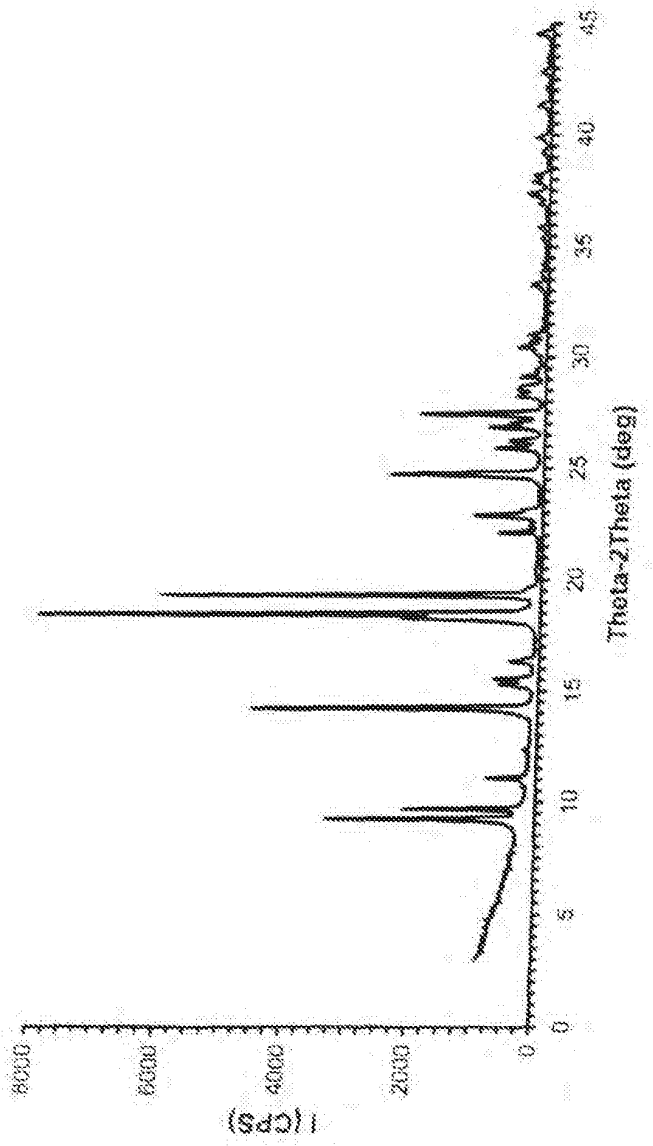
I (CPS)
8000
6000
4000
2000
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 4C

