in improvements in triglycerides that are greater than those achieved with either product alone while at the same time minimizing the potential for increases in LDL cholesterol.

Treatment of hypertriglyceridemic patients by coadministration of fenofibrate and diazoxide choline

[00606] Fibrates, such as fenofibrate, are another class of drugs used to lower triglycerides, but alone may not be enough to allow hypertriglyceridemic patients to reach their triglyceride goal. As described above, fenofibrate co-administered with p-OM3 does not have a significant additive effect in reducing triglycerides, likely due to their similar modes of action (see also Example 15.4 and Figure 29).

[00607] In newly diagnosed very high triglyceride patients who are not anticipated to reach their triglyceride goal with a single agent (i.e., typically patients with circulating triglycerides at diagnosis of 500 mg/dL or higher, such as 1000 mg/dL or higher), it may be preferable to initiate therapy with co-administration of a K_{ATP} channel agonist, e.g. diazoxide or a salt thereof, and a fibrate, such as fenofibrate or a salt thereof. In these combined therapies, the K_{ATP} channel agonist and the fibrate may be co-administered as part of separate formulations, or may be co-formulated.

[00608] There are a number of branded and generic fibrate products that differ in the extent of micronization of the fibrate, the excipients used in the formulation and the dosage form. The Trilipix® product, the leading branded fenofibrate product, makes use of fenofibrate choline as opposed to the fenofibric acid used in the other fenofibrate products. Most fenofibrate products are manufactured in two dose strengths, a starter or titration dose and a maintenance dose, which tends to contain approximately 3 times as much fenofibrate as the titration dose. Depending on the product, these doses may be within the ranges of 35 mg and 105 mg, and 40 mg and 120 mg, 45 mg and 135 mg, 48 mg and 145 mg, and 50 mg and 160 mg. Some fenofibrate products may be manufactured in 3 or more dose strengths. Depending on the product, these may include 50 mg, 100 mg and 150 mg; 43 mg, 87 mg and 130 mg; 45 mg, 90 mg, and 135 mg; or 67 mg, 100 mg, 134 mg, and 200 mg. Fibrates may be formulated as a capsule, tablet or delayed release capsule product.

[00609] Initiation of both a fibrate and a K_{ATP} channel agonist, e.g., diazoxide or a salt thereof, may be titrated; thus if treatment is initiated with both products simultaneously, the treated patient may receive the starter dose for both products. For example, a titration dose of a fibrate may be between about 35 to 100 mg, such as between about 35 mg to 67 mg; and a titration dose of a K_{ATP} channel agonist may be about 70 to 220 mg; such as between about 72.5 to 145 mg of a K_{ATP} channel agonist. Titration of fibrate, e.g. fenofibrate or a salt thereof, and a K_{ATP} channel agonist, e.g. diazoxide or a salt thereof, may extend over 7 to 28 days and may include at least one additional dose level prior to reaching the maintenance dose of either product. The maintenance dose on a fibrate may typically be about 2 times to 3 times the starter dose. For example, the maintenance dose may contain between 100 mg and 200 mg of fenofibrate. The maintenance dose of the K_{ATP} channel agonist, e.g. diazoxide or a salt thereof, may be about 2 times to 3 times the titration dose. For example a diazoxide choline maintenance dose may range from 145 to 435 mg.

[00610] To accommodate initiation of treatment with both products, a titration kit may be prepared in which each product is packaged for daily administration in a blister pack or similar arrangement. Each daily blister may contain either one dose of each drug product or the two drugs blistered separately. The blister material may be any standard blister material known in the art, such as plastic, foil, or a multi-layer product containing both aluminum and one or more layers of either PVC or nylon. Exemplary titration kits may contain from 7 blisters, where both drug products are in the same blister and titration extends only over 7 days, to more than 56 blisters, where each product is packaged separately and titration extends over 28 days. The kit may include up to two dose levels of each product and may also contain the maintenance dose for at least 1 day of treatment. Each blister may be identified as to the day of treatment, or the dose and day of treatment with that dose. The different dose strengths of each drug product may be uniquely identified as to dose either by color, combination of colors for the capsule product, markings or both color and markings. Alternatively, the blister cards may contain sufficient drug product for 7 days and the kit may contain one or more weekly cards. The cards may be identical or may differ and be identified as to dose strength of each product or week of treatment.

Intravenous Administration of Diazoxide and Insulin

[00611] The primary objectives of intervention in patients with acute pancreatitis (AP) who have elevated triglycerides are (1) to rapidly lower triglycerides (TG) and free fatty acids (FFA); (2) to limit pancreatic and peripancreatic necrosis; and (3) to limit organ failure and the associated mortality. The primary means of lowering TG in patients with acute pancreatitis are (1) marked limitations of dietary intake of fat; (2) the use of low molecular weight heparin or insulin to increase disposal of FFA and TG to tissues; and (3) plasmapheresis, in which TG are filtered from blood or the blood volume is replaced by new blood with lower TG concentrations. However, under circumstances where hepatic TG biosynthesis and secretion is markedly elevated, these approaches have limited value.

[00612] An intravenous formulation of diazoxide (Hyperstat®) is known to be used to treat malignant hypertension. The formulation is a sterile solution containing 15 mg/ml of diazoxide at pH 11.5. Administration typically involves the administration of a 300 mg bolus over 5-15 seconds. In some instances, a 150 mg bolus is used, and occasionally the administration is spread over 1 minute. The objective of administration is to rapidly achieve a high free drug concentration in the peripheral arterioles, resulting in extensive vasodilation and rapid reduction in blood pressure. In contrast, intravenous administration of 1.5 mg/kg over 5 minutes has been shown to have little effect on blood pressure (Wang et al. Eur J CardioThoracic Surg, 2003, 24:967-973).

[00613] Administration of intravenous K_{ATP} channel agonist, e.g. diazoxide or a salt thereof, in combination with insulin will result in both the reduction of hepatic TG biosynthesis and secretion and increased disposal of circulating TG and FFA to tissues, more effectively lowering circulating concentrations of both than would the use of either drug separately. Additionally, the combination of an intravenous K_{ATP} channel agonist with insulin and reduced dietary intake of fat maximizes reductions in circulating TG and FFA in patients with acute pancreatitis and elevated TG because under these conditions, new chylomicrons are not being synthesized, hepatic TG biosynthesis is suppressed and the disposal to tissue is maximized. As administration of diazoxide partially suppresses insulin secretion and thus raises fasting and post-prandial glucose, insulin

supplementation will also inhibit a rise in glucose in patients undergoing intravenous K_{ATP} channel agonist therapy as described herein.

[00614] An exemplary intravenous treatment may be as follows. First, a K_{ATP} channel opener, such as diazoxide, may be administered as a bolus at a dose of between about 0.5 to 5 mg/kg over 5 to 10 minutes. Such a bolus administration may result in administration of between about 50 to 200 mg over the administration time. Following the initial bolus, a K_{ATP} channel opener, such as diazoxide, may be administered intravenously at a rate of between about 0.02 to 0.2 mg/kg/hr. During this second K_{ATP} channel opener administration, insulin is administered on a recurring basis at a level and rate sufficient to maintain fasting glucose between about 70 mg/dL and 125 mg/dL and peak post prandial glucose less than 200 mg/dL.

[00615] Plasmapheresis may also be used in conjunction with co-administration of diazoxide choline and insulin. Even under circumstances in which plasmapheresis is used, dietary fat intake needs to be restricted to limit the synthesis of new chylomicrons. Additionally, when plasmapheresis is used, hepatic TG biosynthesis and secretion needs to be down-regulated. Therefore the combination of an intravenous K_{ATP} channel agonist with insulin supplementation and plasmapheresis is also a preferred means to treat patients with AP and elevated TG.

[00616] Additionally, intravenous administration of a K_{ATP} channel agonist described herein, e.g. diazoxide, has the potential to protect pancreatic and peripancreatic tissues from ischemia and other cytotoxic insult, limiting the potential for complications, infection and organ failure, and thereby also reducing mortality risk.

[00617] Nicorandil (2-[(pyridin-3-ylcarbonyl)amino]ethyl nitrate) is a vasodilatory drug combining nitrate functionality with K_{ATP} channel activation. By virtue of its K_{ATP} channel activity, nicorandil has been shown to protect tissue from ischemic injury. Nicorandil may be administered either as an oral product or by intravenous injection. In order to protect tissues in AP patients with elevated TG from ischemic injury and necrosis, it is possible to co-administer nicorandil and diazoxide or a salt thereof, or to develop an intravenous co-formulation of nicorandil and diazoxide or a salt thereof.

Nicarandil has not been demonstrated to suppress hepatic TG biosynthesis and secretion to the degree that diazoxide does, but ischemic protection may be improved.

[00618] Intravenous administration of a K_{ATP} channel agonist described herein, e.g. diazoxide, is easily achieved during the early stages of hospitalization and may continue while patients are in the intensive care unit. It becomes more challenging once they become ambulatory again. Therefore it is optimal to treat patients with AP and elevated triglycerides with intravenous formulations prior to them becoming ambulatory, and transitioning to oral administration of a K_{ATP} channel agonist described herein, e.g. diazoxide choline, thereafter. In some instances, patients may be treated orally with a K_{ATP} channel agonist described herein, e.g. diazoxide choline, only while they are hospitalized. Alternatively, they may receive a K_{ATP} channel agonist described herein orally on a chronic basis for as long as they have risk of recurrence of AP. Oral administration of a K_{ATP} channel agonist described herein may be achieved with suitable delivery form, including oral suspension, fast-melt tab, immediate release capsule or tablet, controlled release capsule or tablet formulations, etc. Optimally, the patient is treated with a controlled-release formulation which facilitates once per day (QD) dosing and provides for high bioavailability of the K_{ATP} channel agonist.

Kits in the Treatment of Dyslipidemia

[00619] Compliance in the treatment of a number of disease conditions requiring treatment with two or more medications, which have not or cannot be co-formulated, is improved if the medications are combined in a kit which includes clear instructions for treatment. Improved compliance results in improved therapeutic outcomes and reduced risk of disease recurrence or relapse. The use of kits to improve compliance in the treatment of chronic asymptomatic diseases is important because the patient is, by definition, unaware or less aware of their disease status. Examples of chronic asymptomatic diseases include hypertension and most lipid abnormalities. Additionally, improved compliance is important to reduce the risk of an uncommon or rare acute effect of the chronic condition. For example, treatments to reduce very high triglycerides are intended to reduce the risk of pancreatitis. Similarly, treatments to reduce elevated LDL are intended to reduce the risk of major cardiovascular adverse events including myocardial infarction and stroke, and to reduce mortality.

[00620] In one example a kit is prepared for the treatment of a patient with a lipid disorder characterized by elevated LDL-C and elevated triglycerides which includes a monthly dose of an oral formulation of a K_{ATP} channel agonist, a monthly dose of a statin, and instructions for the administration of each drug. In this kit, the K_{ATP} channel agonist may be a K_{ATP} channel agonist of Formulae I-IV, or a salt thereof. For example, the K_{ATP} channel agonist may be diazoxide choline. In some examples, the diazoxide choline may be in a controlled, delayed, or sustained release formulation. In some examples, the K_{ATP} channel agonist and the statin may be included as separate formulations. Alternatively, the K_{ATP} channel agonist and statin may be co-formulated, e.g., in a single capsule, pill, or other oral delivery form.

[00621] In another example a kit is prepared for the treatment of a patient with a lipid disorder characterized by elevated triglycerides which includes a monthly dose of an oral formulation of a K_{ATP} channel agonist, a monthly dose of a fibrate, and instructions for the administration of each drug. In this kit, the K_{ATP} channel agonist may be a K_{ATP} channel agonist of Formulae I-IV, or a salt thereof. For example, the K_{ATP} channel agonist may be diazoxide choline. In some examples, the diazoxide choline may be in a controlled, delayed, or sustained release formulation. In some examples, the fibrate may be fenofibrate or a salt thereof. In some examples, the K_{ATP} channel agonist and the fibrate may be included as separate formulations. Alternatively, the K_{ATP} channel agonist and fibrate may be co-formulated, e.g., in a single capsule, pill, or other oral delivery form.

[00622] In yet another example a kit is prepared for the treatment of a patient with a lipid disorder characterized by elevated triglycerides which includes a monthly dose of an oral formulation of a K_{ATP} channel agonist, a monthly dose of an omega-3 fatty acid-based drug, and instructions for the administration of each drug. The kit includes a monthly dose of an oral formulation of a K_{ATP} channel agonist, a monthly dose of a statin, and instructions for the administration of each drug. In this kit, the K_{ATP} channel agonist may be a K_{ATP} channel agonist of Formulae I-IV, or a salt thereof. For example, the K_{ATP} channel agonist may be diazoxide choline. In some examples, the diazoxide choline may be in a controlled, delayed, or sustained release formulation. In some examples, the K_{ATP} channel agonist and the omega-3 fatty acid-based drug may be included as separate formulations. Alternatively, the K_{ATP} channel agonist and omega-3 fatty acid-based drug

may be co-formulated, e.g., in a single capsule, pill, or other oral delivery form. The omega-3 fatty acid-based drug may be based on Lovaza®. The omega-3 fatty acid-based drug may be in a controlled, delayed, or sustained release formulation. The omega-3 fatty acid based drug may contain 90% or higher EPA and no DHA.

[00623] In yet another example, a kit is prepared for the treatment of a patient with a lipid disorder characterized by reduced HDL-C and elevated triglycerides which includes a monthly dose of an oral formulation of a K_{ATP} channel agonist, a pharmaceutical formulation of niacin or an analog thereof, and instructions for the administration of each drug. In this kit, the K_{ATP} channel agonist may be a K_{ATP} channel agonist of Formulae I-IV, or a salt thereof. For example, the K_{ATP} channel agonist may be diazoxide choline. In some examples, the diazoxide choline may be in a controlled, delayed, or sustained release formulation. In some examples, the K_{ATP} channel agonist and the niacin or analog thereof may be included as separate formulations. Alternatively, the K_{ATP} channel agonist and niacin or analog thereof may be co-formulated, e.g., in a single capsule, pill, or other oral delivery form.

[00624] The invention will now be described with reference to the following non-limiting examples.

EXAMPLES

A. Potassium ATP Channel Activator Containing Formulations

1. Compressed Tablet Formulations of Diazoxide salt or derivative

[00625] Diazoxide salt or a derivative thereof at about 15-30% by weight is mixed with hydroxypropyl methylcellulose at about 55-80% by weight, ethylcellulose at about 3-10 wt/vol % and magnesium stearate (as lubricant) and talc (as glidant) each at less than 3% by weight. The mixture is used to produce a compressed tablet as described in Reddy et al., AAPS Pharm Sci Tech 4(4):1-9 (2003). The tablet may be coated with a thin film as discussed below for microparticles.

[00626] A tablet containing 100 mg of diazoxide salt or a derivative thereof will also contain approximately 400 mg of hydroxypropyl cellulose and 10 mg of ethylcellulose. A tablet containing 50 mg of diazoxide salt or a derivative thereof will also contain approximately 200 mg of hydroxypropyl cellulose and 5 mg of ethylcellulose. A tablet containing 25 mg of diazoxide salt or a derivative thereof will also contain approximately 100 mg of hydroxypropyl cellulose and 2.5 mg of ethylcellulose.

[00627] 2. Encapsulated Coated Microparticle Formulation of Diazoxide Salt or derivative

[00628] Diazoxide salt or a derivative thereof is encapsulated into microparticles in accordance with well known methods (see, e.g. U.S. Patent No. 6,022,562). Microparticles of between 100 and 500 microns in diameter containing diazoxide salt or a derivative thereof, alone or in combination with one or more suitable excipient, is formed with the assistance of a granulator and then sieved to separate microparticles having the appropriate size. Microparticles are coated with a thin film by spray drying using commercial instrumentation (e.g. Uniglatt Spray Coating Machine). The thin film comprises ethylcellulose, cellulose acetate, polyvinylpyrrolidone and/or polyacrylamide. The coating solution for the thin film may include a plasticizer which may be castor oil, diethyl phthalate, triethyl citrate and salicylic acid. The coating solution may also include a lubricating agent which may be magnesium stearate, sodium oleate, or polyoxyethylenated sorbitan laurate. The coating solution may further include an excipient such as talc, colloidal silica or of a mixture of the two added at 1.5 to 3% by weight to prevent caking of the film coated particles.

3. Formulations for controlled release of diazoxide or derivative

3.1. Formulation of a tableted form of diazoxide or a derivative for controlled release

[00629] Prior to mixing, both the active ingredient and hydroxypropyl methylcellulose (Dow Methocel K4M P) are passed through an ASTM 80 mesh sieve. A mixture is formed from 1 part diazoxide salt or a derivative thereof to 4 parts hydroxypropyl

methylcellulose. After thorough mixing, a sufficient volume of an ethanolic solution of ethylcellulose as a granulating agent is added slowly. The quantity of ethylcellulose per tablet in the final formulation is about 1/10th part. The mass resulting from mixing the granulating agent is sieved through 22/44 mesh. Resulting granules are dried at 40°C for 12 hours and thereafter kept in a desiccator for 12 hours at room temperature. Once dry the granules retained on 44 mesh are mixed with 15% fines (granules that passed through 44 mesh). Talc and magnesium stearate are added as glidant and lubricant at 2% of weight each. A colorant is also added. The tablets are compressed using a single punch tablet compression machine.

3.2. Formulation of a compression tableted form of diazoxide or a derivative thereof that provides for controlled release.

[00630] Diazoxide salt or a derivative thereof at 20-40% weight is mixed with 30% weight hydroxypropyl methylcellulose (Dow Methocel K100LV P) and 20-40% weight impalpable lactose. The mixture is granulated with the addition of water. The granulated mixture is wet milled and then dried 12 hours at 110°C. The dried mixture is dry milled. Following milling, 25% weight ethylcellulose resin is added (Dow Ethocel 10FP or Ethocel 100FP) followed by 0.5% weight magnesium stearate. A colorant may also be added. The tablets are compressed using a single punch tablet compression machine (Dashbach et al., Poster at AAPS Annual Meeting Nov. 10-14 (2002)).

3.3. Formulation of a compression coated tableted form of diazoxide or a derivative thereof that provides for controlled release.

[00631] The core tablet is formulated by mixing either 100 mg of diazoxide salt or a derivative thereof with 10 mg of ethylcellulose (Dow Ethocel 10FP), or by mixing 75 mg of diazoxide or a derivative thereof with 25 mg lactose and 10 mg of ethylcellulose (Dow Ethocel 10FP), or by mixing 50 mg of diazoxide or a derivative thereof with 50 mg of lactose and 10 mg of ethylcellulose (Dow Ethocel 10FP). The core tablets are formed on an automated press with concave tooling. The compression coating consisting of 400 mg of polyethylene oxide (Union Carbide POLYOX WSR Coagulant) is applied and

compressed to 3000 psi (Dasbach et al., Poster at AAPS Annual Meeting Oct. 26-30 (2003)).

3.4. Formulation of a controlled release tableted form of diazoxide choline salt

3.4.1 Controlled Release Formulations

[00632] Controlled release tableted formulations of diazoxide choline salt were developed and investigated with respect to a variety of properties known by those of skill in the pharmaceutical art relating to the manufacture of tableted formulations including, for example, ease and consistency of manufacture, appearance (e.g., sheen, compressibility, microscopic appearance), and dissolution properties (e.g., rate, order and extent of dissolution). Tablets were produced individually on a press, where the final blend of diazoxide choline salt and excipient was weighed out to the desired total tablet weight prior to compression. As shown in Table 2, Formulations A-H, J, and L contained 50.0 mg diazoxide as the choline salt (i.e., 72.5 mg total diazoxide choline salt present), Formulations I and K contained 200.0 mg diazoxide as the choline salt (i.e., 290.0 mg total diazoxide choline salt present) and Formulation U contained 145 mg diazoxide as the choline salt. The manufacture of formulation L is exemplary of the manufacturing methods available to the skilled artisan. For formulation L, diazoxide choline salt, talc, and approximately half of the colloidal silicon dioxide (Cab-o-sil) were mixed in a KGI-5 mixer bowl with an impeller speed of about 300 rpm and a chopper speed of about 3000 rpm for about 4 min. The mixture was passed through a co-mil equipped with a 024R screen, square-edged paddle, and 0.175" spacer. To this milled mixture in a 8-qt V-shell blender was added Emcompress (dibasic calcium phosphate) through a #20 mesh hand screen with blending for about 10 min. To this mixture was added PEO N750 and PEO 303, which had been passed through a #20 mesh hand screen, with blending for about 10 min. To this mixture was added Prev and the remainder of the Cab-o-sil, having been passed through a #20 mesh hand screen, with blending for about 5 min. The mixture was subjected to pressing (Manesty Beta Press) using 0.2220" x 0.5720" caplet shaped tooling (Set #21.)

Table 2. Exemplary Formulations for Diazoxide Choline salt.

Formulation	INGREDIENT	Amount per tablet (mg)
A.	Diazoxide Choline	72.50
	Kollidon SR	100.0
	PEO N303	25.00
	Emcompress	50.50
	Pruv	2.00
	TOTAL WEIGHT	250.0
B.	Diazoxide Choline	72.50
	Methocel K100M	237.3
	Emcompress	35.00
	Magnesium Stearate	3.50
	Cab-o-sil	1.75
	TOTAL WEIGHT	350.0
C.	Diazoxide Choline	72.50
	Kollidon SR	105.0
	PEO N303	35.0
	Emcompress	134.1
	Pruv	3.50
	TOTAL WEIGHT	350.1
D.	Diazoxide Choline	72.50
	Methocel K100M	175.1
	Emcompress	97.30
	Magnesium Stearate	3.50
	Cab-o-sil	1.75
	TOTAL WEIGHT	350.2
E.	Diazoxide Choline	72.50
	PEO N750 NF	105.0
	PEO N303 NF	52.50
	Emcompress	116.6
	Pruv	3.50
	TOTAL WEIGHT	350.1

Formulation	INGREDIENT	Amount per tablet (mg)
F.	Diazoxide Choline	72.50
	Kollidon SR	105.0
	PEO N303	7.00
	Emcompress	162.1
	Pruv	3.50
	TOTAL WEIGHT	350.1
G.	Diazoxide Choline	72.50
	Methocel K100M	175.1
	Emcompress	105.1
	Magnesium Stearate	3.50
	Cab-o-sil	1.75
	TOTAL WEIGHT	358.0
H.	Diazoxide Choline	72.50
	PEO N750 NF	105.0
	PEO N303 NF	35.01
	Emcompress	134.1
	Pruv	3.50
	TOTAL WEIGHT	350.1
I.	Diazoxide Choline	290.0
	Methocel K100M	240.0
	Emcompress	258.0
	Magnesium Stearate	8.00
	Cab-o-sil	4.00
	TOTAL WEIGHT	800.0
J.	Diazoxide Choline	72.50
	PEO N750 NF	105.0
	PEO N303 NF	52.50
	Emcompress	116.6
	Pruv	3.50
	Talc	3.50

Formulation	INGREDIENT	Amount per tablet (mg)
	Cab-o-sil	1.75
	TOTAL WEIGHT	355.4
K.	Diazoxide Choline	290.0
	PEO N750 NF	249.0
	PEO N303 NF	124.5
	Emcompress	145.3
	Pruv	8.30
	Talc	8.30
	Cab-o-sil	4.15
	TOTAL WEIGHT	829.6
K [*] .	Diazoxide Choline	290.0
	PEO N750 NF	249.0
	PEO N303 NF	124.5
	Emcompress	137.0
	Pruv	8.30
	Talc	16.6
	Cab-o-sil	4.15
	TOTAL WEIGHT	830.0
L.	Diazoxide Choline	72.51
	PEO N750 NF	105.1
	PEO N303 NF	52.54
	Emcompress	111.4
	Pruv	3.50
	Talc	3.50
	Cab-o-sil	1.75
	TOTAL WEIGHT	350.3
U.	Diazoxide Choline	145
	Pregelatinized starch	177
	PEO N750 NF	20
	PEO N303 NF	10
	Microcrystalline cellulose NF	230

Formulation	INGREDIENT	Amount per tablet (mg)
	Colloidal silicone dioxide NF	6
	Magnesium stearate NF	12
	TOTAL WEIGHT	600

[00633] It is noted that the composition of formula U in Table 2 is for the core tablet. The core tablet U was coated with a 2% opadry clear coat followed by a 3% Surelease coating.