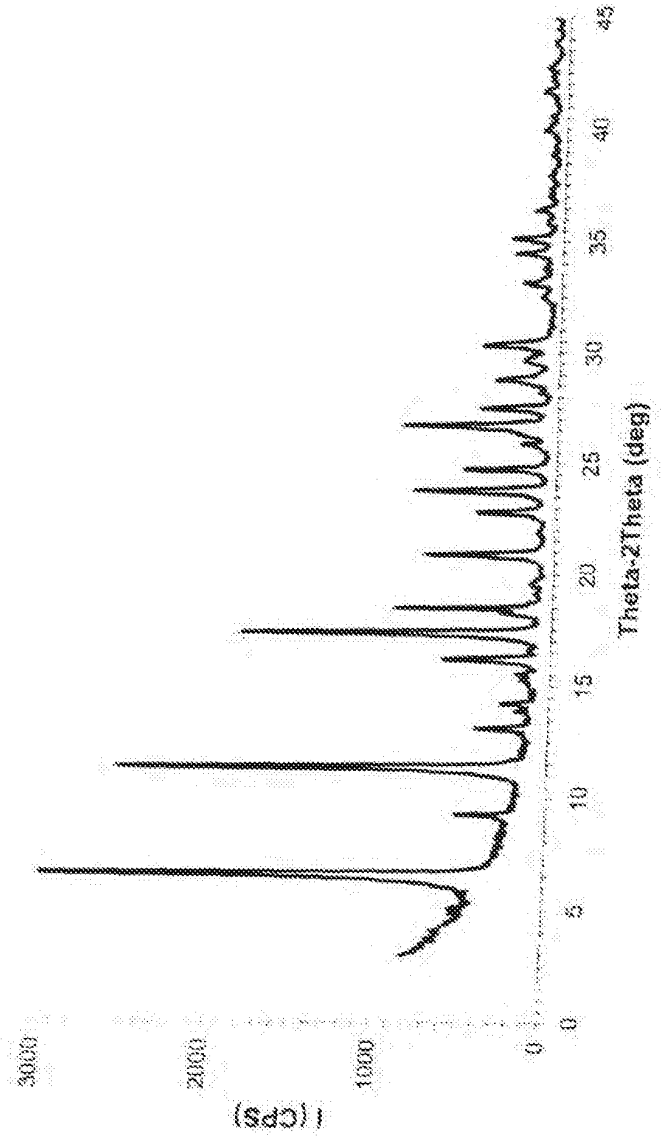

FIG. 4D

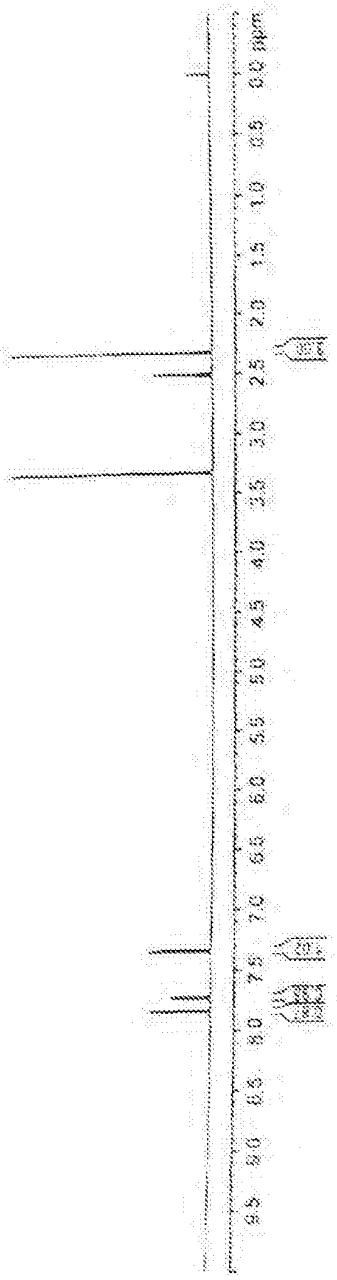

FIG. 5A

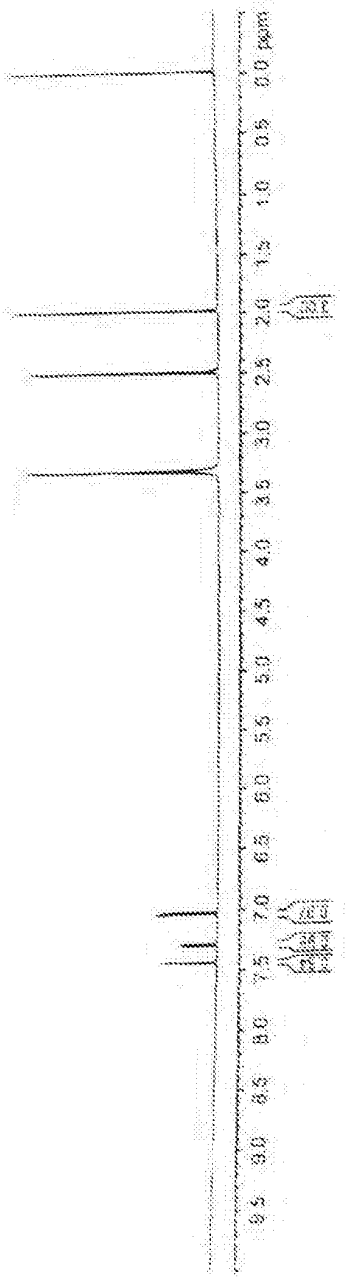

FIG. 5B