[00634] Microscopic observation of the tablets having Formulation A revealed a grainy texture of the diazoxide choline salt, and at the 29% loading of diazoxide choline salt in Formulation A the blend had poor flow characteristics. Accordingly, the loading of diazoxide choline was reduced in Formulation B. A caplet shaped tooling, approximately 6 mm x 15 mm was found to result in acceptable tablet appearance, sheen, and ease of compressibility. However, Formulation B also exhibited poor blend flow.

[00635] Subsequent formulations (e.g., Formulations C-L) incorporated a milling step of the diazoxide choline salt prior to incorporation into the tablet blend. A milling study was conducted using a test mill equipped with different screen sizes to evaluate and determine a suitable milling process. Particle size was determined by visual comparison with 40 μ m reference beads. As shown in Table 3.1, use of the 024R screen resulted in the best recovery of API (i.e., "active pharmaceutical ingredient" = diazoxide as the diazoxide choline salt) providing the broadest range of particle sizes. Accordingly, material milled through a 024R screen was selected for subsequent formulation.

Table 3.1. Milling study for diazoxide choline salt prior to formulation

Screen/Paddle/Spacer/Speed	API loaded/API recovered (g)	Particle size (μ m)
018R/square/0.200"/80%	50.0/36.5	~100-200
024R/square/0.200"/80%	50.0/42.0	~100-250
039R/square/0.200"/80%	50.0/42.0	~150-250

[00636] Further optimization of formulations containing the diazoxide choline salt were carried out. Previous PEO formulations showed signs of sticking to the punch surface, possibly due to the interaction of PEO and diazoxide choline. Five additional formulations were prepared using polymers such as polyethylene oxide and cellulose in an attempt to discover non-sticking formulations.

[00637] Formulations M-P and R-S were prepared at a 500 g scale with the compositions shown in Table 3.2. Formulation Q was prepared as a small batch of five hand-compressed tablets. Formulation T was prepared at the 2 kg scale. In formulation M, the amount of PEO was reduced from 45% to 25%. In formulation N, PEO was replaced with 25% hydroxypropylmethyl cellulose (HPMC) and microcrystalline cellulose was added. Formulation O was similar to N, but used a different type of HPMC and dropped the starch. In formulation P, less HPMC and more microcrystalline starch were used than in N, and the starch was absent. Formulation Q was identical to P except that a different type of HPMC was used. Formulations R, S, and T included higher loadings of diazoxide choline (290 mg) and reduced tablet size (400, 700, and 830 mg for R, S, and T, respectively).

[00638] Formulations M-T were according to the following general procedure. Diazoxide tablet blend procedure. Diazoxide choline, colloidal silicon dioxide and half the talc were mixed in a v-shell blender for three minutes. The mixture was then co-milled for particle size reduction and to improve flow. The milled diazoxide choline mixture was blended with the remaining talc and either microcrystalline cellulose or starch in a v-shell blender for three minutes. The resulting mixture was subjected to roller compaction with a #12 mesh in line mill to provide granules. The granules were sieved through #16 and #40 mesh sieves. Material retained by the #16 mesh and passing through the #40 mesh were passed through the compactor again. Properly sized granules were roller compacted with half of the magnesium stearate and blended for three minutes in a v-shell blender. PEO and dibasic calcium phosphate were blended with the resulting mixture for three minutes in a v-shell blender. The remaining magnesium stearate was blended into the mixture for two minutes using a v-shell blender.

[00639] All the tablets produced had a nice appearance with good clean edges and most likely could easily withstand the coating process. No signs of sticking or picking

were present. The roller compaction method worked well for these formulations. Tablets prepared from formulations N, O, and P reached a maximum hardness of about 8 kp, while tablets of formulation M reached a maximum hardness of about 2.8 to 3.0 kp; the latter may have been due to obtaining a maximum of 3 tons of compression during manufacture. Formulations S and T showed signs of lamination, but that may be overcome by, e.g., precompression, use of a different roller compaction screen, and increasing the amount of fines in final blend.

Table 3.2 Additional Diazoxide Choline Salt Formulations

INGREDIENT	FORMULATION (wt %)				
	M	N	O	P	Q
Diazoxide Choline	34.94	34.90	34.90	34.90	34.90
Polyethylene Oxide, N750	17.00	-	-	-	-
Polyethylene Oxide, 303	8.00	-	-	-	-
Methocel A15	-	-	25.00	-	15.00
Methocel K100M	-	25.00	-	15.00	-
Avicel PH101	-	10.00	9.50	19.50	19.50
Emcompress	-	24.60	24.60	24.60	24.60
Talc, USP	2.00	2.00	2.00	2.00	2.00
Starch 1500	34.06	16.78	-	-	-
Magnesium Stearate	3.00	3.00	3.00	3.00	3.00
Cab-o-sil M5P	1.00	0.50	1.00	1.00	1.00
Total	100.0	100.0	100.0	100.0	100.0

Table 3.2 continued

INGREDIENT	FORMULATION (wt %)		
	R	S	T
Diazoxide Choline	72.5	41.43	34.90
Polyethylene Oxide, N750	2.00	10.00	17.00
Polyethylene Oxide, 303	1.00	5.00	8.00
Methocel A15	-	-	-
Methocel K100M	-	-	-
Avicel PH101	-	-	-
Emcompress	-	-	-
Talc, USP	2.00	2.00	2.00
Starch 1500	18.5	37.57	34.06
Magnesium Stearate	3.00	3.00	3.00
Cab-o-sil M5P	1.00	0.50	1.00
Total	100.0	100.0	100.0

3.4.2. Dissolution Studies

[00640] Dissolution of tablets with formulation as set forth in Table 4 was investigated. One or more tablets (e.g., 1 or 2) of the indicated tableted formulation were placed into a volume of buffer (e.g., 900 mL) with known buffer salt concentration (e.g., 0.05 M potassium phosphate, pH 8.6; 0.05 M potassium phosphate, pH 7.5), with or without surfactant (e.g., 0.05% CTAB), at a known temperature (e.g., 37 °C). Stirring conditions employed paddles at, for example, 50 RPM. Aliquots (e.g., 10 mL) removed as a function of time were filtered (e.g., 0.45 μ m GMP Filter) prior to analysis.

Table 4. Dissolution study for formulations of diazoxide choline salt (entries are % dissolved diazoxide)

Entry	Protocol	Time (hr)								
		0	1	2	3	6	9	12	18	24
C	a	0.0	2.9	4.5	5.7	9.4	13.0	16.6		
D	a	0.0	4.5	7.8	11.0	19.1	25.6	31.3		
F	b				29	36		44		54
G	b				30	39		50		67
H	b				50	75		91		101
I	b				25	37		48		57
J	b				34	53		76		104
K	b				25 24	43 41		64 62		94 92
U	b	0			6	32		77		101
M	b				18	34		57		90
N	b									56
O	b				23	42		61		71
P	b				22	37		51		65
R	b				102	104		105		106
Q	b				27	45		62		74
S	b				30	56		85		106
T	b				24	44		73		99

Column 1: Entry from Table 2.

Column 2: Protocol a) 0.05 M potassium phosphate, pH 8.6, 37 °C; Protocol b) 0.05 M potassium phosphate, pH 7.5, 0.05% CTAB, 37 °C.

[00641] Subsequently, 200 mg tablets of formulations R, S and T were coated with a 1-2% clearcoat undercoat and with 1-7% ethycel (Surelease) overcoat. This combination of undercoat and Surelease overcoat delayed release of drug from the formulation by approximately 1 hour followed by linear release through 24 hours. Adjustment of the Surelease concentration from 7% to 3% results in increases in the rate of release without impacting the linearity of release. For example formula R with a polymeric undercoat and 7% surelease coat results in 61% release by 24 hours using protocol b (See Table 4.1). Similarly, a 600 mg tablet of formulation U (core tablet) was coated with a 2% opadry clear coat, and then with a 3% Surelease coating.

Table 4.1 Dissolution of Coated Tablets Formulations at 7%, 5%, and 3% Overcoating

Time (h)	R 7%	S 5%	T 3%
0	0	0	0
1	0	0	1
3	2	4	5
6	8	13	15
12	25	36	39
24	61	73	81

[00642] The dissolution profile (i.e., % dissolved with time) of Proglycem® capsules (100 mg) and controlled-release tablet formulations of diazoxide as provided herein is shown in Table 5. The 50 mg tablet entry of Table 5 refers to Formulation J (Table 2) wherein talc and cab-o-sil was present at 2% and 1%, respectively. The 200 mg tablet entry of Table 5 refers to Formulation K (Table 2) wherein talc and cab-o-sil are present at 2% and 1%, respectively.

Table 5. Dissolution profile of 100 mg Proglycem® (capsule) and diazoxide choline salt (tablet)

Time (hr)	100 mg capsule Proglycem®	200 mg tablet diazoxide choline salt	50 mg tablet diazoxide choline salt
0	0	0	0
3	79	22	25
6	85	36	39
12	92	54	70
24	98	88	99

[00643] As evidenced by Table 5, the 100-mg Proglycem® capsule provides for faster dissolution of diazoxide relative to tablets described herein. Approximately 79% diazoxide component of Proglycem® is recovered in dissolution buffer after 3-hr. In contrast, the 50 and 200-mg tablets described in Table 5 dissolved at levels of 25% and 22%, respectively, at 3-hr. At 12-hr, 100-mg Proglycem® capsule dissolved at 92%, whereas the 50 and 200-mg tablets dissolved at 70% and 54%, respectively. Approximately total dissolution is observed with 100-mg Proglycem® capsule and 50-mg tablet at 24 hrs.

3.4.3. Excipient Compatibility Studies

[00644] Studies to determine the compatibility of diazoxide choline salt for various excipients are summarized in Table 6. Each mixture of excipient (100 mg) and diazoxide choline salt (100 mg) was made in acetonitrile to 10 mL. Samples were assayed immediately (i.e., "Initial" column of Table 6) and at one-month storage under conditions a) 40 °C/75% RH (relative humidity), and b) 50 °C.

Table 6. Excipient compatibility study for diazoxide choline salt.

Excipient	Initial % (w/w)	1 Month 40 °C/75% RH % (w/w)	1 Month 50 °C % (w/w)
Hydroxypropylmethyl cellulose (HMPC)	98.8	101.4	96.6
Hydroxypropylcellulose (HPC)	103.1	97.4	100.8
Ethylcellulose (EC)	90.6 99.5*	102.0	99.7
Methylcellulose (MC)	102.3	100.3	99.1
Carboxymethyl cellulose Na (CMC Na)	96.8	101.6	99.5
Starch 1500	103.3	90.6	95.2
Kollidon SR	81.2 100.2*	99.8	100.9
Polyethyleneoxide N3 03 (PEO)	81.0 99.1*	99.2	99.0
Dibasic Calcium Phosphate	98.4	102.9	102.2
Sodium Stearyl Fumarate	98.9	101.1	103.7
Magnesium Stearate	100.1	101.4	99.3
Colloidal Silicon Dioxide (Cab-o-sil)	99.0	99.4	104.5
Microcrystalline Cellulose	96.8	98.6	107.0
Lactose Monohydrate	94.5	99.2	103.0
Mannitol	111.7	98.1	81.3
Diazoxide Control	N/A	99.0	99.4

* Re-assayed

[00645] Initial low results for ethylcellulose, Kollidon SR, and polyethyleneoxide were investigated by re-preparing samples of diazoxide choline salt and excipient. As shown in Table 6, initial sample recovery (i.e., column "Recovery") of the re-prepared samples indicates method accuracy.

[00646] No reportable impurities were detected in any sample, and no degradation was observed in the samples stored for one-month with the exception of mannitol wherein 81.3% of diazoxide was recovered after 1-month at 50 °C.

3.4.3. Stability Studies for Diazoxide Choline Controlled Release Tablets

[00647] Studies to determine the stability of formulations of diazoxide choline salt as the controlled release tablet were conducted on sample formulations as described in Table

2, results of which are shown in Table 7. In these studies, storage conditions were the following: a) 25 °C/60% RH, and b) 40 °C/75% RH. In Table 7, the term "Appearance" refers to the physical appearance of the tablets of the study. The term "Assay (%)" refers to the percentage of diazoxide choline salt assayed with respect to nominal (i.e., 50 mg or 200 mg) content of the sample. The term "Dissolution (%)" refers to the amount, expressed as a percentage, of diazoxide choline salt assayed by method described herein.

Table 7. Stability Study for Formulations of Diazoxide Choline Salt.

Test	Time point		
	Initial	1 month	2 months
<i>50 mg tablet, Formulation J, 25 °C/60% RH,</i>			
Appearance	White tablets	White tablets	White tablets
Assay (%)	95.8	102.9	99.3
Dissolution (%):			
3 hr	24	19	15
6 hr	41	30	27
12 hr	62	48	52
24 hr	92	90	94
<i>50 mg tablet, Formulation J, 40 °C/75% RH,</i>			
Appearance	White tablets	White tablets	White tablets
Assay (%)	95.8	103.2	99.4
Dissolution (%):			
3 hr	24	10	10
6 hr	41	22	21
12 hr	62	50	46
24 hr	92	90	84
<i>200 mg tablet, Formulation K, 25 °C/60% RH</i>			
Appearance	White tablets	White tablets	White tablets
Assay (%)	95.9	100.9	100.3

Test	Time point		
	Initial	1 month	2 months
Dissolution (%):			
3 hr	34	15	13
6 hr	53	31	30
12 hr	76	69	68
24 hr	104	101	96
<i>200 mg tablet, Formulation K, 40 °C/75% RH</i>			
Appearance	White tablets	White tablets	White tablets
Assay (%)	95.9	99.6	100.0
Dissolution (%):			
3 hr	34	10	10
6 hr	53	26	28
12 hr	76	60	61
24 hr	104	90	90

3.5. A controlled release dosage form of diazoxide or a derivative thereof using an osmotically controlled release system.

[00648] Diazoxide salt or a derivative thereof is formulated as an osmotically regulated release system. In general, two components, and an expandable hydrogel that drives release of the active drug is assembled with diazoxide salt or a derivative thereof into a semipermeable bilaminate shell. Upon assembly a hole is drilled in the shell to facilitate release of active upon hydration of the hydrogel.

[00649] A dosage form adapted, designed and shaped as an osmotic delivery system is manufactured as follows: first, a diazoxide salt or a derivative thereof composition is provided by blending together into a homogeneous blend of polyethylene oxide, diazoxide salt or a derivative thereof and hydroxypropyl methylcellulose. Then, a volume

of denatured anhydrous ethanol weighing 70% of the dry mass is added slowly with continuous mixing over 5 minutes. The freshly prepared wet granulation is screened through a 20 mesh screen through a 20 mesh screen, dried at room temperature for 16 hours, and again screened through a 20 mesh screen. Finally, the screened granulation is mixed with 0.5% weight of magnesium stearate for 5 minutes.

[00650] A hydrogel composition is prepared as follows: first, 69% weight of polyethylene oxide weight, 25% weight of sodium chloride and 1% weight ferric oxide are separately screened through a 40 mesh screen. Then, all the screened ingredients are mixed with 5% weight of hydroxypropyl methylcellulose to produce a homogeneous blend. Next, a volume of denatured anhydrous alcohol equal to 50% of the dry mass is added slowly to the blend with continuous mixing for 5 minutes. The freshly prepared wet granulation is passed through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen. The screened granulation is mixed with 0.5% weight of magnesium stearate for 5 minutes (see U.S. Patent No. 6,361,795 by Kuczynski, et al.).

[00651] The diazoxide salt composition, or a derivative thereof, and the hydrogel composition, are compressed into bilaminate tablets. First the diazoxide salt or a derivative thereof composition is added and tamped. The hydrogel composition is then added and the laminae are pressed under a pressure head of 2 tons into a contacting laminated arrangement.

[00652] The bilaminate arrangements are coated with a semipermeable wall (i.e. thin film). The wall forming composition comprises 93% cellulose acetate having a 39.8% acetyl content, and 7% polyethylene glycol. The wall forming composition is sprayed onto and around the bilaminate.

[00653] Finally, an exit passageway can be drilled through the semipermeable wall to connect the diazoxide salt or a derivative thereof drug lamina with the exterior of the dosage system. Residual solvent is removed by drying at 50° C and 50% humidity. The osmotic systems are dried at 50° C to remove excess moisture (see U.S. Patent No. 6,361,795 by Kuczynski, et al.).

4. Preparation of Diazoxide Salts

4.1. Preparation of the Sodium Salt

[00654] The sodium salt of diazoxide was prepared by dissolving 300 mg of diazoxide in approximately 45 mL methyl ethyl ketone (MEK). The diazoxide/MEK solution was heated at 75°C on an orbital shaker to ensure dissolution. To the solution was added 1.3 mL of 1M NaOH (1 molar equivalent). The combined solutions were heated at 75°C for approximately 30 minutes and allowed to cool to room temperature. The mixture was concentrated under reduced pressure, and dried in vacuo at 55°C and 30 in. Hg. Elemental analysis: Calculated, 38.03% C, 2.39% H, 11.09% N and 9.1% Na; Found, 38.40% C, 2.25% H, 10.83% N and 7.4% Na.

[00655] A sodium salt of diazoxide was also prepared by dissolving 300 mg of diazoxide in approximately 45 mL acetonitrile. The diazoxide/acetonitrile solution was heated at 75°C on an orbital shaker to ensure dissolution. To the solution was added 1.3 mL of 1M NaOH (approximately 1 molar equivalent). The combined solutions were heated at 75°C for approximately 30 minutes and allowed to cool to room temperature. The mixture was concentrated under reduced pressure, and dried in vacuo at 55°C and 30 in. Hg.

4.2. Preparation of the Potassium Salt

[00656] The potassium salt of diazoxide was prepared by dissolving 300 mg of diazoxide in approximately 45 mL methyl ethyl ketone (MEK). The diazoxide/MEK solution was heated at 75°C on an orbital shaker to ensure dissolution. To the solution was added approximately 1.3 mL of 1 M KOH (1 molar equivalent) and the solution was returned to the orbital shaker, heated at 75°C for approximately 30 minutes and allowed to cool to room temperature. The solvent was removed under reduced pressure and the solid was dried in vacuo at 55°C and 30 in. Hg. Elemental analysis: Calculated, 33.59% C, 2.81% H, 9.77% N and 13.63% K; Found, 34.71% C, 2.62% H, 9.60% N and 10.60% K.

[00657] The potassium salt of diazoxide was also prepared by dissolving 300 mg of diazoxide in approximately 45 mL tetrahydrofuran (THF). The diazoxide/THF solution was heated at 75°C on an orbital shaker to ensure dissolution. To the solution was added approximately 1.3 mL of 1 M KOH (1 molar equivalent) and the resulting solution was returned to the orbital shaker, heated at 75°C for approximately 30 minutes and allowed to cool to room temperature. THF was removed under reduced pressure and the solid was dried in vacuo at 55°C and 30 in. Hg.

4.3. Preparation of Choline Salt

4.3.1. Preparation of the Choline Salt: proof of concept

[00658] The choline salt of diazoxide was prepared by dissolving 300 mg of diazoxide in approximately 45 mL methyl ethyl ketone (MEK). The diazoxide/MEK solution was heated at 75°C on an orbital shaker to ensure dissolution. To the solution was added approximately 315 mg of 50 wt. % of choline hydroxide (1 molar equivalent) and the solution was returned to the orbital shaker and stirred at 75°C for approximately 30 minutes. The solvent was removed under reduced pressure, and the solid was dried in vacuo at 55°C and 30 in. Hg. Elemental analysis: Calculated, 46.77% C, 5.86% H, and 12.00% N; Found, 46.25% C, 6.04% H, and 12.59% N.

4.3.2. Process of preparation of the Choline Salt

[00659] An investigation of the minimum solvent volumes required to optimize the formation of the diazoxide choline salt was performed in MeCN, THF, MEK, and 2-MeTHF on small scale in the presence and absence of MTBE. Analyses by ¹H NMR and XRPD of all reactions were consistent with the assigned structure and Form B of diazoxide choline salt.

4.3.2.1. Solvent Efficiency Study with Single Solvent System.

[00660] Investigation of single solvent system synthesis of diazoxide choline salt using solvents THF, MEK, and 2-MeTHF were conducted, results of which are shown in Table

8. These results suggest that precipitation can be achieved with a single solvent system in THF or 2-MeTHF. The best results, (i.e., Table 8 entries 14-17) obtained with 2-MeTHF. However, it was observed that in 2-MeTHF at 3-volumes and above, complete dissolution was not achieved after addition of choline hydroxide.

Table 8. Solvent Efficiency of a Single Solvent System

Entry	Solvent	Solvent volume	Yield (%)	Polymorphic Form
1	THF	1.0	7	B
2	THF	2.0	n/a	n/a
3	THF	3.0	20	B
4	THF	4.0	28	B
5	THF	5.0	32	B
6	THF	6.0	42	B
7	THF	7.0	53	B
8	THF	8.0	50	B
9	MEK	4.0	n/a	n/a
10	2-MeTHF	1.0	n/a	n/a
11	2-MeTHF	2.0	48	B
12	2-MeTHF	3.0	41	B
13	2-MeTHF	4.0	48	B
14	2-MeTHF	5.0	71	B
15	2-MeTHF	6.0	71	B
16	2-MeTHF	7.0	72	B
17	2-MeTHF	8.0	67	B

n/a: Samples were either seen to form a gum, or no precipitate was observed.

4.3.2.2. Solvent Efficiency Study with Binary Solvent Systems.

[00661] The addition of a second solvent at 1-20 volumes (i.e., 1-8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20) to the solvent volumes of Table 8 was envisaged to optimize diazoxide salt production yields. Results of investigation of methods to enhance precipitation and increase yield employing binary solvent system synthesis of diazoxide choline salt using solvents THF, MeCN, MEK, and 2-MeTHF and co-solvent MTBE are shown in Table 9. Optimum conditions for the preparation of the diazoxide choline salt obtained with 1-3 volumes of THF (see Table 8, entries 1-3), with 3 volumes being the ratio of choice to eliminate excessive drag during stirring of slurry in large scale production.

Table 9. Solvent Efficiency of a Binary Solvent System

Entry	Solvent	Solvent Volume	Co-Solvent (12 Vol)	Yield (%)	Polymorphic Form
1	THF	1.0	MTBE	96	B
2	THF	2.0	MTBE	96	B
3	THF	3.0	MTBE	91	B
4	THF	4.0	MTBE	90	B
5	THF	5.0	MTBE	84	B
6	THF	6.0	MTBE	90	B
7	THF	7.0	MTBE	94	B
8	THF	8.0	MTBE	94	B
9	MeCN	1.0	MTBE	92	B
10	MeCN	2.0	MTBE	90	B
11	MeCN	3.0	MTBE	87	B
12	MeCN	4.0	MTBE	79	B
13	MeCN	5.0	MTBE	79	B
14	MeCN	6.0	MTBE	75	B

Entry	Solvent	Solvent Volume	Co-Solvent (12 Vol)	Yield (%)	Polymorphic Form
15	MeCN	7.0	MTBE	70	B
16	MeCN	8.0	MTBE	74	B
17	MEK	4.0	MTBE	83	B
18	2-MeTHF	1.0	MTBE	97	B
19	2-MeTHF	2.0	MTBE	94	B
20	2-MeTHF	3.0	MTBE	94	B
21	2-MeTHF	4.0	MTBE	95	B
22	2-MeTHF	5.0	MTBE	97	B
23	2-MeTHF	6.0	MTBE	94	B
24	2-MeTHF	7.0	MTBE	97	B
25	2-MeTHF	8.0	MTBE	>99	B

4.3.2.3. Co-Solvent Efficiency and Optimization with MTBE.

[00662] Results of optimization of co-solvent (MTBE) volume in the presence of 3 volumes of solvent are shown in Table 10.

Table 10. Co-Solvent Efficiency and Optimization with MTBE

Entry	Solvent	MTBE Volume	Yield (%)	Form
1	MeCN	8.0	76	B
2	MeCN	14.0	85	B
3	THF	6.0	93	B
4	THF	8.0	93	B
5	THF	14.0	98	B

[00663] Optimized conditions for the production of the choline salt of diazoxide in a binary solvent system obtained with 3:14 (i.e., 1:4.7) THF/MTBE (v/v).

4.3.2.4. Optimization of Cooling Profile.

[00664] Optimization for the controlled precipitation of diazoxide choline salt was conducted by varying the cooling temperatures and hold times. Reactions were carried out in MeCN, THF, and 2-MeTHF (3 vol) with MTBE (14 vol). The results are presented in Table 11. These results suggest that optimum crystal growth was achieved with cooling to 0–5 °C for eight hours in THF and 2-MeTHF (Entries 5–6) when compared to those in MeCN (Entries 1, 2, and 4). These results however did not indicate enhanced precipitation when compared to previous studies carried out in THF and 2-MeTHF when the slurries were allowed to stir for two hours. In addition no notable improvements were observed for the additional cooling to –15 °C or with the filtration at ambient temperature.

Table 11. Cooling Profile Optimization for Controlled Precipitation

Entry	Solvent	Cooling Temp. (°C)	Hold Time (hr)	Yield (%)	Form
1	MeCN	0–5	2	89	B
2	MeCN	–10 → –15	2	85	B
3	THF	RT	2	80	B
4	MeCN	RT	2	85	B
5	THF	0–5	8	94	B
6	2-MeTHF	0–5	8	95	B

4.3.2.5. Optimization of Rate of Co-solvent addition.

[00665] The effect of rate and hold time of co-solvent addition on the precipitation of diazoxide choline salt was examined. The reactions were carried out on 500 mg scale in three volumes of primary solvent and 14 volumes of MTBE (THF and 2-MeTHF) or 1:3 volume ratio (MeCN). Addition of the co-solvent was made dropwise in one portion for Entry 1, and for Entries 2 and 3 the co-solvent was added at a rate of 1 mL/20 minutes for

a total hold time of 140 minutes for the addition of 7 mL. The results, presented in Table 12, indicate that optimum precipitation of diazoxide choline salt was achieved by the addition of MTBE with 20 minute hold times in between additions in THF or 2-MeTHF (entries 2-3).

Table 12. Optimization of Rate of Co-solvent addition

Entry	Solvent	Hold Time (min)	Addition Rate (mL/min)	Yield (%)	Form
1	MeCN	60	n/a	87	B
2	THF	140	1.0/20	96	B
3	2-MeTHF	140	1.0/20	96	B

4.3.2.6. Thermal Stability Study.

[00666] The stability of the isolated diazoxide choline salt was investigated to determine optimal drying conditions to minimize residual solvents without degradation. Samples of the diazoxide choline salt prepared in THF and MTBE (Entries 1–4) were dried under vacuum at 40 °C for various durations on small scale (100 mg). The study was then carried out on 5 g scale (Entry 5) at 30 °C for eight hours under vacuum to show reproducibility on large scale. The results are presented in Table 13. Analyses of the samples of Table 13 by ¹H NMR, XRPD, and HPLC indicated that elevated temperatures and prolonged drying times did not degrade the compound or affect the form of the compound.

Table 13. Thermal Stability Study

Entry	Drying Temp (°C)	Time (h)	OVI (THF/MTBE) (ppm)	Polymorphic Form
1	RT	12	376/248	B
2	40	20	317/160	B
3	40	28	276/127	B

4	40	42	268/128	B
5	30	8	241/509	B

4.3.2.6. Demonstration of 50-g Scale synthesis of Diazoxide Choline Salt in THF.

[00667] The preparation of the diazoxide choline salt was carried out in a binary-solvent system of THF and MTBE with a ratio of 1:4.7 (solvent/co-solvent) volumes and cooling to 0–5 °C for two hours with stirring. A demonstration run for the large scale production utilizing the modified procedure was carried out on 50 g-scale. Diazoxide (50 g) as a hot (62 °C) suspension in THF (140 mL) was treated with choline hydroxide (45% solution in MeOH, 1.0 equiv) added (2 mL/min) over 30 minutes. The resulting solution was stirred for 30 minutes, followed by cooling to 52 °C for the addition of MTBE (14 vol) over 45 minutes. On addition of two volumes of co-solvent precipitation was observed. The resultant slurry was then allowed to cool naturally to ambient temperature followed by further cooling to 0–5 °C with an ice/water bath and an additional 2 hr stirring. The precipitate was isolated by vacuum filtration, and the filter cake rinsed with ice cold MTBE (~50 mL) and dried under vacuum at room temperature for 12 hours. OVI analysis indicated that THF levels were above the recommended ICH guidelines (799 ppm) and the material was returned to the oven at 30 °C for eight hours to give diazoxide choline salt [70.87 g, 97% yield, 97% purity AUC] as a white crystalline solid. Analyses by ¹H NMR, XRPD, and HPLC were consistent with the assigned structure of Form B while maintaining a high purity with good yield.

4.3.2.7. Demonstration of 50-g Scale synthesis of Diazoxide Choline Salt in 2-MeTHF.

[00668] A 50-g level synthesis was duplicated in 2-MeTHF/MTBE as an alternative to THF/MTBE for the large scale production of the diazoxide choline salt described above. No issues or concerns arose during the reaction other than complete dissolution was not achieved after addition of the choline hydroxide. A white precipitate formed after addition of the co-solvent, which was isolated via vacuum filtration and dried under vacuum at 30 °C for eight hours to give diazoxide choline salt [71.51 g, 97% yield] as a

white crystalline solid. Analyses by ¹H, XRPD, and HPLC were consistent with the assigned structure and Form B. OVI analysis showed 2-MeTHF and MTBE levels of 125 and 191 ppm, respectively, which were below the ICH guidelines.

4.3.2.8. 250-g Scale synthesis of Diazoxide Choline Salt in THF.

[00669] Larger scale preparation of the diazoxide choline salt was carried out in a binary-solvent system of THF and MTBE with a ratio of 1:4.7 (v/v) volumes. Diazoxide as a hot (62 °C) suspension in THF (745 mL) was treated with choline hydroxide as a 45% solution in MeOH (1.0 equiv) added over 30 minutes. The resulting solution was stirred for 30 minutes, followed by cooling to 52 °C for the addition of MTBE (14 vol) over 45 minutes. On addition of two volumes of co-solvent, precipitation was observed. The resultant slurry was then allowed to cool naturally to ambient temperature followed by cooling to 0–5 °C with an ice/water bath. The precipitate was isolated by vacuum filtration, and the filter cake rinsed with ice cold MTBE (approximately 250 mL) and dried under vacuum at 30 °C for 38 hours to give diazoxide choline salt (350.28 g, 97.7% yield) as a white crystalline solid. Analyses by ¹H NMR, XRPD, and HPLC were consistent with the assigned structure of Form B while maintaining a high purity with good yield.

4.3.2.9. 2-kg Scale Synthesis of Diazoxide Choline Salt in THF.

[00670] A 12-L reaction flash was charged with 2.0 kg diazoxide and 5.0-L THF with stirring and heating to 55 °C. Choline hydroxide (45% solution in methanol, 2.32 L) was added dropwise to this reaction mixture over about 2.5 hr with stirring. The temperature was maintained at 60 ± 5 °C. After addition of choline hydroxide, stirring was continued for about 30 min. The reaction mixture was clarified by in-line 10 micron filtration upon transfer to a 22-L reaction flask pre-charged with 2-L pre-filtered THF, into which was added 10-L pre-filtered MTBE dropwise. This reaction mixture was transferred to another flask which was then charged with an additional 30-L pre-filtered MTBE dropwise, with adjustment of temperature to < 5 °C and stirring for about 2 hr. Diazoxide choline salt was recovered by vacuum filtration to afford 2.724 kg (94%) diazoxide choline salt (99.8%, HPLC purity), confirmed by ¹H NMR, IR, and UV/Visible analysis.

4.4. Preparation of the Hexamethyl Hexamethylene Diammonium Hydroxide Salt

[00671] The hexamethyl hexamethylene ammonium salt of diazoxide was prepared by dissolving 50 mg of diazoxide in approximately 7.5 mL methyl ethyl ketone (MEK). The diazoxide/MEK solution was heated at 75°C on an orbital shaker to ensure dissolution. To the solution was added approximately 2.17mL of 0.1M hexamethyl hexamethylene ammonium hydroxide solution (1 molar equivalent) and the solution was stirred at 75°C for an additional 10 minutes and then cooled to room temperature at the rate of 30°C/h. The solvent was removed under reduced pressure, and the solid was dried in vacuo at 55°C and 30 in. Hg.

4.5. Failure to Obtain Salts of Diazoxide and derivatives

4.5.1. Failure to Obtain Salts from Alkali Metal Hydroxides

[00672] U.S. Patent Number 2,986,573 ("the '573 patent") describes the synthesis of diazoxide metal salts in aqueous or non-aqueous solutions in the presence of an alkali metal alkoxide. According to the '573 Patent, diazoxide can be dissolved in an alkali metal solution, and the salt obtained upon evaporation. Also described is a method for forming salts from non-aqueous media wherein diazoxide and sodium methoxide are dissolved in anhydrous methanol and the solvent is evaporated to obtain the sodium salt of diazoxide as a white solid.

[00673] Attempts were made to prepare a diazoxide salt from alkali metal hydroxides by the method described in the '573 patent. Salt preparation was carried out in aqueous media by dissolving diazoxide in a basic solution 1M NaOH, followed by evaporation of the solvent. A solid was obtained and analyzed by XRPD (X-Ray Powder Diffraction) and NMR. However, this analysis confirmed that the solid obtained was the diazoxide starting material and not a salt.

[00674] Salt preparation was carried out in non-aqueous media by dissolving diazoxide in anhydrous methanol in the presence of either sodium methoxide or potassium

methoxide and stirring the mixture at 60°C for 15 minutes. The mixture was then cooled to room temperature while stirred. After approximately two hours, a solid was recovered, isolated by filtration, and dried in vacuo. Analysis by XRPD confirmed that the solid obtained was the diazoxide starting material and not a salt.

4.5.2. Preparation of Salts in Methanol or Ethanol According to the '573 Patent

[00675] The preparation of diazoxide salts in methanol and ethanol was attempted using 22 different counter-ions according to the methods described by the '573 Patent. For example, 20 mg of diazoxide was dissolved in 5 mL of ethanol and stirred and heated to ensure dissolution of the diazoxide. To the stirred solution was added approximately 1 molar equivalents of sodium methoxide. The solution was stirred for approximately 10-15 minutes at 60°C, and cooled to room temperature for approximately 2 hours. The resulting solid precipitate was concentrated under a nitrogen stream, and collected by filtration. The product was dried in vacuo and analyzed by XRPD. As shown in Figure 15, XRPD of the solids collected from the sodium methoxide experiment, (as well as the solids collected from the potassium methoxide experiment, which was run under similar conditions), revealed that the solid was the diazoxide starting material and that no sodium or potassium salt was prepared. In Figure 15, (d) is the XRPD pattern of free form diazoxide, (b) is the XRPD pattern of the product of potassium methoxide in methanol, and (c) is the XRPD pattern of the product of sodium methoxide in methanol.

[00676] Although not wishing to be bound by any theory, it is believed that a possible explanation for the failure to prepare diazoxide salts by the methods of the '573 Patent (i.e., in the presence of alcohols, e.g., methanol or ethanol), is that the alcohol may have an effect on the stability of the alkali salts of diazoxide. This was supported by UV spectroscopy analysis of alkali salts of diazoxide (sodium and potassium). Both the sodium and potassium salts of diazoxide were synthesized by reacting diazoxide with NaOH or KOH in MEK. Elemental analysis, NMR and XRPD confirmed that the salts were made.

[00677] Upon dissolution of the sodium or the potassium salt in acetonitrile, the UV spectrum shows a shift into the red region of the spectrum for the λ_{max} from

approximately 268 nm for the free form of diazoxide to approximately 298 nm for both the potassium and sodium salt (see Figure 1). Similarly, these salts can be stabilized in aqueous solutions by elevating the pH to above 9.0. A similar shift in the absorption maximum at pH 9.0 is measured using UV spectroscopy. Subsequent adjustment of the pH from greater than 9.0 to less than 6.2 results in the hydrolysis of the salt as measured by the recovery of the UV absorption pattern of the diazoxide free base (see Figure 2). In contrast, when the sodium or the potassium salt is dissolved in methanol, the UV-Vis spectrum of the salt was identical to that of the diazoxide starting material, (see Figure 3).

[00678] These results demonstrate that using methanol as the solvent is incompatible with the synthesis of alkali salts of diazoxide. In addition, the results show that isolation of an alkali metal salt of diazoxide (or any other salt) in the presence of an alcohol, such as methanol, may not be possible.

4.5.3. Failure to Obtain Salts from Acidic Counter Ions

[00679] Salt formation with diazoxide was also attempted using acidic counter-ions, such as, for example, hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, benzoic acid, undecylenic acid, salicylic acid and quinic acid. However, no salt formation was observed for any acid in any solvent.

[00680] For example, 100 mg of diazoxide was dissolved in 50 mL of acetone and heated to 35°C. To a stirred solution was added approximately 4.65 molar equivalents of HCl. The reaction mixture was allowed to cool to room temperature for approximately 3 hours, with no precipitation observed. Solvent was removed in vacuo. The resulting solid was analyzed by XRPD, and the observed XRPD pattern was consistent with the free form diazoxide starting material. In all cases, the attempted synthesis of diazoxide salts from acids was unsuccessful in all solvents attempted.

4.6. Preparation of Salts of Compounds of Formulae V-VIII

[00681] The chloride salt of 3-amino-4-methyl-1,2,4-benzothiadiazine-1,1-dioxide is prepared dissolving approximately 300 mg (1.4 mmol) in 45 mL acetonitrile. The mixture is heated to approximately 75°C and stirred for 30 min. To the stirred solution, approximately 1 molar equivalent of HCl is added dropwise, and stirred for approximately 30 min at 75°C. The mixture is cooled to room temperature and the solvent is removed under reduced pressure, affording the chloride salt as a solid.

[00682] The sodium salt of 3-amino-4-methyl-1,2,4-benzothiadiazine-1,1-dioxide is prepared dissolving approximately 300 mg (1.4 mmol) in 45 mL acetonitrile. The mixture is heated to approximately 75°C and stirred for 30 min. To the stirred solution, approximately 1 molar equivalent of NaOH is added dropwise, and stirred for approximately 30 min at 75°C. The mixture is cooled to room temperature and the solvent is removed under reduced pressure, affording the sodium salt as a solid.

5. Characterization of Prepared Diazoxide Salts

[00683] Synthesis of the desired salts was confirmed by X-Ray Powder Diffraction (XRPD), UV-Vis spectroscopy, and NMR. All spectra were compared with the spectra of the free form diazoxide (i.e., not a salt). Differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), FTIR (Fourier transform infrared spectroscopy), NMR, UV-vis spectroscopy and moisture sorption analysis were also performed.

5.1. Experimental Procedures

[00684] DSC analysis were conducted with a Mettler 822 DSC, by measuring the amount of energy released by a sample, as the sample was heated from 30°C to between 300-500°C at a rate of 10°C/min. Typical applications of DSC analysis include determination of melting point temperature and the heat of melting; measurement of the glass transition temperature; curing and crystallization studies; and identification of phase transformations.

[00685] TGA measurements were conducted with a Mettler 851 SDTA/TGA, by measuring weight loss as a function of increasing temperature, as the samples were heated from 30°C to 230°C at a rate of 10°C/min. The TGA can be used to analyze desorption and decomposition behavior, characterize oxidation behavior, set burnout or conditioning parameters (temperature/ramp rate/time), and determine chemical composition.

[00686] XRPD samples were analyzed with a Shimadzu XRD-6000 system, using a Cu K α , 40 kV, 40 mA X-ray tube. The divergence and scatter slits were 1.00 deg, and the receiving slit was 0.30 mm. Samples were continuously scanned at a range of 3.0-45.0 deg, with a step size of 0.04 deg., at a scan rate of 2 deg/min.

[00687] Fourier Transform Infrared Spectroscopy was measured with a Thermo-Nicolet Avatar 370 with a Smart Endurance Attenuated Total Reflection (ATR) attachment. Compressed samples were analyzed, with corrections for background noise being made. Using the IR spectrum, chemical bonds and the molecular structure of organic compounds can be identified. Attenuated total reflectance (ATR) allows for the analysis of thin films, organic and inorganic, in areas as small as 10-15 microns.

[00688] Nuclear Magnetic Resonance (NMR) was performed with a 400 MHz Bruker Avance with a 4mm CP/MAS H-X probe. Acquisition of ¹H NMR spectra were performed by taking between 5-10 mg of the sample, dissolved in approximately 0.78 mL of DMSO-d₆. Spectra were acquired with either 16 or 32 scans, using a pulse delay of 1.0 sec, with a 10 μ sec (30°) pulse width.

[00689] UV spectroscopy was performed with a Perkin-Elmer Lambda 25 spectrometer. Samples were dissolved in acetonitrile, water and a buffer system having a pH between 5.6 and 10. Spectra were acquired between 340 and 190 nm, using a 1 cm path length with background correction.

[00690] Moisture Sorption Analysis was performed with a Hiden IGAsorp Moisture Sorption Instrument. Samples were first dried at 0% relative humidity at 25°C until an equilibrium weight was reached, or for a maximum of 4 hours. Samples were then subjected to an isothermal (25°C) scan from 10 – 90% relative humidity in steps of 10%. The samples were allowed to equilibrate to an asymptotic weight at each point for a maximum of 4 hours. Following absorption, a desorption scan from 85% relative

humidity (at 25°C) was run in steps of ~10%, again allowing a maximum of 4 hours for the samples to equilibrate. The resulting samples after desorption were dried at 80°C for two hours and analyzed by XRPD.

5.2. Free Form Diazoxide Characterization

[00691] The free form of diazoxide was characterized by XRPD, differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), moisture sorption, ¹H NMR, FTIR and UV-vis spectroscopy to provide a baseline for comparison with the salts. Free form diazoxide is highly crystalline, as shown by the XRPD pattern. (See Figure 4(a)). The DSC shows a large endothermic event at 330°C, and TGA shows that the free form of diazoxide is anhydrous, where diazoxide shows no weight loss below 200°C, and a weight loss of only 0.2% below 230°C. Moisture absorption of the free form diazoxide shows the material to be non-hygroscopic. Absorption of water by diazoxide was tested at between 0 – 90% relative humidity (RH) at 25°C, showing absorption of approximately 0.04 wt% at 60% RH and 0.20 wt% at 90% RH. The molecule does not form a stable hydrate, as shown by the lack of hysteresis during desorption. Additionally, the XRPD pattern for the diazoxide before and after absorption of water indicate the same crystalline form.

[00692] UV-vis spectroscopy measurements taken of the free form diazoxide in neutral aqueous solution show a λ_{max} at approximately 268 nm. In acetonitrile, the λ_{max} was 264 nm, demonstrating a small solvatochromic shift. As shown in Figure 2, as pH increased the λ_{max} also increased, from approximately 265 nm to approximately 280 nm, due to a change in the electronics of the molecule.

[00693] Studies were also conducted to evaluate the likelihood for conversion and degradation under thermal stress. Samples were heated in a closed environment, protected from light, at 60°C for approximately 14 days. The diazoxide showed no conversion or degradation at 7 days or 14 days. Diazoxide samples were found to be consistent with the starting material with respect to XRPD and DSC.

[00694] Slurry studies to determine propensity of inter-conversion of the solid form were conducted on the free form diazoxide at room temperature, in the absence of light,

using water, isopropyl alcohol, dichloromethane and toluene. Approximately 20 mg of the free form diazoxide was stirred for 14 days. Analysis by XRPD, DSC and HPLC were consistent with the starting material, indicating that the free form of diazoxide did not convert to alternate crystal forms.

5.3. Characterization of Sodium Diazoxide Salt

[00695] The XRPD pattern of the sodium salt of diazoxide was analyzed, showing the material to be crystalline. (See Figure 4(d)). The DSC analysis revealed a major exothermic event at 448°C. Small transitions below 400°C are likely due to sample imperfections. TGA analysis showed weight loss of 0.2% and 0.03% below 120°C, which may be the result of bound solvent. Moisture absorption performed from 0 – 90% relative humidity at 25°C showed the material to be hygroscopic as the sample deliquesced at 90% relative humidity. The sample absorbed 1.2 wt% of water at 60% RH, and 6.6 wt% water at 80% RH. Hysteresis was observed upon desorption at 65 and 55% RH, indicating possible hydrate formation. (Possible hydrate formation was noted, although the amount of water absorbed was less than 0.5 mole). ¹H NMR showed a chemical shift in the aromatic and methyl resonances of the sodium salt, as expected due to changes to the aromatic system. See Figure 5 showing NMR spectrum for the free form of diazoxide (a) and the sodium salt of diazoxide (c). FTIR showed expected changes for the sodium salt.

[00696] Elemental analysis of the salt indicated that the salt was formed in a ratio of approximately 1:1, with the percentage of sodium being slightly low (approximately 3.4%). This deficiency may be due to matrix effects, as NMR indicated the sample had a relatively high purity.

[00697] UV-vis measurements in neutral aqueous solution show a λ_{max} of approximately 271 nm. (See Figure 1). This value is slightly higher than free form diazoxide (265 nm). In acetonitrile, the λ_{max} of the sodium salt exhibits a solvatochromic shift to approximately 296 nm. (See Figure 3). An increase in the pH of the solution is expected to produce a bathochromic shift from approximately 265 nm to approximately 280 nm.

[00698] Solubility measurements performed at pH 2, 7, and 12 in 10 mM phosphate buffer at room temperature showed solubility of the sodium salt of diazoxide to be 13.0 mg/mL, 18.1 mg/mL and 48.6 mg/mL, respectively.

[00699] Form conversion and degradation under thermal stress were conducted as described for the free form diazoxide salt and showed the salt had little propensity to change form or degrade over a period of 14 days. Similarly, slurry studies were conducted as described for the free form diazoxide in n-heptane, dichloromethane and toluene showed no propensity of inter-conversion. See Figure 6, wherein (a) is the XRPD pattern for the sodium salt of diazoxide, (b) is the XRPD pattern for the sodium salt after the slurry study, and (c) the XRPD of the free form of diazoxide.

5.4. Characterization of Potassium Diazoxide Salt

[00700] The XRPD pattern for the potassium salt of diazoxide was analyzed, showing the material to be crystalline. (See Figure 4(b)). The DSC analysis revealed two major exothermic events at 128 and 354°C. (See Figure 7). Small endotherms are likely due to sample impurities or the presence of solvent. TGA analysis showed weight loss of 7.7% below 220°C, which may be the result of moisture sorption. (See Figure 8). Theoretical weight loss for a monohydrate of the diazoxide salt is 6.6%. Moisture absorption performed from 0 – 90% relative humidity at 25°C showed the material to be hygroscopic as the sample deliquesced at 90% relative humidity, showing 38.3 wt% water. The sample absorbed 5.4 wt% of water at 60% RH. Hysteresis was observed upon desorption, however the material was determined to be a hemihydrate from 0 – 30% RH and a monohydrate from 35 – 75% RH. XRPD following the desorption analysis indicated that the sample had changed to an alternate crystalline form. ¹H NMR showed a chemical shift in the aromatic and methyl resonances of the sodium salt, as expected due to changes to the aromatic system. (See Figure 5 showing spectrum of the free form diazoxide (a) and the Potassium salt of diazoxide (b)). FTIR showed expected changes for the potassium salt.