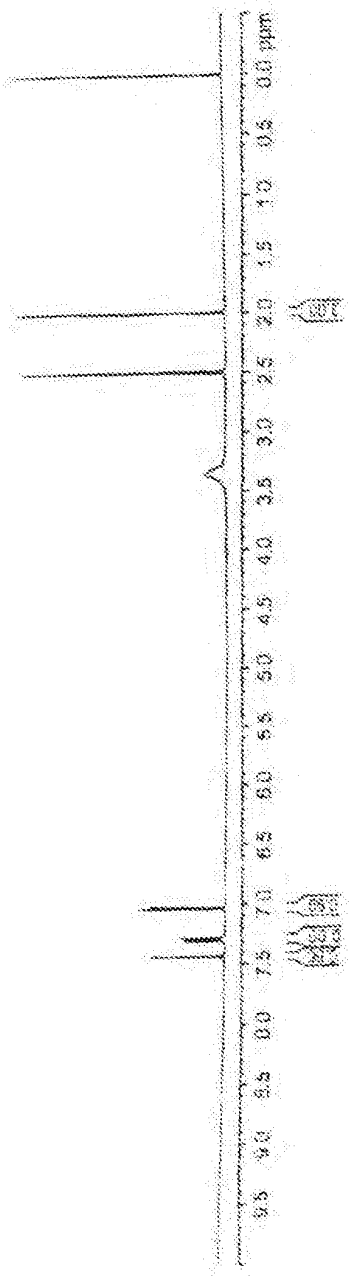

FIG. 5C

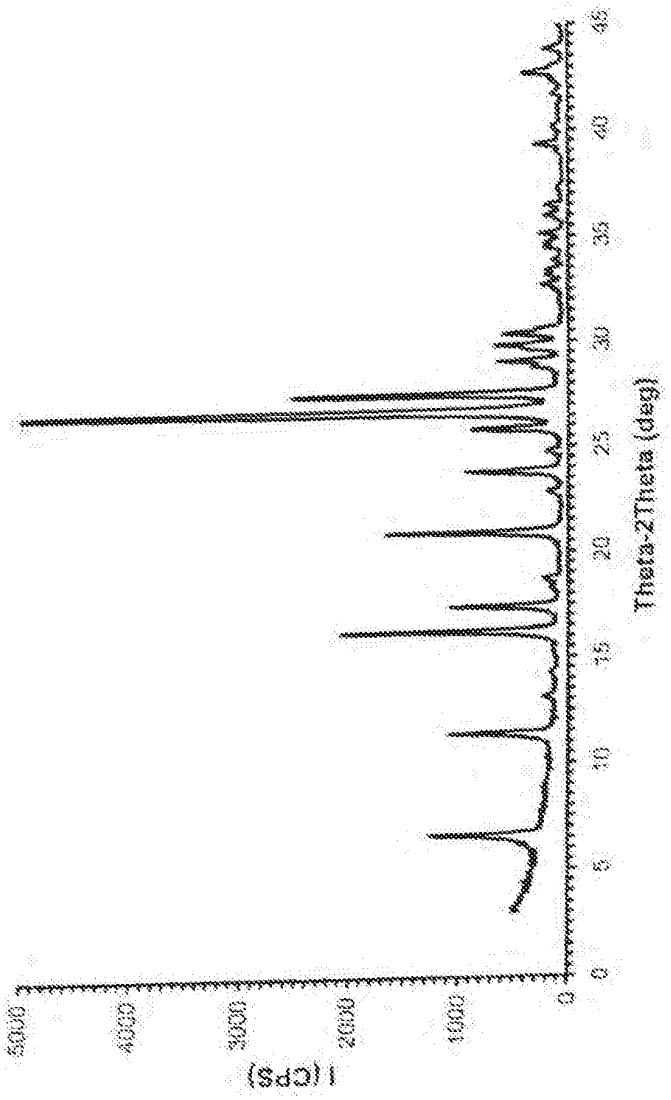
I (CPS)
5000
4000
3000
2000
1000
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 6A