[00701] Elemental analysis of the potassium salt indicated that the salt was formed in a ratio of approximately 1:1, with the percentage of potassium being slightly low.

(approximately 1.6%). This deficiency may be due to matrix effects, as NMR indicated the sample had a relatively high purity.

[00702] UV-vis measurements of the potassium diazoxide salt in neutral aqueous solution show a λ_{max} of approximately 265 nm, which is equivalent to the diazoxide free form λ_{max} . (See Figure 1. In acetonitrile, the λ_{max} of the potassium salt exhibits a solvatochromic shift to approximately 296 nm. (See Figure 3). The potassium salt was used in a pH dependency study and showed that increasing the pH of the solution resulted in a bathochromic shift of the λ_{max} from approximately 265 nm to approximately 280 nm.

[00703] Solubility measurements performed at pH 2, 7, and 12 in 10 mM phosphate buffer at room temperature showed solubility of the sodium salt of diazoxide to be 9.9 mg/mL, 14.4 mg/mL and 43.0 mg/mL, respectively. The potassium salt displayed greater solubility than the free form diazoxide, and demonstrated similar solubility to the sodium diazoxide salt. The XRPD pattern of solids obtained after the solubility analysis indicated that the potassium salt had changed back to the free form diazoxide material.

[00704] Propensity for form conversion and degradation under thermal stress were conducted as described for the free form diazoxide salt. The XRPD pattern of the sample after 7 and 14 days showed unique peaks, as compared with the potassium salt starting material. Analysis by DSC after 14 days also showed unique peaks as well. Using a gradient area percent assay, HPLC did not show any significant degradation of the potassium salt.

[00705] Slurry studies were conducted as described for the free form diazoxide in n-heptane, dichloromethane and toluene showed no propensity of inter-conversion. XRPD analysis of samples after 7 and 14 days showed unique peaks similar to those observed with the thermal stress study. See Figure 9, wherein (a) is the XRPD pattern of the potassium salt of diazoxide, (b) is the XRPD pattern of the potassium salt of diazoxide after the slurry study in toluene, and (c) the XRPD pattern of the potassium salt after 14 days of the slurry study in toluene. Analysis by DSC after 14 days also showed unique peaks as compared with the starting material. HPLC using a gradient area percent assay did not show any significant degradation after the study.

5.5. Characterization of Choline Diazoxide Salt

[00706] The XRPD pattern of the choline salt of diazoxide was analyzed, showing the material to be crystalline. (See Figure 10 (b)). The DSC analysis revealed a major exothermic events at 167°C. (See Figure 11). A smaller endothermic event was seen at 119°C and is likely due to sample impurities or the presence of residual solvent. TGA analysis showed weight loss of 0.8% between 100 and 140°C, which may be the result of residual solvents. (See Figure 12). Moisture absorption performed from 0 – 90% relative humidity at 25°C showed the material to be hygroscopic as the sample absorbed over 28% at 80% relative humidity, and deliquesced at 90% RH. Hysteresis was not observed upon desorption, indicating the choline salt does not form a stable hydrate. The XRPD pattern following the desorption analysis indicated that the sample had changed to an alternate crystalline form during the hydration and subsequent desorption. (See Figure 13 (c)) ¹H NMR was consistent with a 1:1 molar ratio of diazoxide to counter-ion, and had the expected differences in the chemical shift of the aromatic and methyl resonances, as expected due to the change in the local environment of the aromatic system due to the presence of the choline counter-ion. (See Figure 14 (b)). FTIR showed expected changes for the choline salt, similar to those seen with the sodium and potassium salts.

[00707] Elemental analysis of the choline salt indicated that the salt was formed in a ratio of approximately 1:1. This is consistent with the ¹H NMR.

[00708] UV-vis measurements of the choline diazoxide salt in neutral aqueous solution show a λ_{max} of approximately 268 nm, which is close to the λ_{max} for the diazoxide free form of 265 nm. In acetonitrile, the λ_{max} of the choline salt exhibits a solvatochromic shift to approximately 296 nm, which is consistent with the sodium and potassium diazoxide salts. The potassium salt was used in a pH dependency study and showed that increasing the pH of the solution resulted in a bathochromic shift of the λ_{max} from approximately 265 nm to approximately 280 nm.

[00709] Solubility measurements performed at pH 2, 7, and 12 in 10 mM phosphate buffer at room temperature showed solubility of the sodium salt of diazoxide to be 28.2 mg/mL, 41.5 mg/mL, and greater than 293 mg/mL, respectively. The choline salt displayed greater solubility than the free form diazoxide after being allowed to equilibrate

for 12 hours. The XRPD pattern of the solids obtained after the solubility analysis (at pH 2 and 7 only) indicated that the choline salt had changed back to the free form diazoxide material.

[00710] Propensity of the choline salt for form conversion and degradation under thermal stress were conducted as described for the free form diazoxide salt. XRPD analysis of the sample after 7 and 14 days showed an XRPD pattern consistent with the starting material, as well as the presence of additional unique peaks. (More unique peaks were present after 14 days than after 7 days). Analysis by DSC after 14 days did not show any significant difference, with a small endotherm at 117°C and a large endotherm at 168°C. (Initial DSC showed endotherms at 119°C and a large endotherm at 167°C). Using a gradient area percent assay, HPLC did not show any significant degradation of the choline salt.

[00711] Slurry studies were conducted as described for the free form diazoxide in n-heptane, dichloromethane and toluene showed no propensity of inter-conversion. XRPD analysis of samples after 7 and 14 days showed signal associated with the starting material, with additional unique peaks present. (See Figure 13 (c)). The XRPD pattern of slurry study samples from n-heptane showed signals associated with the starting material, as well as other additional unique signals. The XRPD pattern of slurry samples from dichloromethane and toluene were consistent with spectra obtained after the thermal studies and the moisture sorption analysis. Analysis by DSC after 14 days revealed a small endotherm at 109°C, and a major endotherm at 167°C. HPLC using a gradient area percent assay did not show any significant degradation after the study.

5.6. Characterization of Diazoxide Salt of Hexamethyl Hexamethylene Diammonium Hydroxide (HHDADH)

[00712] The XRPD pattern of the HHDADH salt of diazoxide was analyzed, showing the material to be a crystalline solid. (See Figure 10(c)). Integration of the ¹H NMR spectra was consistent with a 2:1 molar ratio of diazoxide to counter-ion (wherein the HHDADH counter-ion is divalent), and had the expected differences in the chemical shift of the aromatic and methyl resonances due to the change in the local environment of the aromatic system due to the presence of the choline counter-ion. (See Figure 14(c)). The

λ_{max} of the HHDADH diazoxide salt in acetonitrile measured by UV-vis is 296 nm, which is consistent with the sodium, potassium and choline diazoxide salts.

[00713] A summary of the characterization of the free form diazoxide and the potassium, sodium, choline and hexamethyl hexamethylene diammonium hydroxide salts of diazoxide are presented in Table 14.

Table 14: Summary of Characterization and Solubility for Diazoxide and Salts

Test	Free form	Potassium diazoxide salt	Sodium diazoxide salt	Choline diazoxide salt	HHDADH
XRPD	crystalline	crystalline	crystalline	crystalline	crystalline
FTIR	consistent	consistent	consistent	consistent	N/A
DSC	single endotherm at 330°C	multiple endotherms below 300°C	Single exotherm above 400°C	two endotherms below 200°C	N/A
UV in aqueous acetonitrile	268 nm 264 nm	265 nm 296 nm	271 nm 296 nm	268 nm 296 nm	N/A 296 nm
TGA	<1%	7.7 (monohydrate 6.7%)	<1%	<1%	N/A
Moisture Sorption	non-hygroscopic – no hysteresis	deliquescent – hemi/monohydrate	deliquescent – potential hemihydrate	deliquescent – no hysteresis	N/A
Solubility					N/A
pH 2.0	0.4 mg/mL	9.9 mg/mL	13.0 mg/mL	28.2 mg/mL	
pH 7.0	0.04 mg/mL	14.4 mg/mL	18.1 mg/mL	41.5 mg/mL	
pH 12.0	4.8 mg/mL	43.0 mg/mL	48.6 mg/mL	>293 mg/mL	

[00714] Additional solubility studies were conducted for diazoxide free base form and diazoxide choline salt, as reported in Table 15. Each determination was carried out in duplicate, slurrying each sample in a 100 mM phosphate buffer solution, pH 7.00.

Duplicate samples were then titrated to pH 7.0 and pH 8.8 using a 0.1 N phosphoric acid solution, followed by stirring for 18h at ambient temperature. After this time all samples were centrifuged, and the supernatant was diluted with mobile phase (MeCN/ Water.).

Solubility was then obtained using a calibration curve for diazoxide by HPLC analysis.

In Table 15, the term “Diazoxide, free from” refers to the free base of diazoxide; the term

"Diazoxide, choline salt" is the choline salt of diazoxide as described herein; the term "Diazoxide, choline salt, milled" refers to the choline salt of diazoxide which has been milled by methods described herein. Table 15 shows that in 100mM phosphate buffer, pH 7, and with titration with 0.1N phosphoric acid to a pH of about 6.8 to 8.8, solubility is notably suppressed compared to solubility at pH 10-11. Furthermore, the diazoxide choline salts were found to have increased solubility when compared to the parent free base.

Table 15: Summary of Solubility for Diazoxide and Diazoxide Choline Salt.

Sample	Sample amount (mg)	Phosphate buffer amount (mL)	1N H_3PO_4 (mL)	pH after titration with 0.1N H_3PO_4	pH after 18h slurry	Solubility [mg/mL]
Diazoxide, free form	49.23	1	0.01	6.87	6.90	0.07
Diazoxide, free form	47.64	1	---	7.30	7.31	0.07
Diazoxide, choline salt	44.34	1	0.15	7.22	7.45	0.12
Diazoxide, choline salt	48.26	1	0.11	8.81	8.64	0.18
Diazoxide, choline salt, milled	45.35	1	0.14	7.32	7.36	0.12
Diazoxide, choline salt, milled	53.15	1	0.16	8.50	8.52	0.20
Diazoxide, choline salt	50.0	1	---	---	10.57	42.11
Diazoxide, choline salt, milled	50.0	3	---	---	10.52	32.88

"---" Indicates no titration was conducted.

6. Polymorphic Forms of Diazoxide Salts

[00715] Polymorphic forms of the salts of diazoxide, characterization, and preparation thereof are described.

6.1. Polymorphic Forms of the Choline Salt of Diazoxide

6.1.1. Demonstration of Preparation of Polymorphic Form B of the Choline Salt of Diazoxide

[00716] A 1-L round bottom flask was charged with diazoxide (5 g), MEK (750 mL) and choline hydroxide (5.25 g of 50 wt % solution in water), and heated to 77°C. The mixture was allowed to cool to approximately -30 °C, and filtered to remove insoluble brown residues. The filtrate was then concentrated under reduced pressure to afford yellow oil, which was dried in vacuo at 55°C and 30 in. Hg to afford approximately 7.8 g as a waxy solid. The solids were dried in vacuo at 55°C and 30 in. Hg to afford 7.13 g of the choline salt of diazoxide as a crystalline solid. Elemental analysis. Theoretical: C 46.77%, H 6.04% and N 12.59%. Measured: C 45.44%, H 5.98% and N 11.46%.

6.1.2. Characterization of the Polymorphic Form B of the Choline Salt of Diazoxide

[00717] The polymorphic Form B of the choline salt of diazoxide was analyzed by XRPD, DSC, and ¹H NMR. As shown in Figure 16, the two identified polymorphic forms of the choline salt of diazoxide show different XRPD patterns. See Figure 16, wherein (a) shows the polymorphic Form A of the choline salt of diazoxide.

[00718] As shown in Figure 17, ¹H NMR of the polymorphic Form B of the choline salt of diazoxide shows no change from the polymorphic Form A.

[00719] Moisture absorption of the polymorphic Form B crystal structure of the choline salt of diazoxide performed from 0 – 80% relative humidity (RH) at 25°C showed the material to be hygroscopic as the sample absorbed over 14.5% at 70% relative humidity, and deliquesced at 80% RH. The XRPD pattern following the desorption

analysis indicated that the sample remained in the Form B crystal structure during the hydration and subsequent desorption.

[00720] Solubility measurements performed at pH 2, 7, and 12 in 10 mM phosphate buffer at room temperature showed solubility of the Form B crystal structure of the choline salt of diazoxide to be 32.8 mg/mL, 80.1 mg/mL and 216 mg/mL, respectively. The XRPD pattern of the solids obtained after the solubility analysis (at pH 2 and 7) indicated that Form B of the choline salt of diazoxide was still present.

[00721] Slurry experiments were performed on each form to determine the propensity for conversion and to search for possible new and/or unique forms. Upon slurrying Form B in CH₂Cl₂, n-heptane, and toluene, form conversion was not observed.

6.1.3. Demonstration of Preparation of the Polymorphic Form A of the Choline Salt of Diazoxide from the Polymorphic Form B of the Choline Salt of Diazoxide

[00722] Approximately 20 mg of the Form B polymorph of the choline salt of diazoxide was added to approximately 1 mL of acetone and heated to approximately 55°C. The mixture was filtered while hot and placed in a refrigerator (4°C) for 16 hours. No precipitate was observed. The solvent was evaporated down to dryness using a gentle stream of nitrogen. The resultant solids were also dried in vacuo at room temperature and 30 in. Hg. XRPD analysis showed the salt had converted from the Form B polymorph to the Form A polymorph.

6.1.4. Characterization of the Polymorphic Form A of the Choline Salt of Diazoxide

[00723] Form A is an anhydrous crystalline form of diazoxide choline, with an endothermic event at approximately 165 °C in the DSC (see Figure 20). The XRPD pattern for Form A is unique compared to that of Form B as shown in Figure 21. FTIR (ATR) spectroscopy additionally indicates differences between the two forms. ¹H NMR analysis affords a spectrum consistent with diazoxide and a 1:1 ratio of compound/counterion. NMR data also indicate that the magnetic environment of the

diazoxide structure changes between free and polymorph forms, as evidenced by a movement in chemical shift of the aromatic and methyl proton resonances. In addition, the resonance due to the amine proton is not observed which suggests deprotonation in solution. Weight loss by TGA is less than 1% and may be due to residual solvent. The temperature of weight loss is above 100 °C which suggests that solvent may have been bound (i.e., solvate material). Moisture-sorption analysis conducted at 25 °C from 0 to 80% RH (adsorption) and 75 to 0% RH (desorption) shows Form A to be a hygroscopic solid, showing 2.4 wt % water at 60% RH. The sample was found to have deliquesced above 75% RH. In comparison, Form B is also hygroscopic and showed 7.4 wt % water at 60% RH and deliquesced at 80% RH. XRPD analysis following the moisture-sorption experiment affords a pattern consistent with Form A. Solubility studies conducted on both forms at pH 2, 7, and 12 in phosphate buffer showed differences, with Form A showing 28, 41, and >293 mg/mL, respectively. Solubility concentrations were determined using area-percent calculations with HPLC calibration curves. Slurry experiments were performed on each form to determine propensity for conversion and to see if a unique form could be generated. Upon slurrying Form A in CH₂Cl₂, n-heptane, and toluene, conversion to Form B was observed after seven days. These results suggest that Form A is less thermodynamically stable under these conditions than Form B according to Ostwald's Rule of Stages.

6.1.5. Screening for Polymorphic Forms of Diazoxide Choline Salt.

[00724] A polymorph screening study of diazoxide choline salt was conducted with a series of crystallization and slurry conditions. As described herein, interconversion of diazoxide choline salt forms A and B was observed during this investigation. Each polymorphic form of diazoxide choline salt resulting from this study was characterized using the techniques and procedures described herein. A summary of characterization tests is listed in Table 16.

Table 16. Characterization of Forms A and B of Diazoxide Choline Salt In Screening Study

Experiment	Form A	Form B
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Experiment	Form A	Form B
XRPD*	Crystalline	Crystalline
DSC	Endotherm ≈ 165 °C	Endotherm ≈ 160 °C
TGA	<1%	$\approx 1\%$
FTIR (ATR)**	Consistent w/ structure	Consistent w/ structure
¹H NMR	Consistent w/ 1:1 ratio	Consistent w/ 1:1 ratio
Moisture Sorption	Hygroscopic – deliquesced at 90% RH	Hygroscopic – deliquesced at 80% RH
Solubility	pH 2: 28 mg/mL. pH 7: 41 mg/mL. pH 12: >293 mg/mL.	pH 2: 33 mg/mL. pH 7: 80 mg/mL. pH 12: 216 mg/mL.
Thermal	Started to convert to Form B after 14 days at 60 °C	Stable after 14 days at 60 °C
Slurries	Converted to Form B after 7 days in <i>n</i> -heptane, toluene, and CH ₂ Cl ₂	Stable after 14 days in CH ₂ Cl ₂ , THF, and <i>t</i> -AmOH

*Major peaks (2- θ):

Form A (9.8, 10.5, 14.9, 17.8, 17.9, 18.5, 19.5, 22.1, 22.6, 26.2, 29.6, 31.2);

Form B (8.9, 10.3, 12.0, 18.3, 20.6, 24.1, 24.5, 26.3, 27.1, 28.9).

** Unique FTIR (ATR) absorbances (cm⁻¹):

Form A (2926, 2654, 1592, 1449, 1248);

Form B (3256, 2174, 2890, 1605, 1463, 1235).

6.1.5.1. Solubility Screen in organic solvents.

[00725] Diazoxide choline, prepared in MEK using choline hydroxide as 50 wt % solution in water (see above) displayed some solubility in the following solvents: acetonitrile, acetone, ethanol, IPA, MEK, DMF, and methanol. These solvents were chosen due to differences in functionality, polarity, and boiling points and their ability to dissolve diazoxide. Other solvents which showed poor ability to dissolve salts were used as antisolvents and in slurry experiments where some solubility was observed: dioxane, MTBE, EtOAc, IPAc, THF, water, cyclohexane, heptane, CH₂Cl₂, and toluene.

[00726] Solvents for crystallizations during screening were chosen based on the solubility screen summarized in Table 17. Crystallizations of diazoxide choline from all conditions afforded a total of two forms, A and B. Forms A and B were found to be anhydrous polymorphs of diazoxide choline. Form B was observed to be generated from most solvents used. It was difficult to isolate pure Form A on large scales (>50 mg) as conditions observed to produce Form A on a smaller scale (approximately 50 mg or less) were found to result in Form B or mixtures of both forms on larger scales. Based on room-temperature slurry experiments, anhydrous Form B was found to be the most thermodynamically stable form in this study. Form A readily converted to Form B in all slurry solvents utilized.

Table 17. Solubility Screen for Diazoxide Choline Salt

Solvent	Cmpd (mg)	Solvent (mL)	Conc. (mg/mL)	Temp. (°C)	Soluble
MeCN	1.7	0.25	>6.80	rt	Yes
Dioxane	1.4	5.00	0.28	55	No
Acetone	1.9	0.25	7.60	55	Yes
MTBE	2.4	5.00	0.48	55	No
EtOH	1.5	0.25	>6.00	rt	Yes
EtOAc	1.2	5.00	0.24	55	No
IPAc	1.4	5.00	0.28	55	No
IPA	1.8	0.25	7.20	55	Yes
THF	1.1	5.00	0.22	55	No
MEK	1.8	1.00	1.80	55	Yes
DMF	1.2	0.25	>4.80	rt	Yes
Water	2.0	5.00	0.40	55	No
MeOH	1.9	0.25	7.60	55	Yes
<i>n</i> -Hexane	2.0	5.00	0.40	55	No
Heptane	1.9	5.00	0.38	55	No

Solvent	Compd (mg)	Solvent (mL)	Conc. (mg/mL)	Temp. (°C)	Soluble
CH ₂ Cl ₂	1.3	5.00	0.26	55	Partially
Toluene	1.4	5.00	0.28	55	No

6.1.5.2. Single-Solvent Crystallizations

[00727] Fast cooling procedure: Diazoxide (approximately 20 mg) was weighed out into vials and enough solvent (starting with 0.25 mL) was added until the material completely dissolved at elevated temperature. After hot filtration the vials were placed in a refrigerator (4 °C) for 16 hours. After the cooling-process the samples were observed for precipitates which were isolated by filtration. Vials not demonstrating precipitates were evaporated down to dryness using a gentle stream of nitrogen. All solids were dried in vacuo at ambient temperature and 30 in. Hg.

[00728] Slow cooling procedure: Diazoxide (approximately 30 mg of choline salt) was weighed out into vials and enough solvent was added until the material went into solution at elevated temperature. After hot filtration the vials were then slowly cooled to room temperature at the rate of 20 °C/h and stirred at room temperature for 1–2 hours. All solids were dried in vacuo at ambient temperature and 30 in. Hg.

[00729] Based on the initial solubility study, seven solvents were selected for the fast-cooling crystallization: acetonitrile, acetone, ethanol, IPA, MEK, DMF, and methanol. Table 18 shows a list of the solvents that were used and the amount of solvent needed to dissolve the material. After the cooling-process precipitates were noticed in samples # 2, 3, 5, and 6, the solids were isolated by filtration. The other samples (# 1, 4, and 7) were evaporated down to dryness using a gentle stream of nitrogen. The diazoxide choline salts were found to be consistent with Form A by XRPD analysis for all solids with the exception of sample #2 (consistent with the freeform) and sample #5 (consistent with Form B with preferred orientation observed).

Table 18. Single-Solvent Crystallization of Diazoxide Choline Salt Using Fast-Cooling Procedure

Entry	Solvent	BP (°C)	Cmpd (mg)	Solvent Amt (mL)	Conc (mg/mL)	Temp. (°C)	Precipitate	Form
1	Acetone	56	21.0	1.00	21.00	55	No/Evap	A
2	MeOH	64	20.3	0.25	81.20	55	Yes	FF*
3	EtOH	78	21.3	0.25	85.20	62	Yes	A
4	MEK	80	19.6	1.25	15.68	75	No/Evap	A
5	MeCN	81	20.6	0.25	82.40	55	Yes	Unique
6	IPA	82	22.8	0.25	91.20	62	Yes	A
7	DMF	153	26.0	0.25	104.00	55	No/Evap	A

[00730] In accordance with the data obtained from fast-cooling experiments, four solvents which showed precipitation of solids were chosen for the slow-cooling experiments: MeOH, EtOH, MeCN, and IPA (Table 19). All obtained analyzable solids of the choline salt were found to be consistent with Form B by XRPD with the exception of Entry #1 which was consistent with diazoxide freeform and Entry #2 which was not analyzable. Mother liquor of Entry #2 was concentrated to dryness and the residual solids were analyzed by XRPD and found to be Form B material. As a result of obtaining freeform material from the single-solvent crystallizations in methanol, three more alcohols were tested for the single-solvent crystallizations using fast- and slow-cooling procedures. Tables 20 and 21 provide a list of the solvents that were used and the amount of solvent needed to dissolve the material. XRPD patterns of the fast-cooling procedure showed freeform of diazoxide from isobutanol, Form B from isoamyl alcohol, and Form A from tert-amyl alcohol compared to the slow-cooling procedure, which afforded Form B material from all three solvents.

Table 19. Single-Solvent Crystallization of Diazoxide Choline Salt Using Slow-Cooling Procedure

Solvent	Boiling Point (°C)	Material Amount (mg)	Solvent Amount (mL)	Conc. (mg/mL)	Temp. (°C)	Precipitate	Form
MeOH	64	32.1	0.3	107.00	62	Yes	F†*
EtOH	78	33.3	0.3	111.00	75	Yes	NA**
MeCN	81	30.9	0.3	103.00	62	Yes	B
IPA	82	33.7	0.3	112.33	80	Yes	B

Table 20. Single-Solvent Crystallization of Diazoxide Choline Salt Using Fast-Cooling Procedure

Solvent	Boiling Point (°C)	Material Amount (mg)	Solvent Amount (mL)	Conc. (mg/mL)	Temp. (°C)	Precipitate	Form
<i>i</i> -BuOH	108	29.7	0.3	99.00	78	Yes	(sm)†*
<i>i</i> -AmOH	130	29.6	0.3	98.67	82	Yes	B
<i>t</i> -AmOH	102	29.5	0.3	98.33	95	No/Evap	A

Table 21. Single-Solvent Crystallization of Diazoxide Choline Salt Using Slow-Cooling Procedure

Solvent	Boiling Point (°C)	Material Amount (mg)	Solvent Amount (mL)	Conc. (mg/mL)	Temp. (°C)	Precipitate	Form
<i>i</i> -BuOH	108	33.0	0.3	110.00	92	Yes	B
<i>i</i> -AmOH	130	28.2	0.3	94.00	92	Yes	B
<i>t</i> -AmOH	102	29.0	0.4	72.50	92	Yes	B

[00731] The results of the choline salt single-solvent fast- and slow-cooling crystallizations (see Tables 19 to 21) indicated that Form A was more likely to be isolated with fast-cooling profiles and Form B with slow-cooling profiles.

6.1.5.3. Binary Solvent Crystallizations

[00732] Binary-solvent crystallizations of the choline salt were performed using four primary solvents (MeOH, EtOH, IPA, and MeCN) and nine cosolvents (MTBE, EtOAc, IPAc, THF, *n*-hexane, heptane, toluene, CH₂Cl₂, and dioxane) with a fast-cooling profile (*supra*). XRPD patterns showed that Form B was obtained from mixtures of MeOH with MTBE, EtOAc, IPAc, toluene, and dioxane. As shown in Table 22, Form A was obtained from mixtures of MeOH with THF and with CH₂Cl₂ after evaporating the solvent to dryness. The mixtures of MeOH with cyclohexane and heptane provided the freeform of diazoxide. All solids obtained from fast-cooling procedures with EtOH, IPA, and MeCN as primary solvents provided Form B material.

Table 22. Binary-Solvent Crystallizations of Choline Salt of Diazoxide Using Fast-Cooling Procedure and MeOH as a Primary Solvent

Diazoxide Amt (mg)	MeOH* (mL)	Antisolvent	Amount (mL)	Precipitate	Form
27.8	0.3	MTBE	1.4	Yes	B
30.7	0.3	EtOAc	6.0	Yes	B
32.0	0.3	IPAc	6.0	Yes	B
31.9	0.3	THF	6.0	No/Evap to Dry	A
29.5	0.3	<i>n</i> -Hexane	2.0	Yes (small)	FF**
30.2	0.3	Heptane	2.0	Yes	FF**
29.3	0.3	Toluene	6.0	Yes	B
32.0	0.3	CH ₂ Cl ₂	6.0	No/Evap to Dry	A
28.8	0.3	Dioxane	6.0	Yes	B

* Solids were dissolved at 62 °C.

** Freeform of diazoxide.

[00733] Binary-solvent recrystallizations of the choline salt with the slow-cooling procedure were performed using two primary solvents (IPA and MeCN) and nine cosolvents (MTBE, EtOAc, IPAc, THF, *n*-hexane, heptane, toluene, CH₂Cl₂, and dioxane). All solids obtained from a slow-cooling procedure with IPA and MeCN as primary solvents provided Form B material based on XRPD analysis. The results of

binary-solvent crystallizations indicated that Form B was the most thermodynamically stable form of diazoxide choline.

6.1.5.4. Binary Solvent Crystallizations Using Water as a Cosolvent

[00734] In an attempt to investigate the formation of hydrates of the choline salt, experiments was performed using fast- and slow-cooling procedures and water as a cosolvent.

[00735] The fast cooling procedure (supra) was used with the exception of using different primary solvents which were miscible with water: acetone, acetonitrile, DMF, IPA, *i*-BuOH, *i*-AmOH, and *t*-AmOH. Water was utilized in these crystallizations as a cosolvent. All solids obtained from the fast-cooling procedure with water as the cosolvent provided diazoxide freeform material by XRPD analysis.

[00736] To compare the results obtained from the fast-cooling procedure a set of experiments was performed using a slow-cooling procedure and water as a cosolvent. All obtained solids were analyzed by XRPD and afforded patterns consistent with diazoxide freeform. Without wishing to be bound by theory, these results suggest that the conditions used for crystallization caused dissociation of the choline salt. A small amount of a second crop was obtained in each sample, but only two samples were analyzable by XRPD and indicated that the samples were freeform material. All mother liquors were evaporated to dryness and the residual solids were also analyzed by XRPD to afford patterns consistent with Form B of the choline salt.

6.1.5.5. Metastable Zone Width Estimation

[00737] Form B: To produce a robust process, an understanding of the solubility profiles of the various solid forms under consideration is required. From a practical standpoint, this involves the measurement of the metastable zone width (MSZW) of pure forms, whereby the saturation and supersaturation curves of the different forms are generated over a well defined concentration and temperature range. This knowledge can then be used to design a crystallization protocol that should ideally favor a selective crystal growth of the desired form.

[00738] Form B of diazoxide choline salt showed moderate solubility in a solvent mixture made of MeCN/MeOH/MiBE (10:1:12, volume ratios). The wide width of the metastable zone as shown in Table 23 gives many seeding options. During the MSZW measurement, aliquots from the crystallizing material were withdrawn and analyzed by XRPD to ensure that no form conversion occurred during the experiment. Indeed, the material remained unchanged during the test.

Table 23. Meta-Stable Zone Width For Form B Diazoxide Choline Salt in MeCN/MeOH/MiBE (10:1:12) (v/v).

Conc. I (mg/mL)	Temp. In (°C)	Temp. Out (°C)	Temp. Range (°C)
30.8	53.2	35.0	18.2
28.5	49.0	33.6	15.4
26.5	47.0	32.0	15.0
24.7	43.8	29.1	14.7
23.2	40.5	28.5	12.0
21.9	38.0	26.0	12.0

[00739] Form A: The metastable zone width for Form could not be estimated because this polymorphic form converted during the experiment to Form B.

6.1.5.6. Crystallization of Form A of Diazoxide Choline Salt

[00740] The choline salt of diazoxide (160.3 mg) was dissolved in 1 mL of IPA at 55 °C which was then passed through a Millipore 0.45 µm filter into a clean vial. This vial was placed in freezer at -20 °C overnight. Solids were not noticed and the flask was scratched with a micro-spatula. The vial was placed back in the freezer and nucleation was noticed after ten minutes. The solids were collected by vacuum filtration and washed with 1 mL of MiBE. The solids were dried in vacuo at 40 °C and 30 in. Hg to afford 70 mg (43.6% recovery) of Form A as determined by XRPD.

6.1.5.7. 500-mg Scale Crystallization of Form B of Diazoxide Choline Salt

[00741] The choline salt of diazoxide (524.3 mg) was dissolved in 3 mL of IPA at 78 °C and this solution was then cooled to 55 °C for the addition of MtBE. The MtBE (4 mL) was added until nucleation was observed. After nucleation the batch was allowed to cool to room temperature at a rate of 20 °C /h. The solids were collected by vacuum filtration and washed with 1 mL of MtBE. The solids were dried in vacuo at 40 °C and 30 in. of Hg to afford 426.7 mg (81.3% recovery) of Form B as determined by XRPD.

6.1.5.8. 2-g Scale Crystallization of Form B of Diazoxide Choline Salt

[00742] The choline salt of diazoxide (2.0015 g) was dissolved in 5.5 mL of IPA at 78 °C to afford a clear solution. This solution was passed through a Millipore Millex III 0.45 µm filter. This solution was then cooled to 55 °C. MtBE was added in 1 mL portions, with a two minute interval between portions. Nucleation was noted after the second addition of MtBE. This suspension was allowed to cool to room temperature at a rate of 20 °C /h and stirred at this temperature for 16 hours. The solids were collected by vacuum filtration and washed with 1 mL of MtBE. The solids were dried in vacuo at 40 °C and 30 in. of Hg to afford 1.6091 g (80.4% recovery) of Form B as determined by XRPD.

6.1.5.9. Detection of Form Impurities

[00743] Mixtures of diazoxide choline Forms A and B were prepared by adding a minor amount of Form A to Form B. Samples were lightly ground by hands with a mortar and pestle for approximately one minute. Samples were then analyzed by XRPD analysis. XRPD analysis was found to be suitable for detecting 5% of Form A in Form B.

6.2. Polymorphic Forms of the Potassium Salt of Diazoxide

[00744] A summary of characterization tests for three common crystalline forms of diazoxide potassium salt are listed in Table 24. Solvents for crystallizations were chosen

based on the solubility screen summarized below. Crystallizations of diazoxide potassium salt from all conditions provided herein afforded a total of seven unique crystalline forms, A through G. Forms C, D, and F were found to be the most common during the crystallization screen, and were therefore scaled up for further characterization.

Table 24. Results Summary of Characterization Tests for Salt of Diazoxide Potassium

Experiment	Form C	Form D	Form F
XRPD*	Crystalline	Crystalline	Crystalline
DSC	187, 360 °C	130, 191, 352 °C	191, 363 °C
TGA	8.4%**	4.5%**	13.1%**
FTIR (ATR)*	Consistent w/ structure	Consistent w/ structure	Consistent w/ structure
¹H NMR	Consistent w/ structure**	Consistent w/ structure	Consistent w/ structure***

Moisture Sorption	Hygroscopic – deliquesced at 90% RH Hygroscopic – deliquesced at 90% RH	Hygroscopic – deliquesced at 90% RH	
Solubility	N/A	pH 2: 29 mg/mL pH 7: 33 mg/mL pH 12: 59 mg/mL	N/A
Thermal	Stable (7 days)	Stable (7 days)	Stable (7 days)
Slurries	Converted to Form D	Converted to Form D	Converted to Form D

*XRPD Major peaks (2-θ):

Form A (6.0, 8.1, 16.3, 17.7, 18.6, 19.1, 22.9, 23.3, 23.7, 24.7, 25.4, 26.1, 28.2, 29.6, 30.2);

Form B (8.5, 10.8, 16.9, 18.2, 21.6, 25.5, 26.1, 28.9);

Form C (5.7, 6.1, 17.9, 23.9, 25.1, 37.3);

Form D (5.7, 6.2, 8.1, 8.5, 8.8, 16.9, 18.6, 23.2, 24.5, 25.8, 26.1);

Form E (6.7, 7.1, 14.1, 21.2);

Form F (8.5, 9.0, 18.7, 20.6, 23.5, 27.5, 36.3);

Form G (5.2, 5.5, 13.1, 16.5, 19.3, 22.8, 24.8, 26.4, 28.7, 34.1);

**Unique FTIR (ATR) absorbances (cm⁻¹):

Form A (1503, 1374, 1339, 1207, 1131, 1056, 771);

Form B (1509, 1464, 1378, 1347);

Form C (1706, 1208, 1146, 746);

Form D (1595, 1258, 1219, 890);

Form E (1550, 1508, 1268, 1101, 1006).

Form F (1643, 1595, 1234, 1145, 810).

Form G (1675, 1591, 1504, 1458, 1432, 1266, 999, 958, 905, 872).

** Data indicates a half-molar equivalent of acetone, water, or dioxane for Forms C, D, and F respectively.

[00745] Diazoxide potassium Forms C, D, and F were observed to be an acetone solvate, a hemihydrate, and a dioxane solvate of diazoxide potassium, respectively. Form C is an acetone solvate that was generated predominantly when acetone was used in the crystallization. Form D, a hemihydrate, was observed to be generated from most solvents used. Form F is a dioxane solvate generated when dioxane was used as an antisolvent. Forms A, B, E, and G were not commonly observed during the crystallization. Elemental analysis data indicated that the unique forms observed may be mixtures and/or have residual solvent(s) present.

[00746] Based on room-temperature slurry experiments presented, Form D was found to be the most thermodynamically stable form of those discovered in this study. Forms C and F readily converted to Form D in all slurry solvents utilized. Without wishing to be bound by theory, since nonaqueous solvents were used, the material may have converted to the hemihydrate, Form D, upon removal from the solvent.

6.2.1. Demonstration of Preparation of Polymorphic Form A of the Potassium Salt of Diazoxide

[00747] The polymorphic Form A of the potassium salt of diazoxide was prepared as described above.

6.2.2. Demonstration of Preparation of the Polymorphic Form B of the Potassium Salt of Diazoxide

[00748] Diazoxide (2.95 g) was combined with 450 mL of methyl ethyl ketone and heated to approximately 77°C to dissolve the diazoxide. To the solution was added approximately 13 mL of 1M potassium hydroxide at a rate of approximately 20 mL/min, stirred and allowed to cool to room temperature. The solution was stirred at room temperature for ~16 h. The solvent was removed under reduced pressure, and the residual solids were dried in vacuo at 57 °C and 30 in. Hg to afford 3.7 g of the potassium salt.

6.2.3. Characterization of the Polymorphic Form B of the Potassium Salt of Diazoxide

[00749] The Form B polymorph of the potassium salt of diazoxide was analyzed by XRPD, and ¹H NMR. Figure 18 shows the XRPD pattern of (a) the Form A polymorph of the potassium salt of diazoxide and (b) the Form B polymorph of the potassium salt of diazoxide.

[00750] The ¹H NMR of the Form B polymorph of the potassium salt of diazoxide shows no change from the Form A polymorph.

6.2.4. Demonstration of Preparation of the Polymorphic Form A of the Potassium Salt of Diazoxide from Form B

[00751] Approximately 20 mg of the Form B polymorph of the diazoxide potassium salt was added to 2 mL of acetone and heated until the material completely dissolved at 55°C. The solution was hot filtered and placed in a refrigerator (4°C) for 16 hours. No precipitate was formed. The solvent was evaporated down to dryness using a gentle stream of nitrogen and the resultant solids were dried in vacuo at room temperature and 30 in. Hg. The solid was analyzed by XRPD to determine the physical form. See Figure 18(a).

6.2.5. Preparation of the Polymorphic Form C of the Potassium Salt of Diazoxide from Form B

[00752] Approximately 20 mg of the Form B polymorph of the diazoxide potassium salt was added to 6 mL of ethyl acetate and heated until the material completely dissolved at 75°C. The solution was hot filtered and placed in a refrigerator (4°C) for 16 hours. No precipitate was formed. The solvent was evaporated down to dryness using a gentle stream of nitrogen and the resultant solids were dried in vacuo at room temperature and 30 in. Hg. The solid was analyzed by XRPD to determine the physical form. See Figure 18(c).

6.2.6. Preparation of the Polymorphic Form D of the Potassium Salt of Diazoxide from Form B

[00753] Approximately 20 mg of the Form B polymorph of the diazoxide potassium salt was added to 0.3 mL of isopropyl alcohol and heated until the material completely dissolved at 62°C. The solution was hot filtered and placed in a refrigerator (4°C) for 16 hours. No precipitate was formed. The solvent was evaporated down to dryness using a gentle stream of nitrogen and the resultant solids were dried in vacuo at room temperature and 30 in. Hg. The solid was analyzed by XRPD to determine the physical form. See Figure 19(a).

6.2.7. Preparation of the Polymorphic Form E of the Potassium Salt of Diazoxide from Form B

[00754] Approximately 20 mg of the Form B polymorph of the diazoxide potassium salt was added to 2.5 mL of tert-amyl alcohol and heated until the material completely dissolved at 95°C. The solution was hot filtered and placed in a refrigerator (4°C) for 16 hours. No precipitate was formed. The solvent was evaporated down to dryness using a gentle stream of nitrogen and the resultant solids were dried in vacuo at room temperature and 30 in. Hg. The solid was analyzed by XRPD to determine the physical form. See Figure 19(b).

6.2.8. Preparation of the Polymorphic Form F of the Potassium Salt of Diazoxide from Form B

[00755] Approximately 20 mg of the Form B polymorph of the diazoxide potassium salt was added to 0.6 mL of acetonitrile and heated until the material completely dissolved at 80°C. The solution was hot filtered, 6 mL of dioxane was added, and the solution was placed in a refrigerator (4°C) for 16 hours. No precipitate was formed. The solvent was evaporated down to dryness using a gentle stream of nitrogen and the resultant solids were dried in vacuo at room temperature and 30 in. Hg. The solid was analyzed by XRPD to determine the physical form. See Figure 19(c).

6.2.9. Preparation of the Polymorphic Form G of the Potassium Salt of Diazoxide from Form B

[00756] Approximately 22.3 mg of the Form B polymorph of the diazoxide potassium salt was added to 0.5 mL of isoamyl alcohol and heated until the material completely dissolved at 73°C. The solution was hot filtered, 6 mL of isopropyl acetate was added, and the solution was placed in a refrigerator (4°C) for 16 hours. No precipitate was formed. The solvent was evaporated down to dryness using a gentle stream of nitrogen and the resultant solids were dried in vacuo at room temperature and 30 in. Hg. The solid was analyzed by XRPD to determine the physical form. See Figure 19(d).

[00757] As shown in Tables 25 and 26, both the solvent used for recrystallization and the rate of cooling (i.e., fast cooling vs. slow cooling during the recrystallization) effect the crystal structure obtained once the product is isolated.

Table 25. Fast cooling of Potassium Salt of Diazoxide in Various Solvents

Solvent	Cmpd (mg)	Solvent (mL)	Recovery (mg)	Form
THF	20.8	6.5	14.2	B
EtOAc	21.1	6.0	10.6	C
MeCN	21.2	0.5	n/a	C + D
IPA	22.7	0.3	n/a	D

Solvent	Cmpd (mg)	Solvent (mL)	Recovery (mg)	Form
Water	20.6	1.5	n/a	Free form diazoxide
tAA	21.9	2.5	16.7	E
IAA	19.7	0.3	n/a	D
DMF	21.6	0.3	15.9	G

Table 26. Slow cooling of Potassium Salt of Diazoxide in Various Solvents

Solvent	Cmpd (mg)	Solvent (mL)	Recovery (mg)	Form
EtOAc	20.4	6.0	7.1	D
MeCN	22.8	0.5	13.8	C
IPA	21.5	0.3	13.2	C
Water	20.9	1.5	1.2	Free form diazoxide
tAA	21.5	2.5	15.4	E
IAA	20.6	0.3	6.6	D

6.2.10. Polymorphs Obtained by Recrystallization of the Potassium Salt of Diazoxide in Binary Solvents

[00758] As shown in Tables 27 and 28, recrystallization of the potassium salt of diazoxide from a variety of binary solvent systems also demonstrated conversion of the potassium salt to an alternate form. Use of acetonitrile as the primary solvent is shown in Table 27 and use of acetone as the primary solvent is shown in Table 28. As shown in Table 27, recrystallization of the Form B polymorph of the potassium salt of diazoxide from acetonitrile using methyl tert-butyl ether, ethyl acetate, isopropyl acetate, tetrahydrofuran, n-hexane, heptane, toluene and dichloromethane as the secondary solvent

all yielded the D Form polymorph of the potassium salt. Recrystallization from acetonitrile using dioxane as the secondary solvent yielded the F Form polymorph of the diazoxide salt of potassium.

Table 27. Recrystallization in Acetonitrile

Acetonitrile (mL)	Secondary solvent	Cmpd (mg)	Recovery (mg)	Form
0.6	MTBE	20.7	13.7	D
0.6	EtOAc	23.4	9.5	D
0.6	IPAc	20.0	13.3	D
0.6	THF	20.3	6.4	D
0.6	c-Hexane	20.4	9.6	D
0.6	Heptane	20.3	10.8	D
0.6	Toluene	23.6	16.1	D
0.6	Dichloromethane	21.3	12.7	D
0.6	Dioxane	20.7	12.6	F

[00759] As shown in Table 28, recrystallization of the Form B polymorph of the potassium salt of diazoxide from acetone using methyl tert-butyl ether, tetrahydrofuran, and c-hexane as the secondary solvent all yielded the Form A polymorph of the potassium salt of diazoxide. Recrystallization from acetone using ethyl acetate, heptane, toluene and dichloromethane as the secondary solvent all yielded the C Form polymorph of the potassium salt. Recrystallization from acetone using isopropyl acetate as the secondary solvent yielded the D Form polymorph of the diazoxide salt of potassium. Recrystallization from acetone using dioxane as the secondary solvent yielded the F Form polymorph of the diazoxide salt of potassium.

Table 28. Recrystallization in Acetone

Acetone	Other Solvent	Amt	Recovery	Form
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(mL)		(mg)	(mg)	
2.0	MTBE	20.2	13.9	A
2.0	EtOAc	21.6	4.8	C
2.0	IPAc	20.6	11.6	D
2.0	THF	20.9	12.0	A
2.0	c-Hexane	21.3	12.3	A
2.0	Heptane	20.6	12.7	C
2.0	Toluene	20.4	13.3	C
2.0	Dichloromethane	21.1	13.0	C
2.0	Dioxane	20.4	12.5	F

6.2.11. Screening for Polymorphic Forms of Diazoxide Potassium Salt.

[00760] A polymorphic screening study of diazoxide potassium salt was conducted with a series of crystallization conditions described below.

6.2.11.1. Solubility Screening for Polymorphic Forms of Diazoxide Potassium Salt.

[00761] Diazoxide potassium, prepared in MEK using 1 M potassium hydroxide solution in water, displayed some solubility in the following ten solvents: acetone, THF, EtOAc, MEK, MeCN, IPA, water, *t*-AmOH, *i*-AmOH, and DMF. These solvents were chosen due to differences in functionality, polarity, and boiling points and their ability to dissolve diazoxide. Solvents affording poor to fair solubility were used as antisolvents in binary/ternary crystallizations as well as slurry studies. Table 29 summarizes the results of the solubility screen.

Table 29. Solubility of Diazoxide Potassium Salt in Various Solvent

Solvent	Compd Amt (mg)	Solvent (mL)	Conc. (mg/mL)	Temp. (°C)	Soluble
MeCN	1.7	2.00	0.85	55	Yes
Dioxane	1.4	5.00	0.28	55	No
Acetone	1.6	4.00	0.40	55	Yes
MTBE	1.8	5.00	0.36	55	No
EtOH	2.2	0.75	2.93	55	Yes
EtOAc	1.8	5.00	0.36	55	No
IPAc	1.7	5.00	0.34	55	No
IPA	2.1	1.00	2.10	55	Yes
THF	1.8	5.00	0.36	55	Partially
MEK	1.5	5.00	0.30	55	Partially
DMF	1.6	0.25	>6.40	n	Yes
Water	1.5	5.00	0.30	55	No
MeOH	1.5	0.25	6.00	55	Yes
<i>n</i> -Hexane	1.5	5.00	0.30	55	No
Heptane	1.2	5.00	0.24	55	No
CH ₂ Cl ₂	1.3	5.00	0.26	55	No
Toluene	1.4	5.00	0.28	55	No

6.2.11.2. Single-Solvent Screening for Polymorphic Forms of Diazoxide Potassium Salt.

[00762] Single-solvent crystallizations of potassium salt were performed using ten solvents: acetone, THF, EtOAc, MEK, MeCN, IPA, water, *t*-AmOH, *i*-AmOH, and DMF for the fast-cooling procedure and six solvents (EtOAc, MeCN, IPA, water, *t*-AmOH, and *i*-AmOH) for the slow-cooling procedures. The “fast” and “slow” cooling procedures were as described above. Four of the solvents were excluded from the slow-cooling

experiments because they did not provide solids during fast-cooling experiments and needed to be evaporated to dryness. Tables 30 and 31 provide a list of the solvents that were used and the amount of solvent needed to dissolve the material. All solids were analyzed by XRPD to determine the physical form and six unique patterns (Forms A–E, G) were observed.