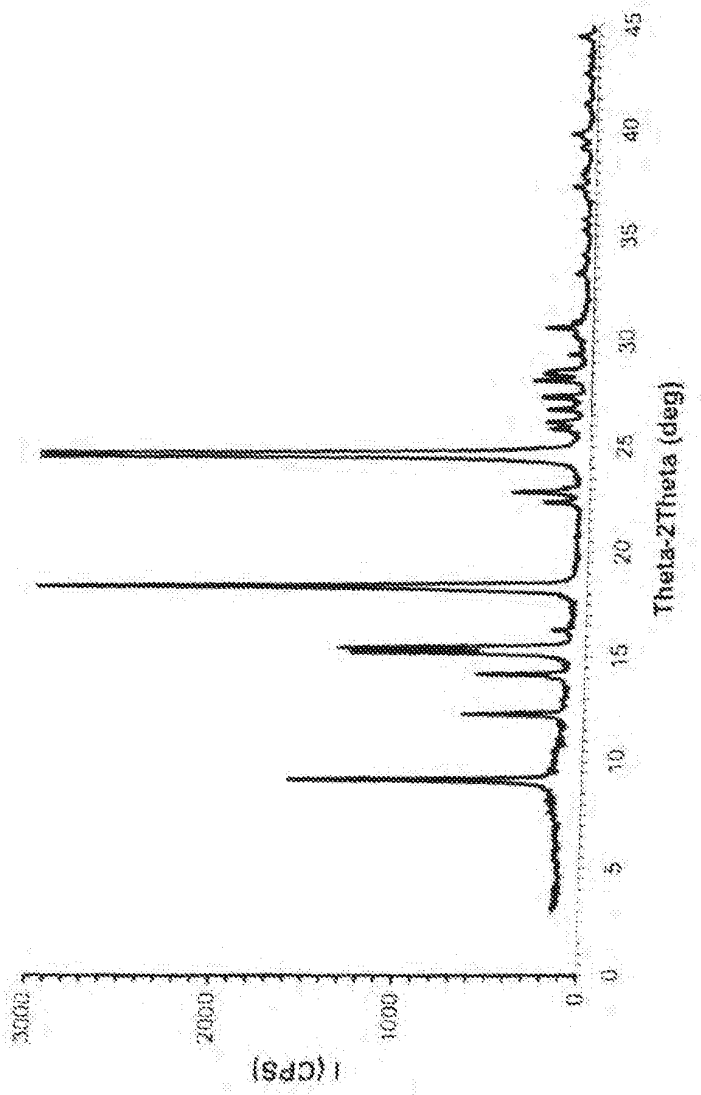

FIG. 6B

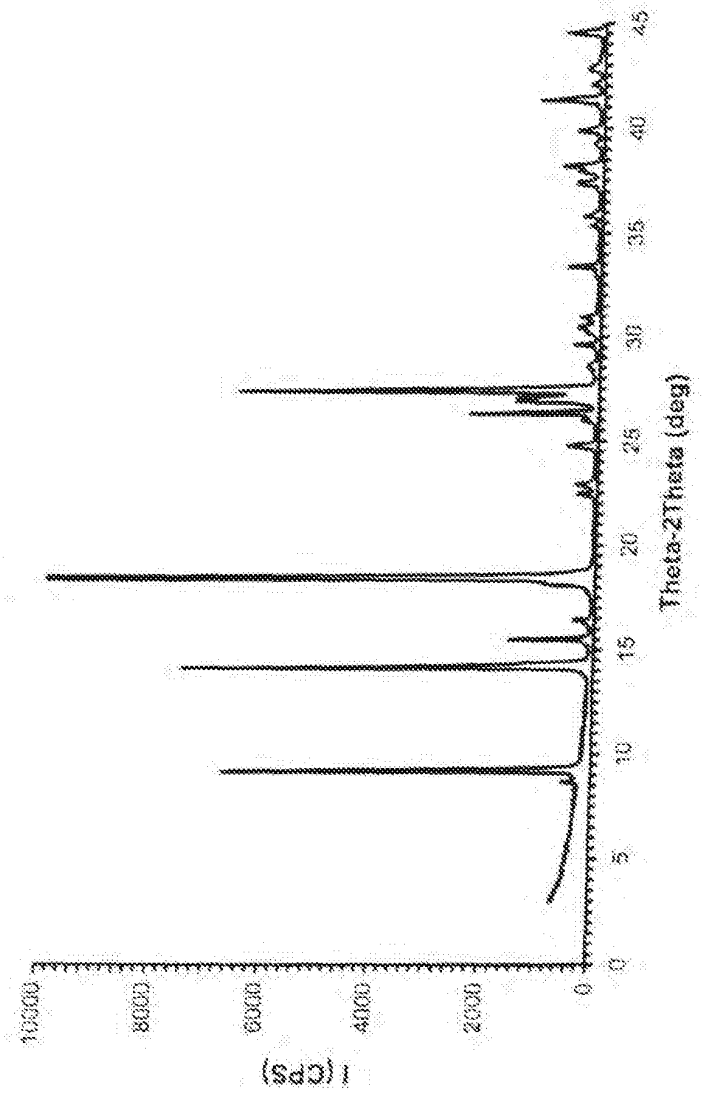
I (CPS)
10000
8000
6000
4000
2000
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 6C