Table 30. Single-Solvent Crystallizations of Potassium Salt of Diazoxide Using Fast-Cooling

Solvent	BP (°C)	Cmpd Amt (mg)	Solvent Amt (mL)	Conc (mg/mL)	Temp (°C)	Precipitate	Form
Acetone	56	20.7	2.0	10.35	55	No/Evap	A
THF*	65	20.8	6.5	3.20	63	No/Evap	B
EtOAc	76	21.1	6.0	3.52	75	Yes	C
MEK	80	20.2	4.0	5.05	75	No/Evap	A
MeCN	81	21.2	0.5	42.40	80	Yes	C+D
IPA	82	22.7	0.3	75.67	62	Yes	D
Water	100	20.6	1.5	13.73	95	Yes	FF
<i>t</i> -AmOH	103	21.9	2.5	8.76	95	Yes	E
<i>i</i> -AmOH	130	19.7	0.3	65.67	73	Yes	D
DMF	153	21.6	0.3	72.00	RT	No/Evap	G

*Solids were not completely dissolved.

Table 31. Single-Solvent Crystallizations of Potassium Salt of Diazoxide Using Slow-

Solvent	BP (°C)	Cmpd Amt (mg)	Solvent Amt (mL)	Conc (mg/mL)	Temp (°C)	Precipitate	Form
EtOAc	76	20.4	6.0	3.40	75	Yes	D
MeCN	81	22.8	0.5	45.60	80	Yes	C
IPA	82	21.5	0.3	71.67	80	No/Evap	C
Water	100	20.9	1.5	13.93	95	Yes	FF

<i>t</i> -AmOH	103	21.5	2.5	8.60	95	Yes	E
<i>t</i> -AmOH	130	20.6	0.3	68.67	80	Yes	D

6.2.11.3. Binary-Solvent Screening for Polymorphic Forms of Diazoxide Potassium Salt.

[00763] Binary-solvent crystallizations of the potassium salt utilizing fast-cooling procedure were performed using MeCN, acetone, and isoamyl alcohol as primary solvents and the following nine cosolvents: MTBE, EtOAc, IPAc, THF, *n*-hexane, heptane, toluene, CH₂Cl₂, and dioxane. Table 32 is representative, employing acetonitrile as primary solvent. XRPD patterns from crystallizations using acetonitrile as a primary solvent were consistent with Form D with only one exception being the solids obtained from the mixture of MeCN/dioxane afforded a unique pattern (Form F) material.

Table 32. Binary-Solvent Crystallizations of Potassium Salt of Diazoxide Using Fast-cooling Procedure and MeCN as a Primary Solvent

Cmpd Amt (mg)	MeCN* (mL)	Anti-solvent	Amt (mL)	Precipitate	Form
20.7	0.6	MTBE	1.0	Yes	D
23.4	0.6	EtOAc	6.0	Yes	D
20.0	0.6	IPAc	3.0	Yes	D
20.3	0.6	THF	6.0	No/Evap. To ppt	D
20.4	0.6	<i>n</i> -Hexane	2.0	Yes	D
20.3	0.6	Heptane	2.0	Yes	D
23.6	0.6	Toluene	1.0	Yes	D
21.3	0.6	CH ₂ Cl ₂	1.0	Yes	D
20.7	0.6	Dioxane	6.0	Yes	F

* Solids were dissolved at 80 °C.

[00764] XRPD patterns from binary crystallizations with acetone as primary solvent employing a fast cooling procedure afforded four forms A, C, D, and F. Mixtures of acetone with MTBE, THF, and cyclohexane provided Form A material; Form C was obtained from the mixtures of acetone with EtOAc, heptane, toluene, and CH₂Cl₂. The mixture of acetone with IPAc afforded Form D, and the mixture of acetone with dioxane afforded Form F solids.

[00765] XRPD patterns from binary crystallizations with isoamyl alcohol as the primary solvent employing a fast cooling procedure afforded five forms: C, D, E, F, and G. Form C was obtained from crystallizations using MTBE and EtOAc as cosolvents; Form D was obtained from mixtures of isoamyl alcohol with heptane, toluene, and CH₂Cl₂; Form E was crystallized out of i-AmOH/THF and i-AmOH/cyclohexane; Form G was obtained from i-AmOH/IPAc and Form F was obtained from i-AmOH/dioxane. Form D was the most common form observed from the crystallizations, and Form F was observed only when dioxane was used as an antisolvent.

[00766] Binary solvent recrystallizations of the potassium salt with the slow-cooling procedure were performed using three primary solvents (MeCN, acetone, and i-AmOH) and eight cosolvents (MTBE, EtOAc, IPAc, c-hexane, heptane, toluene, CH₂Cl₂, and dioxane). All solids were analyzed by XRPD to determine the physical form. Two patterns were observed to be Forms C and D respectively with additional peaks present. Other crystallizations provided Forms D, C, or F. Form D was obtained from the following solvent mixtures: MeCN/MTBE, MeCN/IPAc, MeCN/toluene, MeCN/CH₂Cl₂ and also from the mixtures of i-AmOH with MTBE, IPAc, cyclohexane, heptane, and toluene. Form C was obtained from MeCN/heptane, i-AmOH/EtOAc, and mixtures of acetone with MTBE, EtOAc, IPAc, cyclohexane, heptane, toluene, and CH₂Cl₂. Form F was crystallized from the mixtures of MeCN/dioxane and i-AmOH/dioxane. The solvent mixture of MeCN/EtOH provided amorphous material. Elemental analysis results indicate that the forms observed may not be pure and/or have bound or residual solvents present. Forms C, D, and F were found to be the most common forms of the potassium salt isolated and based on the results, these forms were chosen for scale-up and further characterization. Differences were found in the XRPD patterns and FTIR spectra of the

scale-up lots which were attributed to differences in impurity profiles, crystallinity, and form purity.

6.2.11.4. Characterization of Polymorphic Form C of Diazoxide Potassium Salt.

[00767] Form C of diazoxide potassium salt is an acetone solvate with a 2:1 ratio of diazoxide/solvent. It is a crystalline form of diazoxide potassium, with endothermic events at 187 and 360 °C in the DSC. The XRPD pattern for Form C is unique compared to all other forms observed. FTIR (ATR) spectroscopy showed differences between forms. ¹H NMR spectra were found to be consistent with the structure of diazoxide with a half-molar equivalent of acetone present. NMR data also indicated that the magnetic environment of the diazoxide structure had changed evidenced by a movement in chemical shift of the aromatic and methyl proton resonances. In addition, the resonance due to the amine proton was not observed which suggested deprotonation in solution. Weight loss by TGA was 8.9%, consistent with a half-molar equivalent of acetone, and occurred near 180 °C consistent with the endotherm observed in the DSC experiment. Moisture-sorption analysis conducted at 25 °C from 0 to 90% RH (adsorption) and 85 to 0% RH (desorption) showed Form C to be a hygroscopic solid, showing approximately 47 wt % water at 90% RH which indicated the sample deliquesced. In comparison, Forms D and F (hemihydrate and dioxane solvate) showed approximately 26 and 22 wt % water at 90% RH respectively. XRPD analysis following the moisture-sorption experiment afforded a pattern consistent with Form D. Slurry experiments were performed on 50/50 mixtures of Forms C, D, and F to determine propensity for conversion and to see if a unique form could be generated. Upon slurrying Form C mixtures in ethyl acetate, acetonitrile, and isopropanol conversion to Form D was observed in all solvents. Without wishing to be bound by theory, these results as well as conversion of Form F to Form D in these conditions suggest that Form D is more thermodynamically stable than Form C and F according to Ostwald's Rule of Stages. A thermal-stability experiment on Form C at 60 °C found the form to be stable. Conversion to another form was not observed.

6.2.11.5. Characterization of Polymorphic Form D of Diazoxide Potassium Salt.

[00768] Form D of diazoxide potassium salt is a hemihydrate. It is a crystalline form of diazoxide potassium, with endothermic events at 130, 191, and 352 °C in the DSC. FTIR (ATR) spectroscopy showed differences between forms. ¹H NMR spectra were found to be consistent with the structure of diazoxide. NMR data also indicated that the magnetic environment of the diazoxide structure had changed evidenced by a movement in chemical shift of the aromatic and methyl proton resonances. In addition, the resonance due to the amine proton was not observed which suggested deprotonation in solution. Weight loss by TGA was 4.5%, consistent with a half-molar equivalent of water, and occurred near 110 °C consistent with the endotherm observed in the DSC experiment. Moisture-sorption analysis conducted at 25 °C from 0 to 90% RH (adsorption) and 85 to 0% RH (desorption) showed Form D to be a hygroscopic, showing approximately 26 wt % water at 90% RH. In comparison, Forms C and F (acetone and dioxane solvates) showed approximately 47 and 22 wt % water at 90% RH, respectively. XRPD analysis following the moisture-sorption experiment afforded a pattern consistent with Form D. Solubility studies were conducted at pH 2, 7, and 12 for Form D and showed 29, 33, and 59 mg/mL, respectively. Solubility concentrations were determined using area-percent calculations with an HPLC calibration curve. Slurry experiments were performed on 50/50 mixtures of Forms C, D, and F to determine their propensity for conversion and to see if a unique form could be generated. Upon slurrying mixtures of Form D with Form C or Form F in ethyl acetate, acetonitrile, and isopropanol conversion to Form D was observed in all solvents.

6.2.11.6. Characterization of Polymorphic Form F of Diazoxide Potassium Salt.

[00769] Form F of diazoxide potassium salt is a dioxane solvate with a 2:1 ratio of diazoxide/solvent. It is a crystalline form of diazoxide potassium, with endothermic events at 191 and 363 °C in the DSC. The XRPD pattern for Form F is unique compared to all other forms observed. FTIR (ATR) spectroscopy showed differences between forms. ¹H NMR spectra were found to be consistent with the structure of diazoxide with

a half-molar equivalent of dioxane present. NMR data also indicated that the magnetic environment of the diazoxide structure had changed as evidenced by a movement in chemical shift of the aromatic and methyl proton resonances. In addition, the resonance due to the amine proton was not observed which suggested deprotonation in solution. Weight loss by TGA was 13.1%, consistent with a half-molar equivalent of dioxane, and occurs near 180 °C consistent with the endotherm observed in the DSC experiment. Moisture-sorption analysis conducted at 25 °C from 0 to 90% RH (adsorption) and 85 to 0% RH (desorption) showed Form F to be a hygroscopic solid, showing approximately 22 wt % water at 90% RH. In comparison, Forms C and D (acetone solvate and hemihydrate) showed approximately 47 and 26 wt % water at 90% RH, respectively. XRPD analysis following the moisture-sorption experiment afforded a pattern consistent with Form D. Slurry experiments were performed on 50/50 mixtures of Forms C, D, and F to determine their propensity for conversion and to see if a unique form could be generated. Upon slurrying mixtures of Form F with Form C and Form D in ethyl acetate, acetonitrile, and isopropanol conversion to Form D was observed in all solvents.

B. *In vivo* Obesity Testing

I. Obesity animal model

[00770] Formulations of salts of any of the compounds of Formulae I–IV prepared as described herein can be tested for efficacy in an animal model of obesity as described by Surwit et al. (*Endocrinology* **141**:3630–3637 (2000)). Briefly, 4-week-old B6 male mice are housed 5/cage in a temperature-controlled (22°C) room with a 12-h light, 12-h dark cycle. The high fat (HF) and low fat (LF) experimental diets contain 58% and 11% of calories from fat, respectively. A group of mice are fed the HF diet for the first 4 weeks of the study; the remaining 15 mice are fed the LF diet. The mice assigned to the LF diet are maintained on this diet throughout the study as a reference group of lean control mice. At week 4, all HF-fed mice are reassigned to 2 groups of mice. The first group remains on the HF diet throughout the study as the obese control group. The remaining 3 groups of mice are fed the HF diet and administered the controlled release formulation of salts of any of the compounds of Formulae I–IV at about 150 mg of active per kg per day as a single dose administered by oral gavage. Animals are weighed weekly, and food

consumption is measured per cage twice weekly until the diets are changed at week 4, whereupon body weight and food intake are determined daily. The feed efficiency (grams of body weight gained per Cal consumed) is calculated on a per cage basis. Samples for analysis of insulin, glucose, and leptin are collected on day 24 (4 days before the diets are changed), on day 32 (4 days after the change), and biweekly thereafter. In all cases food is removed 8 h before samples are collected. Glucose is analyzed by the glucose oxidase method. Insulin and leptin concentrations are determined by double antibody RIA. The insulin assay is based on a rat standard, and the leptin assay uses a mouse standard. At the termination of the study, a postprandial plasma sample is collected and analyzed for triglyceride and nonesterified fatty acid concentrations. After 4 weeks of drug treatment, a subset of 10 animals from each group is killed. The epididymal white adipose tissue (EWAT), retroperitoneal (RP) fat, interscapular brown adipose tissue (IBAT) fat pads, and gastrocnemius muscle are removed, trimmed, and weighed. The percent body fat is estimated from the weight of the epididymal fat pad. A subset of five animals from each group is injected i.p. with 0.5 g/kg glucose. At 30 min post injection, a plasma sample is collected and analyzed for glucose content by the glucose oxidase method.

2. Treatment of obesity in humans

[00771] Formulations of salts of any of the compounds of Formulae I–IV prepared as described herein can be tested for efficacy in obese humans, as described by Alemzadeh (Alemzadeh et al., *J Clin Endocr Metab* **83**:1911-1915 (1998)). Subjects consist of moderate-to-morbidly obese adults with a body mass index (BMI) greater than or equal to 30 kg/m². Each subject undergoes a complete physical examination at the initial evaluation, body weight being measured on a standard electronic scale and body composition being measured by DEXA.

[00772] Before initiation of the study, all subjects are placed on a hypocaloric diet for a lead-in period of 1 week. This is designed to exclude subjects who are unlikely to be compliant and to ensure stable body weight before treatment. Up to 50 subjects are tested at each dosage of drug. Daily dosage is set at 100, 200, and 300 mg/day. The daily dose is divided into 2 doses for administration. The dose is administered as either one, two or

three 50 mg capsules or tablets at each time of administration. Subjects are dosed daily for up to 12 months. Subjects are reviewed weekly, weighed, and asked about any side effects or concurrent illnesses.

[00773] Twenty-four-hour dietary recall is obtained from each subject. The dietary recalls are analyzed using a standard computer software program. All subjects are placed on a hypocaloric diet and encouraged to participate in regular exercise.

[00774] Before commencing, and after completion of the study, the following laboratory tests are obtained: blood pressure, fasting plasma glucose, insulin, cholesterol, triglycerides, free fatty acids (FFA), and glycohemoglobin, and measures of rate of appearance and oxidation of plasma derived fatty acids. Additionally, routine chemistry profiles and fasting plasma glucose are obtained weekly to identify those subjects with evidence of glucose intolerance and/or electrolyte abnormalities. Glucose is analyzed in plasma, by the glucose oxidase method.

[00775] Insulin concentration is determined by RIA using a double-antibody kit. Cholesterol and triglycerides concentrations are measured by an enzymatic method. Plasma FFA is determined by an enzymatic colorimetric method. SI was assessed by an iv glucose tolerance test (IVGTT) using the modified minimal model. After an overnight fast, a glucose bolus (300 mg/kg) was administered iv, followed (20 min later) by a bolus of insulin. Blood for determination of glucose and insulin is obtained from a contra lateral vein at -30, -15, 0, 2, 3, 4, 5, 6, 8, 10, 19, 22, 25, 30, 40, 50, 70, 100, 140, and 180 min. SI and glucose effectiveness (SG) are calculated using Bergman's modified minimal-model computer program before and after the completion of the study. Acute insulin response to glucose is determined over the first 19 min of the IVGTT, and the glucose disappearance rate (K_{it}) is determined from 8–19 min of the IVGTT. Body composition is measured by bioelectrical impedance before and at the completion of the study. Resting energy expenditure (REE) is measured by indirect calorimetry after an overnight 12-h fast, with subjects lying supine for a period of 30 min. Urine is collected over the corresponding 24 h, for measurement of total nitrogen and determination of substrate use, before and after the study.

3. Treatment of obesity in humans by coadministering diazoxide and phentermine

[00776] Evaluation of a prolonged co-administration of solid oral dosage form of salts of any of the compounds of Formulae I – IV thereof in combination with phentermine can be conducted in humans with moderate-to-morbid obesity and a body mass index (BMI) greater than or equal to 30 kg/m². Each subject undergoes a complete physical examination at the initial evaluation, body weight being measured on a standard electronic scale and body composition by DEXA.

[00777] Before initiation of the study, all subjects are placed on a hypocaloric diet for a lead-in period of 1 week. This is designed to exclude subjects who are unlikely to be compliant and to ensure stable body weight before treatment. Up to 100 subjects are tested. Daily dosage of salts of any of the compounds of Formulae I – IV is set at 200 mg. The daily dose is divided into 2 doses for administration. The dose is administered as either a 100 mg capsule or a 100 mg tablet at each time of administration. Subjects are dosed daily for up to 12 months. Phentermine is administered as a single daily dose of 15 mg. Subjects are reviewed every two weeks, weighed, and asked about any side effects or concurrent illnesses.

[00778] All subjects are continued on a hypocaloric diet and encouraged to participate in regular exercise. Before commencing, and after completion of the study, laboratory tests as described in the example above are obtained.

4. Prevention of diabetes in prediabetic humans

[00779] The example describes use of salts of any of the compounds of Formulae I – IV in a prediabetic subject to prevent the occurrence of diabetes. Subjects included in the study all have elevated risk of developing diabetes as measured by one of two methods. In a fasting glucose assay they have plasma glucose values between 100 and 125 mg/dl indicating impaired fasting glucose, or in an oral glucose tolerance test they have plasma glucose values between 140 and 199 mg/dl at 2 hours post-glucose load indicating they have impaired glucose tolerance. Treatment is initiated in any subject meeting either criteria. Treated subjects receive either 200 mg diazoxide per day as a 100 mg capsule or tablet twice per day or as two 100 mg capsules or tablets once per day. Placebo treated

subjects receive either one placebo capsule or tablet twice per day or two placebo capsules or tablets once per day.

[00780] Treatment is continued for once year with OGTT or fasting glucose measured monthly.

5. A sustained release coformulation of diazoxide HCl and metformin HCl use to treat diabetic patients

[00781] A sustained release co-formulation of diazoxide HCl and metformin HCl is produced by forming a compressed tablet matrix that includes 750 mg of metformin HCl and 100 mg of diazoxide HCl. These active ingredients are blended with sodium carboxymethyl cellulose (about 5% (w/w)), hypromellose (about 25% (w/w)), and magnesium stearate (<2% (w/w)). The compressed tablet is further coated with a combination of ethylcellulose (80% (w/w)) and methyl cellulose (20% (w/w)) as a thin film to control rate of hydration and drug release.

[00782] Type II diabetic patients are treated with the oral dosage form by administration of two tablets once per day or one tablet every 12 hours. Treatment of the patient with the drug is continued until one of two therapeutic endpoints is reached, or for so long as the patient derives therapeutic benefit from administration. The two therapeutic endpoints that would serve as the basis for the decision to cease treatment include the patient reaching a Body Mass Index (BMI (kg/m²)) between 18 and 25 or the re-establishment of normal glucose tolerance in the absence of treatment. The patient is monitored periodically for (a) glucose tolerance using an oral glucose tolerance test, (b) glycemic control using a standard blood glucose assay, (c) weight gain or loss, (d) progression of diabetic complications, and (e) adverse effects associated with the use of these active ingredients.

6. Prevention or treatment of weight gain in a patient treated with olanzapine

[00783] Pharmacotherapy for schizophrenia is initiated for a patient meeting DSM III-R criteria for schizophrenia. The patient is administered 10 mg of olanzapine (Zyprexa, Lilly) once per day. Adjunctive therapy to the patient for schizophrenia includes 250 mg

equivalent of valproic acid as divalproex sodium (Depakote, Abbott Labs). Weight gain, dyslipidemia and impaired glucose tolerance, and metabolic syndrome are high frequency adverse events in patients treated with this combination of anti-psychotics. Weight gain, dyslipidemia, impaired glucose tolerance or metabolic syndrome are treated by the co-administration of a therapeutically effective dose of a KATP channel opener. The patient is treated with administration of 200 mg/day of salts of any of the compounds of Formulae I – IV as a once daily tablet formulation. Administration of salts of any of the compounds of Formulae I – IV continues until the weight gain, dyslipidemia, impaired glucose tolerance or metabolic syndrome is corrected or until treatment of the patient with olanzapine is discontinued. Dyslipidemia is detected by measuring circulating concentrations of total, HDL, and LDL cholesterol, triglycerides and non-esterified fatty acids. Impaired glucose tolerance is detected through the use of oral or IV glucose tolerance tests. Metabolic syndrome is detected by measuring its key risk factors including central obesity, dyslipidemia, impaired glucose tolerance, and circulating concentrations of key proinflammatory cytokines.

7. Comparison of Single Doses of Diazoxide Administered as Proglycem® Oral Suspension or as Diazoxide Choline Controlled-Release Tablets in Obese Subjects.

7.1 Experimental Design

7.1.1. Objective of Study.

[00784] Clinical studies employing a randomized, open-label, parallel protocol comparing the safety, tolerability and bioavailability (i.e., pharmacokinetics) in obese subjects of Proglycem® (oral suspension) and diazoxide choline salt (controlled-release tablet) were conducted. The study evaluated the safety and tolerability of a single 200 mg dose (approximately 2 mg/kg) of diazoxide. The study further compared the single dose pharmacokinetics of an oral suspension of the free base of diazoxide (Proglycem®) with a controlled-release tableted formulation of diazoxide choline salt under fasting conditions in obese subjects.

7.1.2. Rationale for Study.

[00785] Diazoxide choline was selected as an alternative molecule for the oral administration of diazoxide because of significantly greater aqueous solubility over diazoxide free base, rapid conversion to diazoxide base on exposure to an aqueous environment, and incompatibility with incorporation into sustained release formulations. The fate of diazoxide choline in an aqueous medium *in vitro* has been extensively characterized. Without wishing to be bound by theory, once solubilized from the controlled-release tablet formulation, prior to absorption, the salt hydrolyzes to the free base of diazoxide and choline hydroxide. This was extensively characterized using UV/Vis absorbance, and occurred at all physiological relevant pH values from pH 2.0 to pH 8.5. This hydrolysis occurred in deionized water and buffered aqueous solutions, and in polar solvents that contained trace amounts of water. Thus, diazoxide, as the free base, is the molecular form absorbed following oral administration of the choline salt of diazoxide to animals or humans. Serum and plasma assays used in TK and PK analysis measure diazoxide free base concentrations. Dissolution assays measure diazoxide free base. Differences in plasma concentration-time profiles of diazoxide will be dependent on the time course of release of diazoxide choline from the tablet matrix in the intestinal tract. Historically, both oral suspension and immediate release capsule formulations of diazoxide have been commercially available, marketed as Proglycem®. The oral suspension has been shown to be highly bioavailable and rapidly absorbed upon administration. Because of the difficulty in characterizing dissolution from the oral suspension, the *in-vitro* dissolution of Proglycem® capsules was compared under standardized conditions to that of diazoxide choline controlled-release tablets (50 mg and 200 mg).

7.1.3. Inclusion Criteria.

[00786] Inclusion criteria for the present study included age 18 to 65 years old inclusive and BMI between 30 and 45 kg/m², inclusive, and signed informed consent. Female participants were required to be either postmenopausal for at least 1 year, surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy], or practicing a medically acceptable method of birth control. Inclusion criteria further

included freedom from serious medical disorders involving the kidneys, digestive system, heart and blood vessels, lungs, liver, eyes, nerves, brain, skin, endocrine system, bones or blood. Subjects, other than their obese condition, were generally healthy as documented by medical history, physical examination, vital sign, 12-lead ECG, and clinical laboratory assessments. Characteristics of the subjects randomized in the study are provided in Table 33.

Table 33. Characteristics of subjects randomized in the study

Parameter	Proglycem Oral Suspension (n=15)	Diazoxide Choline Controlled-Release Tablet (n=15)
	Mean±SD (range)	Mean±SD (range)
Age (yr)	32.5±12.1 (18-56)	27.9±12.6 (19-54)
BMI (kg/m ²)	32.9±4.3 (30.2-44.8)	33.8±3.2 (31.4-42.1)
Gender (male/female)	9/6	7/8

7.1.4. Exclusion Criteria.

[00787] Exclusion criteria included treatment with an investigational drug within 28 days prior to dosing, presence or history of a clinically significant disorder, clinical laboratory test values outside of the accepted reference range, reactive screen for HBV, HCV, or HIV, use of any medication affecting body weight, lipid or glucose metabolism within 2 months, use of any systemic prescription medication from 14 days prior to screening to dosing except hormonal contraceptives, use of any drug known to induce or inhibit hepatic drug metabolism from 28 days prior to screening until dosing, positive test for drug of abuse, current tobacco use, positive pregnancy screen, or pregnant or breastfeeding.

7.1.5. Randomization.

[00788] A total of 30 subjects were randomized in the present study. Fifteen subjects were randomized to each arm. For convenience, the 30 subjects were broken up into two

cohorts. Cohort 1 checked into the clinic on October 12, 2006, was dosed on October 14, 2006, remained in the clinic for 72 hours following dose administration, returning at 96 and 120 hours after dose administration. Cohort 1 included 10 subjects randomized to receive Proglycem Oral Suspension and 5 subjects randomized to receive a Diazoxide Choline Controlled-Release Tablet. Cohort 2 checked into the clinic on October 14, 2006, were dosed on October 16, 2006, remained in the clinic for 72 hours following dose administration, returning at 96 and 120 hours after dose administration. Cohort 2 included 5 subjects randomized to receive Proglycem® Oral Suspension and 10 subjects randomized to receive a diazoxide choline controlled-release tablet. All subjects completed the study.

7.1.6. Dosing.

[00789] Subjects randomized to the Proglycem® Oral Suspension arm received a single 200 mg dose (4 mL) taken with 240 mL of room temperature water. Subjects randomized to the diazoxide choline controlled-release tablet arm received a single tablet containing 290 mg of diazoxide choline, which is equivalent to 200 mg of diazoxide. Doses were administered after an overnight fast, and fasting continued until approximately 4.25 hours after dose administration at which time a standardized meal was served.

7.1.7. Safety Monitoring.

[00790] Clinical laboratory tests including hematology, clinical serum chemistry and urinalysis were conducted at screening and at end of study. Hematology included measurements of hemoglobin, hematocrit, white blood cell count with differential, red blood cell count and platelet count. Clinical serum chemistry included evaluation of sodium, potassium, BUN, creatinine, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT, glucose, total cholesterol, HDL-cholesterol, and triglycerides. Urinalysis included pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen, leukocytes, and microscopic urine analysis if sample was dipstick positive. All adverse events were recorded. Vital signs were collected at screening, at one hour prior to dosing, and after dose administration at 1, 3, 6, 9, 12, 24, 48, 72 and 120

hours. Continuous two-lead cardiac monitoring (telemetry) was performed on subjects from 24 hours prior to dose administration (to establish baseline data) until 24 hours after dose administration.

7.1.8. Exploratory Endpoints.

[00791] Three exploratory endpoints were evaluated in the study. Blood glucose, insulin and non-esterified fatty acids (NEFA) were measured prior to dosing and at 1, 3, 6, 9, 12, 24, and 48 hours post dosing. Blood glucose and insulin levels were also assessed at end of study. Data collected at times 1, 3, 24, and 48 hours after dose administration were obtained under fasting conditions. The remaining data points were post-prandial measures. Samples for pharmacokinetic analysis to evaluate bioavailability were collected prior to dosing and after dose administration at 1, 2, 4, 6, 8, 12, 16, 20, 24, 32, 40, 48, 72, 96, and 120 hours.

7.2. Results

7.2.1. Adverse Events.

[00792] The adverse events observed with each of the two formulations are summarized in Tables 34 and 35. With the single exception, a moderate headache requiring treatment with acetaminophen in a subject treated with Proglycem® Oral Suspension, all adverse events were mild. Both formulations appeared to be well tolerated in the study. One subject administered with diazoxide choline controlled-release tablet experienced mild loss of appetite. Because most obese and obese diabetic animal model studies of diazoxide show some reduction in feed consumption, loss of appetite was, therefore, considered part of the pharmacodynamic response to the drug in obese patients, rather than an adverse event.

Table 34. Adverse events (AE) in subjects administered Proglycem® Oral Suspension (n=15)

Adverse Event	Hours Post Dosing	Severity	Corrective Treatment	Outcome
Gastrointestinal				
Nausea ^a	2.75	Mild	None	Resolved
Neurological				
Headache	20.0	Moderate	Therapy required acetaminophen	Resolved
Headache ^b	6.25	Mild	None	Resolved
Dizziness ^c	1.0	Mild	Assisted to supine position	Resolved
Dizziness ^c	3.25	Mild	Assisted to supine position	Resolved
Dizziness ^d	1.0	Mild	Assisted to supine position	Resolved
Dizziness ^d	4.25	Mild	Assisted to supine position	Resolved
Miscellaneous				
Chills ^b	6.25	Mild	None	Resolved
Dermatitis from ECG patches ^a	4.75	Mild	None	Resolved

Number of subjects with at least one AE = 5, AEs followed by the same superscript letter are the same subject

Table 35. Adverse events (AE) in subjects administered Diazoxide Choline (200 mg Diazoxide) Controlled-Release Tablet (n=15)

Adverse Event	Hours Post		Corrective	Outcome
	Dosing		Treatment	
Gastrointestinal				
Nausea ^a	1.5	Mild	None	Resolved
Dry Heaves ^c	1.6	Mild	None	Resolved
Neurological				
			Assisted to supine	
Lightheaded	12.0	Mild	position	Resolved
Dizziness ^a	20.0	Mild	None	Resolved
Miscellaneous				
Chills ^f	2.0	Mild	None	Resolved
Back Pain ^f	2.0	Mild	None	Resolved
Warm ^g	20.0	Mild	None	Resolved

Number of subjects with at least one AE = 4, AEs followed by the same superscript letter are the same subject

[00793] In addition, a randomized double-blind, placebo-controlled clinical trial was conducted in 24 healthy volunteers. They were randomized in a 2:1 ratio of treated to placebo. Treated subjects received 300 mg/day diazoxide administered as 3 tablets of the controlled release formulation U described in Table 2. The dose was administered once per day in the morning for a period of 7 days.

[00794] There were more adverse events reported per subject in the placebo controls than in the diazoxide choline treated arm (Table 35⁷). The majority of the events were mild. The frequency of the most common adverse events was identical in the diazoxide choline treated arm and in the controls.

Table 35. Adverse events (AE) in subjects administered Diazoxide Choline (300 mg Diazoxide) Controlled-Release Tablet or Placebo

	Adverse Event	
	Diazoxide choline	Placebo
Headache	4 (25%)	2 (25%)
Nausea	3 (19%)	2 (25%)
Dizziness	2 (13%)	1 (13%)
n	16	8

7.2.2. Clinical Chemistry.

[00795] A summary of fasting glucose, fasting insulin, NEFA, and serum sodium (Na), potassium (K) and creatinine level is provided in Table 36. Neither treatment resulted in significant changes in serum Na, K or creatinine from baseline to end of study. Treatment with diazoxide primarily impacts glucose-stimulated insulin secretion rather than basal insulin secretion. Fasting glucose levels increased slightly in the first 3 hours following dose administration. This increase was more pronounced in the Proglycem® Oral Suspension arm as compared to the diazoxide choline controlled-release tablet arm. These results are consistent with the differences in measured rates of dissolution from these formulations (see Table 5 herein) and the PK levels (see Figures 24 and 25 herein). In this study, there is no evidence for a reduction in fasting insulin after the administration of the single dose of diazoxide. There is also no evidence for a significant increase in fasting glucose as measured at 24 or 48 hours after dose administration. The most sensitive pharmacodynamic response measure is NEFA. Diazoxide treatment normally results in a short-term increase in NEFA, which returns to levels at or below baseline in about 6 hours. Both formulations showed this transient increase in NEFA. Treatment with Proglycem® Oral Suspension resulted in a statistically significant increase ($p < 0.001$) in NEFA at 3 hours, which by 6 hours after dose administration had returned to levels well below baseline. Similarly the increase in NEFA at 3 hours after administration of diazoxide choline controlled-release tablets was statistically significant

($p < 0.0012$). NEFA levels in the diazoxide choline controlled-release tablet treated subjects also returned to levels well below baseline by 6 hours after dose administration.

Table 36. Fasting glucose, fasting insulin, non-esterified fatty acid (NEFA), serum sodium (Na), potassium (K) and creatinine of subjects

Parameter	Proglycem Oral Suspension (n=15)	Diazoxide Choline Controlled-Release Tablet (n=15)
Fasting Glucose (mg/dL)	Mean±SD (range)	Mean±SD (range)
Baseline	93±6 (83-104)	93±6 (83-108)
1 h post-dose	99.4±7 (89-117)	97.9±7 (92-117)
3 h post-dose	102.8±6 (93-113)	98.0±7 (90-112)
24 h post-dose	97±5 (87-106)	98±8 (88-118)
48 h post-dose	92±5 (84-103)	93±5 (83-104)
Fasting Insulin (μU/ml)		
Baseline	8.6±5.2 (2.9-24.1)	9.9±3.3 (4.4-16.3)
24 h post-dose	12.0±8.9 (6.1-41.9)	11.1±3.3 (5.5-17.0)
48 h post-dose	9.5±5.7 (4.0-28.9)	11.1±2.9 (5.3-17.8)
NEFA (μmol/L)		
1 h post-dose	0.36±0.11 (0.21-0.65)	0.34±0.14 (0.09-0.67)
3 h post-dose	0.53±0.13 (0.31-0.78)	0.55±0.19 (0.28-0.88)
6 h post-dose	0.13±0.07 (0.07-0.32)	0.11±0.04 (0.07-0.21)
24 h post-dose	0.36±0.10 (0.23-0.62)	0.40±0.18 (0.25-0.97)
48 h post-dose	0.38±0.13 (0.2-0.66)	0.39±0.15 (0.17-0.65)
Na (mEq/L)		
Baseline	138.0±2.0 (135-142)	138.1±2.6 (134-143)
End of Study	138.7±1.1 (137-141)	139.3±2.3 (135-144)

K (mmol/L)		
Baseline	4.4±0.4 (3.9-5.5)	4.2±0.3 (3.8-5.1)
End of Study	4.4±0.3(3.9-5.2)	4.2±0.3(3.8-5.2)
Creatinine (mg/dL)		
Baseline	0.9±0.1 (0.7-1.1)	0.9±0.2 (0.7-1.4)
End of Study	1.0±0.1 (0.8-1.3)	0.9±0.2 (0.6-1.3)

[00796] All other clinical laboratory tests, including hematology, clinical serum chemistry, and urinalysis were within normal ranges for obese subjects.

7.2.3. Vital Signs.

[00797] A graph depicting sitting blood pressure at baseline and at various times following dose administration is provided in Figure 22. Neither treatment was associated with a sustained reduction or increase in blood pressure, nor was there any clear trend from baseline over 6, 9, 12, or 24 hours after dose administration. Pulse rates dropped incrementally from baseline levels in the period from dose administration to 3 hours post dosing (Figure 23). Pulse rates rose to levels equivalent to baseline or slightly above baseline in the period from 6 to 12 hours after dose administration, and remained at baseline levels from 24 hours after dose administration to the end of the study (Figure 23). Review of the baseline cardiac telemetry data for all subjects was conducted the morning of dosing. Based on the absence of clinical significant abnormalities, all subjects were allowed to proceed with dosing. The cardiac telemetry data from study time 0 to 24 hours after dose administration was evaluated. No clinically significant abnormalities (e.g. arrhythmias) were observed.

7.2.4. Preliminary Evaluation of Diazoxide Plasma Pharmacokinetics.

[00798] Compared to the Proglycem® Oral Suspension, the diazoxide choline controlled-release tablet had a 30% lower peak exposure (C_{max}) and a 15% lower total

exposure (AUC) when the formulations were administered orally as 200 mg equivalents of diazoxide (Table 37). The timing of the peak plasma concentration (T_{max}) occurred at a median time of 4 hr after administration of the oral suspension and 20 hr after administration of the diazoxide choline controlled-release tablet. The terminal half-life for diazoxide was similar with both formulations (29 hr for the oral suspension and 32 hr for the tablet). The two formulations had similar between-patient variability for C_{max} and AUC. The most notable difference between the two formulations following a single dose was the lower, broader peak of the concentration-time profile of the tablet formulation (Figures 24 and 25). The peak concentration for the tablet averaged about 30% less and occurred about 16 hours later than the suspension. Figures 24 and 25 illustrate that the mean peak concentration was virtually unchanged between 12-hr and 24-hr post-dose following administration of the diazoxide choline controlled-release tablet formulation. Because of a more sustained release pattern, the tablet formulation was predicted to have a greater accumulation factor with chronic dosing than was the oral suspensions (3.96 vs. 2.84). Simulations of repeated once-daily dosing with the two formulations (assuming linear pharmacokinetics) predicted that the two formulations would have similar trough concentrations at steady-state (22-23 $\mu\text{g/mL}$) (see Figure 26).

Table 37. Summary Statistics for Plasma Diazoxide Pharmacokinetic Parameters after a Single Dose of Two Formulations

Diazoxide Choline Controlled-Release Tablets								
	C_{max}	T_{max}	AUC(0-24)	AUC(0-120)	AUC(0- ∞)	λ_z	$T_{1/2}$	Accum
	$\mu\text{g/mL}$	hr	$\mu\text{g}\cdot\text{hr/mL}$	$\mu\text{g}\cdot\text{hr/mL}$	$\mu\text{g}\cdot\text{hr/mL}$	1/hr	hr	Factor
N	15	15	15	15	15	15	15	15
Mean	9.25	22.1	166	553	618	0.0242	31.9	3.96
Geomean	9.07	19.6	157	531	588	0.0229	30.2	3.74
St Dev	1.89	11.5	54	160	198	0.0085	10.6	1.48
SEM	0.49	3.0	14	41	51	0.0022	2.7	0.38
CV%	20.5%	52.0%	32.5%	28.9%	32.0%	35.2%	33.3%	37.5%

Median	9.08	20.0	164	518	586	0.0237	29.3	3.80
Min	5.53	8.00	74.6	261	274	0.0144	15.9	2.26
Max	13.2	48.0	266	842	1024	0.0437	48.3	7.84

Diazoxide Oral Suspension (Proglycem)								
	C _{max}	T _{max}	AUC(0-24)	AUC(0-120)	AUC(0-∞)	λ _z	T _{1/2}	Accum
	μg/mL	hr	μg•hr/mL	μg•hr/mL	μg•hr/mL	1/hr	hr	Factor
N	15	15	15	15	15	15	15	15
Mean	13.5	6.67	245	643	696	0.0256	28.6	2.84
Geomean	13.3	5.36	243	629	677	0.0249	27.9	2.79
St Dev	2.3	5.49	35	142	173	0.0068	6.3	0.57
SEM	0.6	1.42	9	37	45	0.0018	1.6	0.15
CV%	17.1%	82.3%	14.4%	22.1%	24.9%	26.7%	22.0%	20.0%
Median	13.3	4.00	245	620	671	0.0234	29.6	2.86
Min	10.1	2.00	183	464	488	0.0180	16.1	1.84
Max	18.0	24.0	314	926	1054	0.0430	38.5	4.25

7.3 Conclusions of Comparison of Single Doses of Diazoxide Administered as Proglycem® Oral Suspension or as Diazoxide Choline Controlled-Release Tablets in Obese Subjects.

[00799] The present clinical study on the comparison of a single dose of diazoxide choline controlled-release tablet with an equivalent dose of diazoxide administered as Proglycem® Oral Suspension in obese patients indicates that both formulations were well tolerated. With a single exception, moderate headache requiring treatment with acetaminophen in one subject treated with Proglycem®, all adverse events were mild.

Diazoxide choline controlled-release tablets appear to have a better CNS safety profile than Proglycem® Oral Suspension as evidenced by the absence of headaches and reduced rate of dizziness. Exploratory endpoints showed no detrimental impact. Preliminary pharmacokinetic analysis showed that compared to Proglycem® Oral Suspension, the diazoxide choline controlled-release tablet had a 30% lower peak exposure (C_{max}) and a 15% lower total exposure (AUC) for the same 200 mg diazoxide equivalent dose. The timing of the peak plasma concentration (T_{max}) occurred at a median time of 4 hr after administration of the oral suspension and 20 hr after administration of the diazoxide choline tablet. The terminal half-life for diazoxide is similar with both formulations (29 hr for the oral suspension and 32 hr for the tablet). The two formulations had similar between-patient variability for C_{max} and AUC.

8. Increasing Insulin Sensitivity

[00800] Type II diabetes is characterized by increasing insulin resistance, ultimately followed in the progression of the disease by beta cell exhaustion and insulin dependence. Improvements in insulin sensitivity without contributing to beta-cell exhaustion are critical to management of type II diabetes. Likewise, preservation of beta-cell mass in newly diagnosed type I diabetics by KATP channel openers is dependent on the ability to provide beta-cell rest. In non-insulin dependent individuals, direct evidence of beta-cell rest is provided by reductions in fasting insulin. In insulin dependent individuals, insulin secretion is measured indirectly as basal c-peptide levels.

[00801] A controlled clinical study was conducted to evaluate the potential for Diazoxide Choline Controlled-Release Tablets administered once daily to improve insulin sensitivity and provide beta-cell rest as evidenced by reductions in homeostasis model assessment-insulin resistance (HOMA-IR) and reductions in fasting insulin. Up to 8 obese individuals with or without hypertension or dyslipidemia, who may also have impaired fasting glucose or impaired glucose tolerance were randomized to received no drug, or diazoxide equivalent doses of 100 mg/day, 200 mg/day or 300 mg/day for 14 days administered as Diazoxide Choline Controlled-Release Tablets. All subjects were placed on a reduced calorie diet. Fasting insulin was measured pre-dose and on day 7, when diazoxide was expected to have achieved steady state pharmacokinetics. Insulin

resistance was reduced in a dose dependent manner by day 7 (Table 38). Reductions in fasting insulin were realized at all dose levels (Table 39). Thus, treatment with Diazoxide Choline Controlled-Release Tablets once per day result is rapid and dramatic improvements in insulin resistance which combined with the beta cell rest provided by reductions in fasting insulin result in preservation of beta cell mass and function while improving glycemic control.

Table 38 Changes in HOMA-IR in treated obese subjects

Cohort	N	Homa-IR		Day 7		Percentage Change
		Pre-dose				
		Mean	SEM	Mean	SEM	
Control	6	2.3	0.51	2.7	0.47	17%
100 mg/day	7	4.0	0.73	2.8	0.52	-30%
200 mg/day	5	3.1	0.80	2.1	0.66	-32%
300 mg/day	8	3.2	0.49	2.0	0.44	-38%

Table 39. Changes in fasting insulin in treated obese subjects

		Fasting Insulin (μ IU/mL)				
		Pre-dose		Day 7		Percentage
Cohort	N	Mean	SEM	Mean	SEM	Change
Control	6	10.9	2.41	13.1	2.13	20%
100 mg/day	7	18.2	3.31	11.7	1.97	-36%
200 mg/day	5	13.7	3.45	9.1	2.72	-34%
300 mg/day	8	13.4	1.97	7.8	1.61	-42%

9. Relationship between PK parameters and weight and Body Mass Index (BMI)

[00802] The historic data relating PK parameters to weight and BMI for the Proglycem oral suspension product suggested that there was a strong negative relationship between diazoxide peak drug levels (C_{max}) and diazoxide area under the curve (AUC) for single doses and the weight and body mass index of dosed patients. A strong negative

relationship between these key PK parameters would result in the need to adjust dose by patient in order to achieve consistent pharmacokinetic profiles in treated patients.

[00803] The relationship between C_{max} and AUC and the weight and BMI of subjects receiving either Proglycem or Diazoxide Choline Controlled-Release Tablets was evaluated in a controlled clinical study. Fifteen overweight or obese subjects with weight ranging from 172 lbs to 345 lbs and BMI ranging from 30.2 to 44.8 were randomized to receive a single 200 mg dose of diazoxide administered as Proglycem oral suspension. Fifteen overweight or obese subjects with weight ranging from 173 lbs to 288 lbs and BMI ranging from 31.4 to 42.1 were randomized to receive a single 200 mg dose of diazoxide administered as a Diazoxide Choline Controlled-Release Tablet. Circulating diazoxide levels were measured on samples collected prior to dosing and after dose administration at 1, 2, 4, 6, 8, 12, 16, 20, 24, 32, 40, 48, 72, 96, and 120 hours.

[00804] The correlation between weight and C_{max} and AUC and between BMI and C_{max} and AUC were evaluated within each of the dosed cohorts of subjects. There was a significant negative relationship between weight and AUC, weight and C_{max} and between BMI and C_{max} in the Proglycem treated subjects (Table 40). No such relationship existed between either weight or BMI and AUC or C_{max} in the Diazoxide Choline Controlled-Release Tablet treated subjects (Table 41).

Table 40. Relationship between PK Parameters and Weight/BMI for Proglycem

Proglycem Oral Suspension		
	AUC	C _{max}
Wt	-0.56*	-0.75**
BMI	-0.31	-0.61*

(* p<0.05, ** p<0.01)

Table 41. Relationship between PK Parameters and Weight/BMI for Proglycem

Diazoxide Choline Controlled-Release Tablet		
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	AUC	C _{max}
Wt	-0.28	-0.23
BMI	-0.04	0.17

10. Clinical Studies of Diazoxide Treatment of Dyslipidemia

[00805] Seven obese subjects including those with and without dyslipidemia were dosed for 7 days with the equivalent of 400 mg per day of diazoxide administered as diazoxide choline controlled-release tablets QD (two tablets taken daily, each containing 200 mg equivalent diazoxide per tablet prepared as formula K' (Table 2)). Subsequently, they were withdrawn from treatment and monitored for an additional 7 days.

[00806] The results of lipid profile taken on day 7 of treatment and on day 7 of monitoring (post treatment) are shown as an average for the treated individuals in Table 42. On day 7 of treatment, treated individuals averaged 8.6% reduction in total cholesterol, an 8.7% increase in HDL cholesterol and a 57.6% reduction in circulating triglycerides. At the end of the 7 day monitoring period, there was a reversal of each of these impacts: Total cholesterol was only 6.9% below baseline, HDL cholesterol had returned to 1 mg/dL below baseline and circulating triglycerides were now 44.4% below baseline. The most dramatic changes were realized in a 46 year old male who started treatment with total cholesterol of 342 mg/dL, HDL cholesterol of 37 mg/dL and circulating triglycerides of 1221 mmol/L. Following treatment, this subject realized a reduction in total cholesterol of 60 mg/dL, increase in HDL cholesterol of 15 mg/dL and a reduction in circulating triglycerides of 980 mmol/L. Seven days after discontinuation of treatment, this individual's total cholesterol had risen by 11 mg/dL, HDL cholesterol had dropped by 4 mg/dL and circulating triglycerides had risen by 124 mmol/L mg/dL.

Table 42. Changes in blood lipid parameters in a group of treated obese dyslipidemic patients

Variable	Baseline	Day 7 of treatment	7 Days post-dosing
Total Cholesterol (mg/dL)	233	213	217
HDL Cholesterol (mg/dL)	46	50	45
Triglycerides (mmol/L)	304	129	169

II. Clinical Studies of Diazoxide Treatment of Hypertriglyceridemia

[00807] Individual patients with elevated fasting triglycerides, with or without elevated total cholesterol or LDL-cholesterol, were treated with diazoxide, administered as Diazoxide Choline Controlled-Release Tablets for 7 to 49 days. All patients were dosed once per day for an uninterrupted period of time. The dosages were achieved by combinations of two tablets, a 50 mg diazoxide equivalent dose tablet of diazoxide choline made as formula J (Table 2) and a 200 mg diazoxide equivalent dose tablet of diazoxide choline made as formula K' (Table 2). Table 43 provides this information.