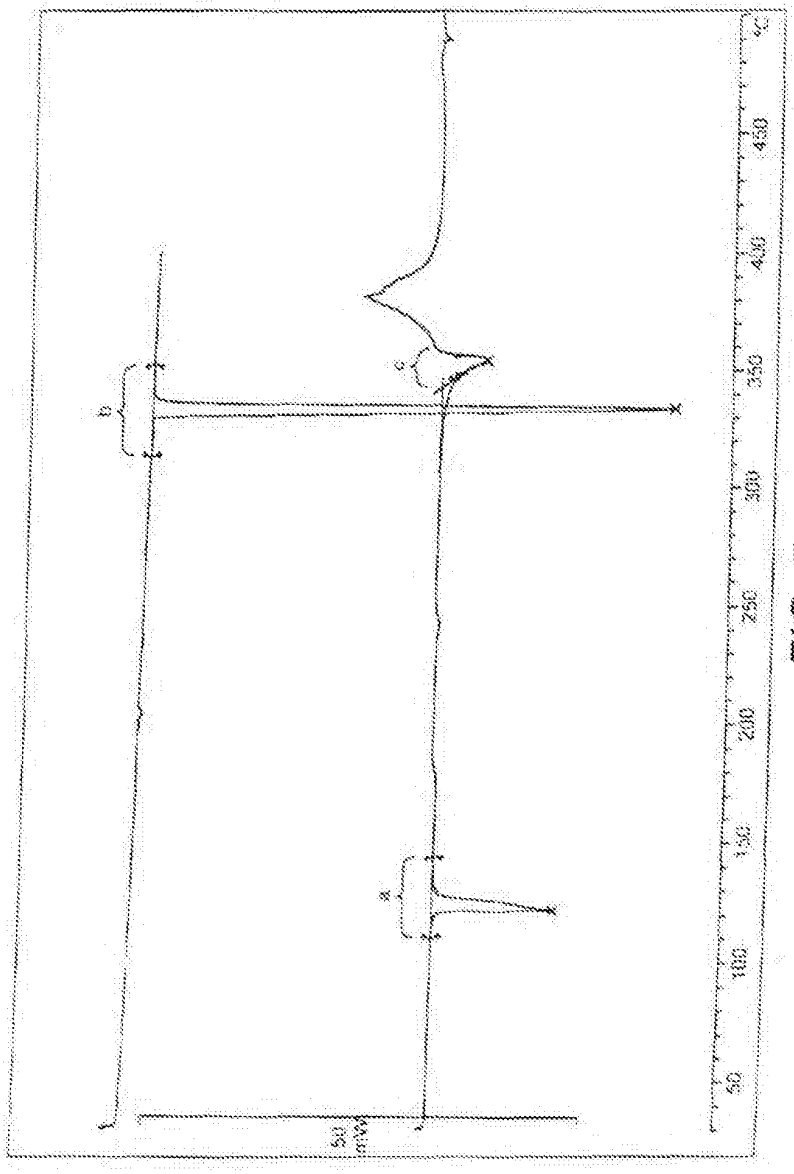

FIG. 7

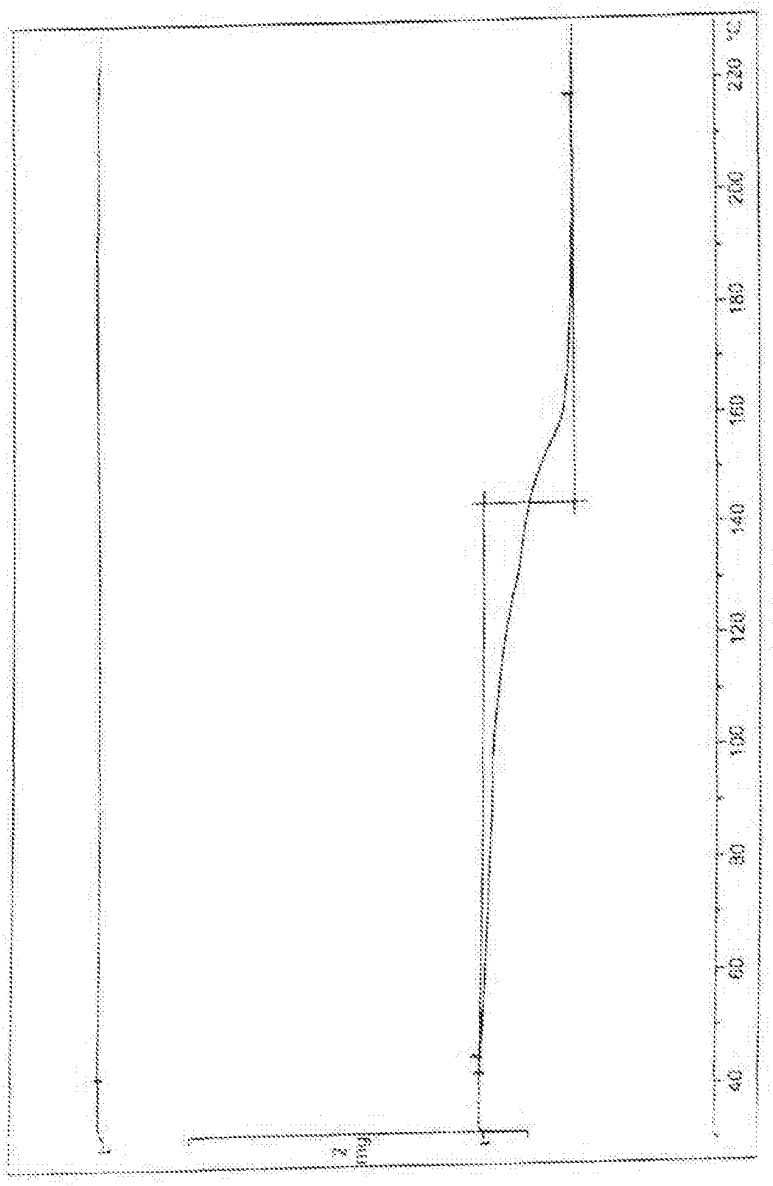

FIG. 8

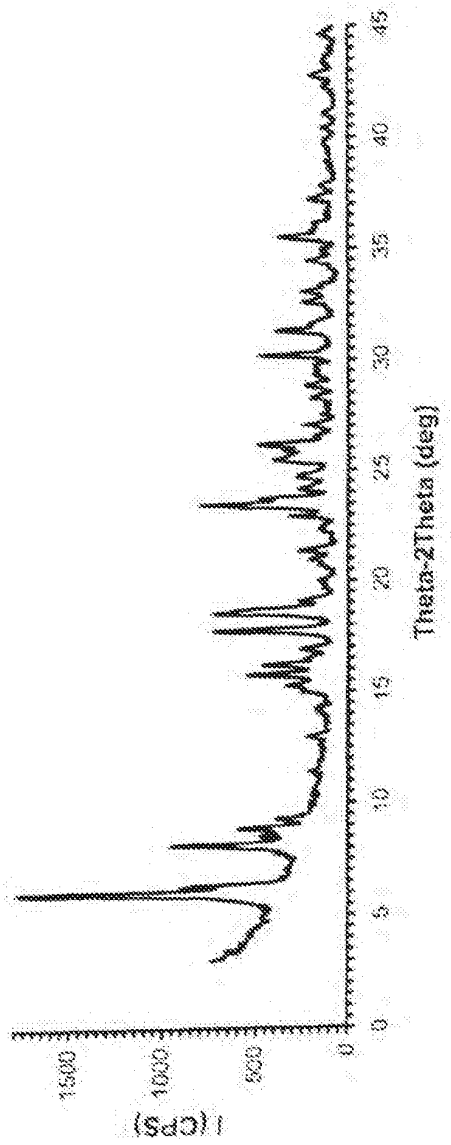

FIG. 9A

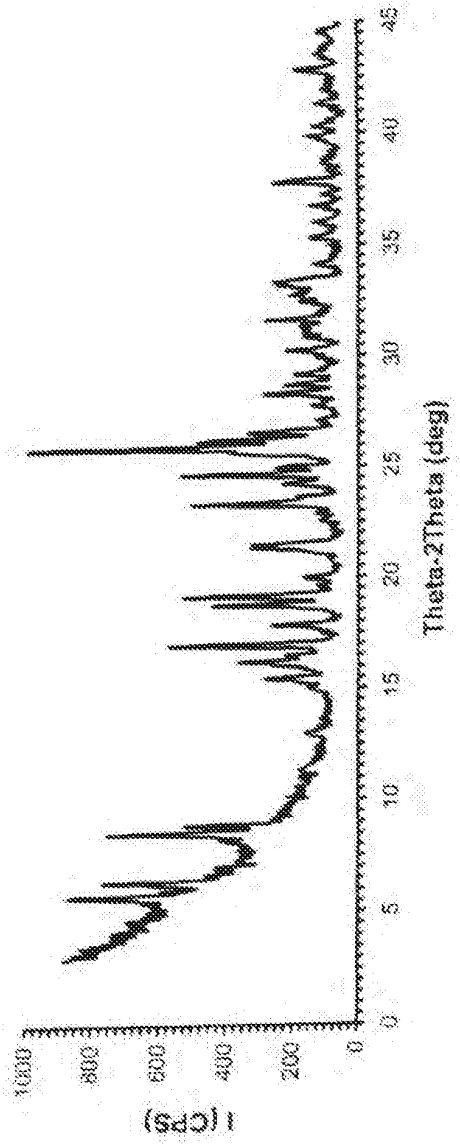
I (CPS)
1000
800
600
400
200
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 9B

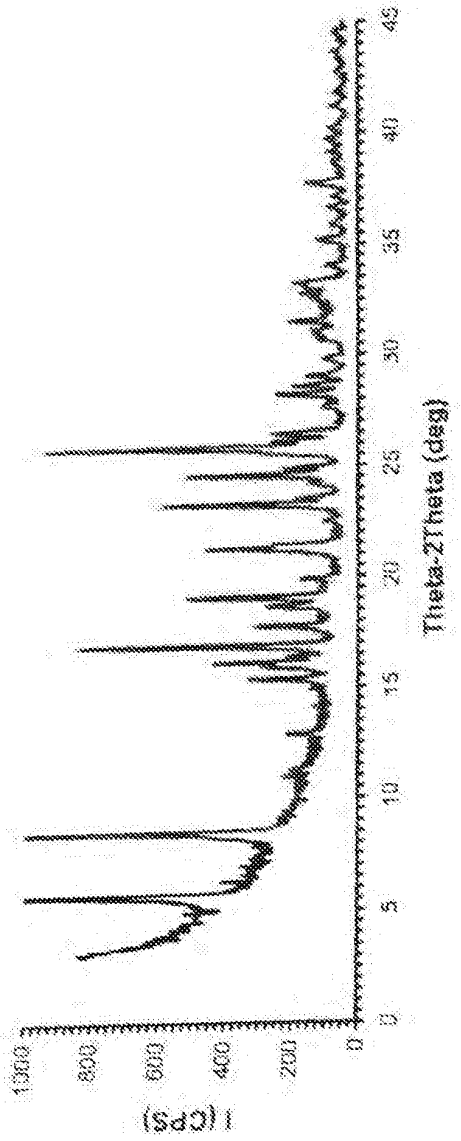
I (CPS)
1000
800
600
400
200