Table 43. Combinations of Diazoxide Choline Controlled-Release Tablets

Diazoxide equivalent dose	Tablets of J	Tablets of K
100 mg	2	0
150 mg	3	0
200 mg	0	1
250 mg	1	1
300 mg	2	1
350 mg	3	1
400 mg	0	2

[00808] Several patients (subjects 1-6 and 8-9) were dosed for day 7 or 14 days at the diazoxide equivalent doses indicated in Table 44. Patient 7 received a diazoxide equivalent dose of 150 mg for 5 days followed by 9 days at a diazoxide equivalent dose of 300 mg (Table 44). Several patients, subjects 10, 12 and 13, were treated for 7 days at a diazoxide equivalent dose of 150 mg, followed by 7 days at a diazoxide equivalent dose of 200 mg, followed by 7 days at a diazoxide equivalent dose of 250 mg, followed by 7 days at a diazoxide equivalent dose of 300 mg, followed by 21 days at a diazoxide equivalent dose of 350 mg (Table 45). One patient, number 11, was treated by titrating the drug using diazoxide equivalent doses of 150 mg, 200 mg, 250 mg and 300 mg for 7, 14, 7 and 17 days, respectively. Patients were placed on a low fat diet at the start of treatment which continued to the end of treatment. A control subject group which did not receive diazoxide met the elevated triglyceride level of the patient group (above 150mg/dl measured in blood under fasting conditions) and were placed on the same low fat diet as the treatment group (Table 46).

[00809] Each subject's baseline circulating triglyceride level was calculated as the average of two measurements of fasting triglycerides taken approximately two weeks apart, with the second taken predose on the first day of treatment. Patients treated for 14 days or less had their fasting triglyceride levels measured on days 1, 3, 7, and 14

following the start of dosing. Patients treated for greater than 14 days had their fasting triglyceride levels measured on days 7, 14, 21, 28, 35, 42 and 49 following the start of dosing.

[00810] The controls, with a single exception with borderline high triglycerides, on average had higher fasting triglycerides at the end of the diet period than when they started.

Table 44. Fasting Triglyceride (mg/dl) Responses in Patients Treated for 7 or 14 days

Subject	Dose	Study Day					Percent change
		Baseline	1	3	7	14	
Baseline triglyceride between 150 and 200 mg/dl							
2	100 mg	173	139	124	85	109	-37%
3	100 mg	180	231	254	133	181	1%
1	200 mg	168	152	112	129	135	-20%
21	150mg/ 300mg	175	207	109	131	---	-25%
4	300 mg	181	159	124	113	106	-41%
22	300 mg	183	177	94	---	---	-48%
6	300 mg	187	188	162	188	157	-16%
5	400 mg	186	245	200	179	---	-4%
Baseline triglyceride between 200 and 500 mg/dl							
7	150mg/ 300mg	205.5	207	145	103	104	-49%
23	300 mg	265	152	101	---	---	-62%
24	300 mg	279	328	217	---	---	-22%
8	400 mg	273	284	207	174	---	-36%

Baseline triglyceride above 500 mg/dl

9	400 mg	723	511	279	241	---	-67%
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Table 45. Fasting Triglyceride (mg/dl) Responses in Patients Treated for 35 to 49 days

Subject	Baseline	7	14	21	28	35	42	49	Percent change
Subjects with baseline triglycerides between 150 and 200 mg/dl									
MSC	153	114	116	111	129	131	132	95	-38%
10	161	169	111	90	108	104	108	99	-39%
Subjects with baseline triglycerides between 200 and 500 mg/dl									
11	202	181	143	155	137	126	---	---	-37%
12	222	194	140	169	161	149	134	139	-37%
13	336	184	230	173	172	176	130	127	-62%

Table 46. Fasting Triglyceride (mg/dl) Responses in Patients on Low Fat Diet for 7 to 21 Days

Study Day							
Subject	Baseline	1	3	7	14	21	Percent change
Baseline triglyceride between 150 and 200 mg/dl							
14	158	151	131	93	133	113	-28%
15	199	190	292	184	165	203	2%
Baseline triglyceride between 200 and 500 mg/dl							
16	212	246	194	274	255	246	16%

17	218	223	272	343	251	252	16%
18	234	227	161	229	208	287	23%
19	248	216	202	363	347	342	38%
20	299	425	308	502	275	---	-8%

[00811] Patients treated with diazoxide equivalent doses of 100 mg per day experienced reductions in fasting triglycerides of 38% at 7 days and 18% at 14 days of treatment. Patients treated with diazoxide equivalent doses of 200 mg per day experienced reductions in fasting triglycerides of 23% at 7 days and 20% at 14 days of treatment. Patients treated with diazoxide equivalent doses of 300 mg per day experienced reductions in fasting triglycerides of 18% at 7 days and 29% at 14 days of treatment. Patients treated with diazoxide equivalent doses of 400 mg per day experienced reductions in fasting triglycerides of 50% at 7 days of treatment. Patients treated with diazoxide equivalent doses of 150 mg and 300 mg for 5 and 9 days, respectively experienced reductions in fasting triglycerides of 50% at 7 and 14 days of treatment. In patients titrated from 150 mg to 300 or 350 mg, fasting triglycerides were reduced by 21%, 31%, 38%, 38% and 49% at the end of treatment with diazoxide equivalent doses of 150 mg, 200 mg, 250 mg, 300 mg and 350 mg, respectively. The response to the drug tended to be more pronounced at any dose level at elevated baseline triglyceride levels. The most pronounced impact on fasting triglycerides were realized in subjects with baseline fasting triglyceride levels greater than 300 mg/dL. There was no consistency tendency for elevations in LDL-cholesterol in treated patients, even those starting with very high fasting triglyceride levels at baseline. For example, patient 8 and 9 had reductions in LDL-cholesterol of -8.6% and -15.3%, respectively. Patient 13, in contrast had a rise in LDL-cholesterol of 6.7% on day 21 and of 11% by day 42.

12. Randomized double-blind, placebo-controlled Diazoxide clinical trial in healthy volunteers

[00812] A randomized double-blind, placebo-controlled clinical trial was conducted in 24 healthy volunteers. They were randomized in a 2:1 ratio of treated to placebo.

Treated subjects received 300 mg/day diazoxide administered as 3 tablets of the formulation I as described in Table 2. The dose was administered once per day in the morning for a period of 7 days. A number of lipid parameters were measured at baseline and again on day 7 including fasting triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, and non-HDL cholesterol. Additionally, blood pressure was measured on a daily basis.

[00813] The lipid response to 7 days treatment with diazoxide choline is provided in table 47. Treatment of subjects with diazoxide choline for 7 days resulted in a reduction of triglycerides of 13.2%. In contrast, in the placebo treated arm there was an increase of 11.7%. There was a reduction in total cholesterol, LDL cholesterol and non-HDL cholesterol from baseline to day 7 in both arms. The reduction in the diazoxide choline treated arm was greater for each lipid parameter than the corresponding reduction in the placebo arm. There was no change in HDL cholesterol in the placebo arm, whereas there was an increase HDL cholesterol of 8.2% in the diazoxide choline treated arm. Seven days of diazoxide choline treatment was associated with a marked decrease in triglycerides, reductions in LDL, non-HDL and total cholesterol and a marked increase in HDL cholesterol in these subjects.

Table 47. Changes in lipid parameters associated with 7 days of treatment with diazoxide choline (300 mg diazoxide/day) or placebo.

Treatment	Lipid parameter	Baseline mean $\pm$ SE M	Day 7 mean $\pm$ SEM	Percent change from baseline
Diazoxide choline	Triglycerides (mg/dL)	76 $\pm$ 7.8	66 $\pm$ 3.9	-13.2%
	Total cholesterol (mg/dL)	175 $\pm$ 7.5	171 $\pm$ 6.4	-2.3%
	LDL cholesterol (mg/dL)	111 $\pm$ 5.8	105 $\pm$ 4.9	-5.4%
	HDL cholesterol (mg/dL)	49 $\pm$ 3.3	53 $\pm$ 2.9	8.2%
	non-HDL cholesterol (mg/dL)	126 $\pm$ 6.6	118 $\pm$ 5.5	-6.3%

Treatment	Lipid parameter	Baseline mean $\pm$ SE M	Day 7 mean $\pm$ SEM	Percent change from baseline
Placebo	Triglycerides (mg/dL)	60 $\pm$ 10.7	67 $\pm$ 9.8	11.7%
	Total cholesterol (mg/dL)	171 $\pm$ 13.7	167 $\pm$ 9.9	-2.3%
	LDL cholesterol (mg/dL)	105 $\pm$ 11.8	101 $\pm$ 11.3	-3.8%
	HDL cholesterol (mg/dL)	53 $\pm$ 4.4	53 $\pm$ 3.7	0.0%
	non-HDL cholesterol (mg/dL)	117 $\pm$ 12.1	114 $\pm$ 10.6	-2.6%

[00814] There was no change in blood pressure in the placebo treated arm over the 7 days of treatment. In contrast, 7 days of diazoxide choline treatment resulted in a reduction in diastolic blood pressure of 6.2 mmHg. This reduction in diastolic blood pressure has been observed in other studies of diazoxide choline and has persisted through the end of 7 weeks of treatment. The blood pressure response to diazoxide choline treatment in two separate clinical studies is shown in table 48. TR002 utilized 435 mg diazoxide choline achieved from one tablet of formulation K' (290 mg diazoxide choline) and two tablets of formulation J (each 72.5 mg diazoxide choline). In PK008, the dose was administered as one and one ½ tablet formulation K'.

Table 48. Blood pressure changes in response to diazoxide choline treatment in two clinical studies.

Study	Diazoxide choline dose	Duration of treatment	Parameter	Baseline	End of treatment
EC004	435 mg	7 days	Systolic	113.2	113.5
			Diastolic	69.4	63.2
TR002	508 mg	49 days	Systolic	118.1	117.0
			Diastolic	77.7	67.0

13. Clinical study in Hypertriglyceridemic patients

[00815] A clinical study was conducted in 12 hypertriglyceridemic patients. Patients received 435 mg/day diazoxide choline (300 mg diazoxide/day equivalent dose), and were dosed once per day in the morning. They were divided into two groups, one initially receiving a formulation which has lower bioavailability (formulation U) and one receiving a formulation with higher bioavailability (formulation K'). After day 8 they were crossed over from one formulation to the other formulation. The dosages were achieved by ingesting 1.5 tablets of formula K' (200 mg diazoxide equivalent dose tablet of diazoxide choline) and 3 tablets of formula U (100 mg diazoxide equivalent dose tablet of diazoxide choline) (Table 2). Treatment continued for 16 days. The endpoint of the study was percentage change from baseline to day 15 of triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol and non-HDL cholesterol. Lipid parameters were measured at baseline and on days 7 and 15. Blood pressure was collected at multiple time points.

[00816] Treatment of hypertriglyceridemic patients with diazoxide choline for 15 days resulted in marked reductions in triglycerides, total cholesterol, LDL cholesterol, and nonHDL cholesterol and a marked increase in HDL cholesterol. The bioavailability of the formulation directly contributed to the therapeutic response, with patients receiving the formulation having higher bioavailability showing improved response to treatment. In general, the longer the patient was treated with diazoxide choline, the greater the therapeutic response. Results are provided in Table 49.

Table 49. Lipid responses in diazoxide choline treated hypertriglyceridemic patients.

Parameter	Formulation U				Formulation K'			
	N	Day 7	N	Day 15	N	Day 7	N	Day 15
Triglycerides	6	-22%±14%	6	-24%±17%	6	-46%±10%	6	-39%±4%
Tot-C	6	-2%±2%	6	-9%±4%	6	-9%±3%	6	-13%±6%
LDL-C	6	1%±4%	6	-11%±4%	6	-7%±5%	6	16%±11%
HDL-C	6	5%±13%	6	10%±5%	6	12%±4%	6	13%±4%
Non-HDL-C	6	-4%±4%	6	-14%±4%	6	-15%±4%	6	-20%±8%

[00817] Treatment with diazoxide choline also resulted in lower supine and standing blood pressure. At baseline patients in the study had supine systolic blood pressure of 121 mmHg and supine diastolic blood pressure of 69 mmHg. Seven days of treatment reduced supine blood pressure to 116/62.5, an average drop in supine blood pressure of nearly 6 mmHg. Similarly, at baseline patients in the study had standing blood pressure of 123/80 mmHg. After 7 days of treatment, this was reduced to 112/75.5 mmHg, an average drop in standing blood pressure of nearly 8 mmHg.

14. Administration with Food to Reduce Adverse Events

[00818] Two studies were conducted to confirm the benefit of administration of diazoxide choline with food to reduce the incidence of adverse events. In each study, the subjects received 435 mg/day of diazoxide choline administered either as one intact 290 mg tablet and two intact 72.5 mg tablets (one tablet of formulation K' (290 mg diazoxide choline) and two tablets of formulation J) or as one intact 290 mg tablet (formulation K') and one half of a 290 mg tablet (formulation K') (latter resulting in a 145 mg dose). The dose was administered either on a fasted basis or within 15 minutes of a meal which included solid food.

[00819] In the study where the dose was administered while subjects were fasted, all of the 16 subjects receiving the drug experienced at least one adverse event. In contrast, in the study where the dose was administered with a meal, only 42% of 12 subjects experienced at least one adverse event. In particular, the incidence of gastrointestinal adverse events was substantially reduced including nausea, abdominal pain, abdominal distention, diarrhea, gastrointestinal reflux, and chest pain (table 50). Similarly, the incidence of headaches, edema, and various types of pain were also reduced or prevented when the drug was dosed with solid food. These results were observed despite the fact that there was no food effect on PK. At steady state, there is no difference in average circulating drug levels, C_{max} or T_{max} when the dose is administered with or without food. Administration with food significantly reduced the incidence of a wide range of adverse events without adversely affecting steady-state pharmacokinetics and therapeutic response. This conclusion is further supported by the data from CS04, in which diazoxide choline was administered with food, where the incidence of adverse events per subject was lower in the drug treated arm than in the placebo treated arm (Table 35).

Table 50: Incidence of adverse events when dosed under fasted or fed conditions

Adverse Event	Incidence under fasted administration	Incidence under fed administration
Nausea	25%	8%
Abdominal pain	6%	0%
Abdominal distention	6%	0%
Diarrhea	6%	0%
GERD	6%	0%
Chest pain	18%	0%
Headache	68%	8%
Pain (extremity, back, neck, joint, etc.)	31%	0%
Swelling and edema	38%	17%

15. Study of Diazoxide Choline Titration in Patients with Very High Triglycerides

15.1 Experimental Design

[00820] A clinical study was conducted in patients with very high triglycerides to test the effects of diazoxide choline controlled release tablets (DCCR tablets) alone and in

combination with fenofibrate choline. The study enrolled 44 male and female ambulatory patients who were at least 18 years old. The primary inclusion criteria included: (1) average fasting triglycerides as measured 7 and 3 days before randomization was ≥ 500 mg/dL and < 1500 mg/dL; (2) if statin treated at screening, patients must have been willing to switch to Atorvastatin 20 mg at the start of the run-in/washout and continue Atorvastatin 20 mg treatment throughout the study; (3) patients must have been willing to washout of all non-statin lipid lowering drugs; (4) fasting glucose must have been < 126 mg/dL and their HbA1c must have been $< 6.5\%$ at screening. Patients with a history of coronary bypass and/or angioplasty, myocardial infarction or stroke were eligible for enrollment.

[00821] Following screening, enrolled patients were subjected to a 6 week run-in/washout period during which subjects discontinued all non-statin lipid lowering medications and became compliant with the NCEP ATPIII TLC diet and lifestyle guidance. Patients not treated with a statin at screening remained statin naïve throughout the study. Patients were then randomized equally to one of two treatment arms: DCCR tablet or placebo. Half of the patients in each treatment arm were treated with atorvastatin (Lipitor®) 20 mg and the other half remained statin naïve.

[00822] Patients then entered a titration phase in which they received 145 mg DCCR or its equivalent placebo once daily for 10 days, followed by 217.5 mg DCCR or its equivalent placebo once daily for 10 days, and then 290 mg DCCR or its equivalent placebo for the remainder of the study. Following the titration phase, patients were treated with a maintenance dose for 9 weeks, followed by 6 additional weeks of treatment with the addition of 135 mg fenofibrate choline (Trilpix®) in patients who were statin naïve. The total duration of treatment for all patients was 18 weeks (126 days). Dosing occurred once daily, typically in the morning with food.

[00823] Collected patient data included levels of fasting triglycerides, Apo B, total cholesterol, VLDL cholesterol, LDL cholesterol, HDL cholesterol, and non-HDL cholesterol, all measured as percent change from baseline to both day 84 and day 126 (after 12 and 18 weeks of treatment).

[00824] DCCR tablets were packaged in Formpack® cold formed blister packs. The blister packs consisted of a cold-formable primary package that included at least one layer of aluminum foil, one layer of polyvinylchloride and one layer of nylon. Blisters were sealed with a flexible aluminum foil affixed with an adhesive, which provided for effective protection of the product from light, moisture, oxygen and other gases. Each tablet of the daily dose was packaged in a separate blister. The blister packaged DCCR was then assembled into a kit that provided clear instruction on dosing and administration. DCCR used in the titration phase of treatment was packaged into a separate titration kit that included the daily dose of each dose strength used during the titration phase. The separate packaging of drug into a titration pack allowed for a high level of patient compliance during the titration phase of the study, thereby improving the likelihood that the patient would not experience an adverse event that might lead to forgoing continued treatment.

15.2 Lipid Changes in DCCR + Fenofibrate Patients vs. Placebo + Fenofibrate Patients

[00825] Lipid data collected from patients in the DCCR + fenofibrate arm of the study from baseline to day 126 were compared with lipid data from patients in the placebo + fenofibrate arm from day 84 to day 126, i.e., the period in which patients were treated with placebo and fenofibrate. Patients in the DCCR + fenofibrate arm showed greater median decreases in levels of triglycerides (TG), total cholesterol (TC), non-HDL-C and VLDL-C compared with patients in the placebo + fenofibrate arm. Patients in the DCCR + fenofibrate arm also showed a greater median increase in HDL-C compared with patients in the placebo + fenofibrate arm. However, the DCCR + fenofibrate arm had smaller median increases in levels of LDL-C compared to the placebo + fenofibrate arm. Median percentage changes for each lipid measure is summarized in Table 51 below.

Table 51. Median Percentage Changes from Baseline for DCCR vs. Placebo (with addition of fenofibrate)

	DCCR + Fenofibrate (Median Change)	Placebo + Fenofibrate (Median Change)
TG	-77.8%	-52%
TC	-21%	-11.3%
Non-HDL-C	-33.8%	-15.9%
VLDL-C	-84.5%	-50.5%
LDL-C	+41.5%	+56.7%
HDL-C	+37.5%	+21.4%

[00826] Thus administration of DCCR with fenofibrate choline shows an additive effect for decreasing levels of TG, TC, non-HDL-C and VLDL-C, as well as increasing levels of LDL-C and HDL-C. Figure 27 shows a graph summarizing the median changes in lipid levels for the DCCR arm compared with placebo arm.

15.3 Lipid Changes in Patients receiving DCCR + Fenofibrate vs. Omega 3 Fatty Acids + Fenofibrate

[00827] Lipid data collected from both arms of the study of DCCR + fenofibrate (from baseline to day 126; described in 15.1), were compared with published lipid data from a double-blind placebo-controlled study in which prescription omega-3 fatty acids (p-OM3; Lovaza®) and fenofibrate and were co-administered to patients with very high triglyceride levels (≥ 500 mg/dL; total of 128 men and women between the ages of 18 and 79 years of age) (Roth et al., J Cardiovasc Pharmacol. 2009 Sep;54(3):196-203; hereinafter "the Roth study"). All patients in the Roth study had a 6 week diet lead-in period, followed by random assignment to receive either p-OM3 (4 g/day) and fenofibrate (130 mg/day) or placebo (4 g/day) and fenofibrate (130 mg/day) for 8 weeks.

[00828] The median decrease in triglycerides, total cholesterol, non-HDL-C and VLDL-C for administration of fenofibrate and p-OM3 was similar to that of fenofibrate-only controls in both the Roth Study and the DCCR study. However, the median decrease observed for all of these lipid levels was much greater with DCCR and fenofibrate co-administration, thus showing a strong additive effect on the reduction of triglyceride levels.

[00829] The median increase in HDL-C was drastically higher for DCCR + fenofibrate vs. p-OM3 + fenofibrate (about a 38% increase vs. about a 2% decrease, respectively). These data show that co-administration of DCCR and fenofibrate provide an substantial additive effect on increasing levels of HDL-C.

[00830] The median increase in levels of LDL-C were lower in the DCCR study compared with the Roth Study (about a 42% increase for DCCR + fenofibrate vs. about a 48% increase for p-OM3 + fenofibrate). This reduced elevation of LDL-C with DCCR + fenofibrate treatment may provide a decreased risk of major cardiovascular events in these patients. The data from the Roth study and the study examining the combination of DCCR and fenofibrate are summarized in Table 53 below and in Figure 29.

Table 53. Median Percentage Changes from Baseline for DCCR + fenofibrate vs. fenofibrate-only

	DCCR + Fenofibrate (Median Change)	p-OM3 + Fenofibrate (Median Change)
TG	-77.8%	-60.8%
TC	-21%	-8.0%
Non-HDL-C	-33.8%	-8.2%
VLDL-C	-84.5%	-57.6%
LDL-C	+41.5%	+48.2%
HDL-C	+37.5	-1.9%

16. Pharmacokinetics of Diazoxide Choline in Humans

[00831] A pharmacokinetic study was conducted in 9 healthy male and female subjects who were between 18 to 75 years of age. In order to be included in the study, the subjects were required to have body mass index (BMI) between 22 and 35 kg/m², inclusive, and were required to weigh at least 50 kg. They had to be generally healthy as documented by the medical history, physical examination, vital sign assessments, 12-lead electrocardiogram (ECG), and clinical laboratory assessments. Their fasting triglyceride had to be ≥ 100 mg/dL and ≤ 1500 mg/dL, their fasting glucose ≤ 110 mg/dL, and their HbA1c ≤ 6.0 %.

[00832] Subjects were dosed for 10 days with a DCCR formulation. Each day they were administered 290 mg DCCR as two DCCR 145 mg tablets formulated as shown in

Table 54. The study medication was taken orally, once daily, in the morning, within 15 minutes of a meal that included solid food. Pharmacokinetic samples were collected before initiation of treatment, and pre-dose after 2, 4, 6, and 8 days into the study. On the 10th day of dosing, pharmacokinetic samples were collected pre-dose and 2, 4, 6, 8, 10, 12, 15 and 24 hours post-dosing.

Table 54. DCCR tablet composition for pharmacokinetic studies

Component	% wt
Diazoxide choline	26.4%
PEO N750	30%
PEO 303	15%
Dibasic calcium phosphate (Encompress)	5%
Talc	2%
Colloidal silicon dioxide	1%
Microcrystalline cellulose	19.1%
Magnesium Stearate	1.5%
Opadry white (tablet coating)	3%

[00833] Steady state circulating drug levels were observed between 8 and 9 days after the start of treatment. Circulating diazoxide concentrations were measured using a sensitive, precise, reproducible, validated assay. The following pharmacokinetic variables were measured on study day 10 (representing steady state): $AUC_{(0-24h(ss))}$, the area under the plasma concentration-time curve from time zero to 24 hours at steady state, using the linear trapezoidal rule; $C_{max(ss)}$, the maximum or peak measured plasma concentration at steady state; $C_{min(ss)}$, the minimum or trough plasma concentration at steady state; $C_{av(ss)}$, the average plasma concentration at steady state obtained by dividing $AUC_{(0-24h(ss))}$ by 24; Fluctuation Index, the fluctuation at steady state calculated as $[(C_{max(ss)} - C_{min(ss)}) / C_{av(ss)}]$; and % Peak-to-Trough Fluctuation, the Fluctuation Index x 100. The collected data are summarized in Table 55 below.