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 9C

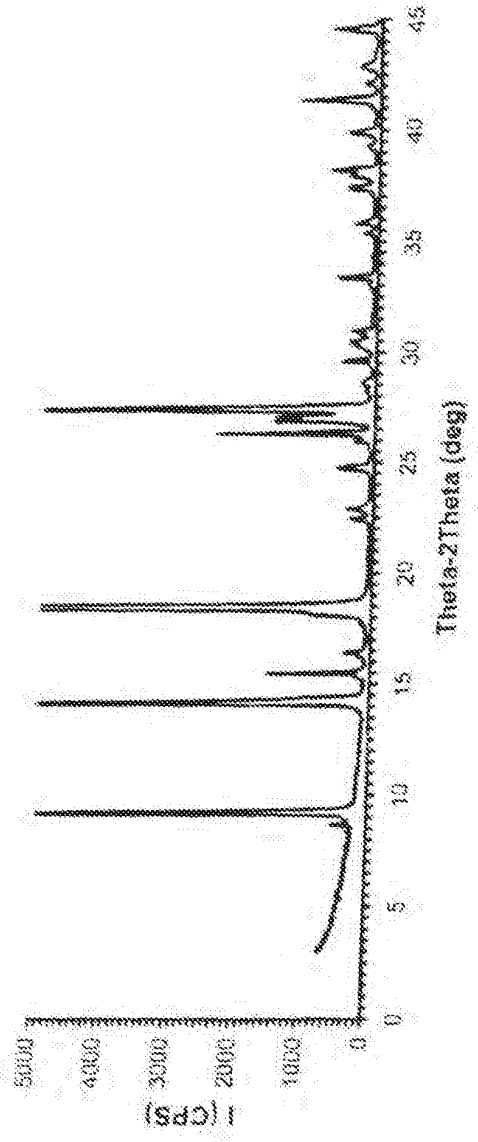
I (CPS)
5000
4000
3000
2000
1000
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 10A

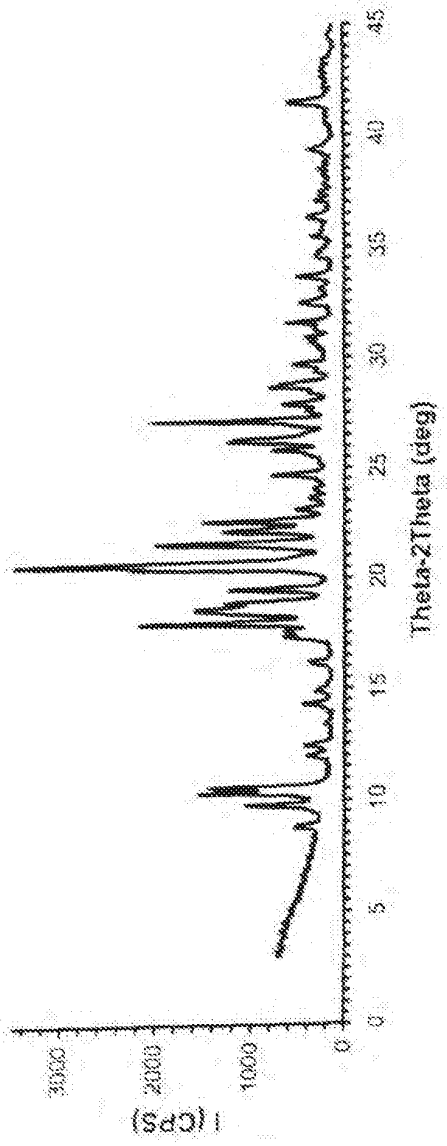

FIG. 10B

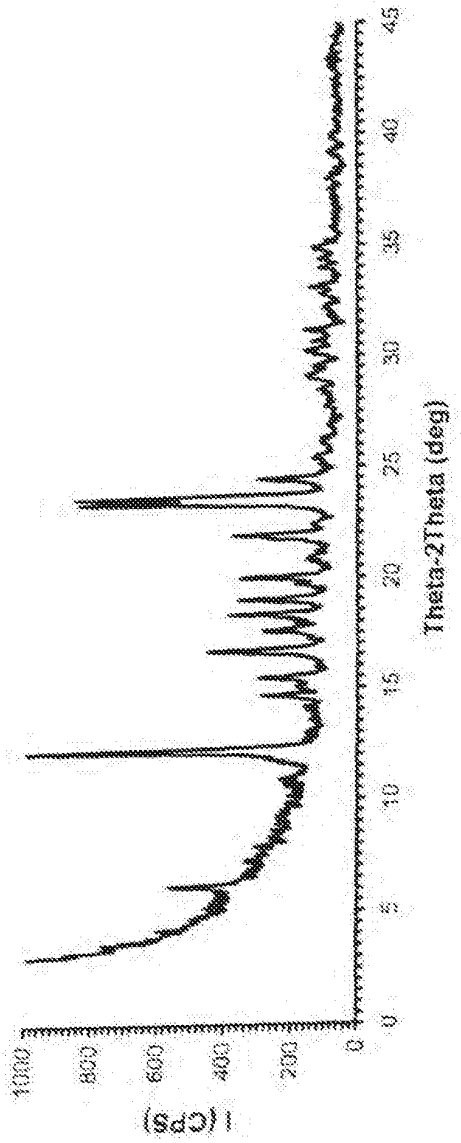
I (CPS)
1000
800
600
400
200
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 10C

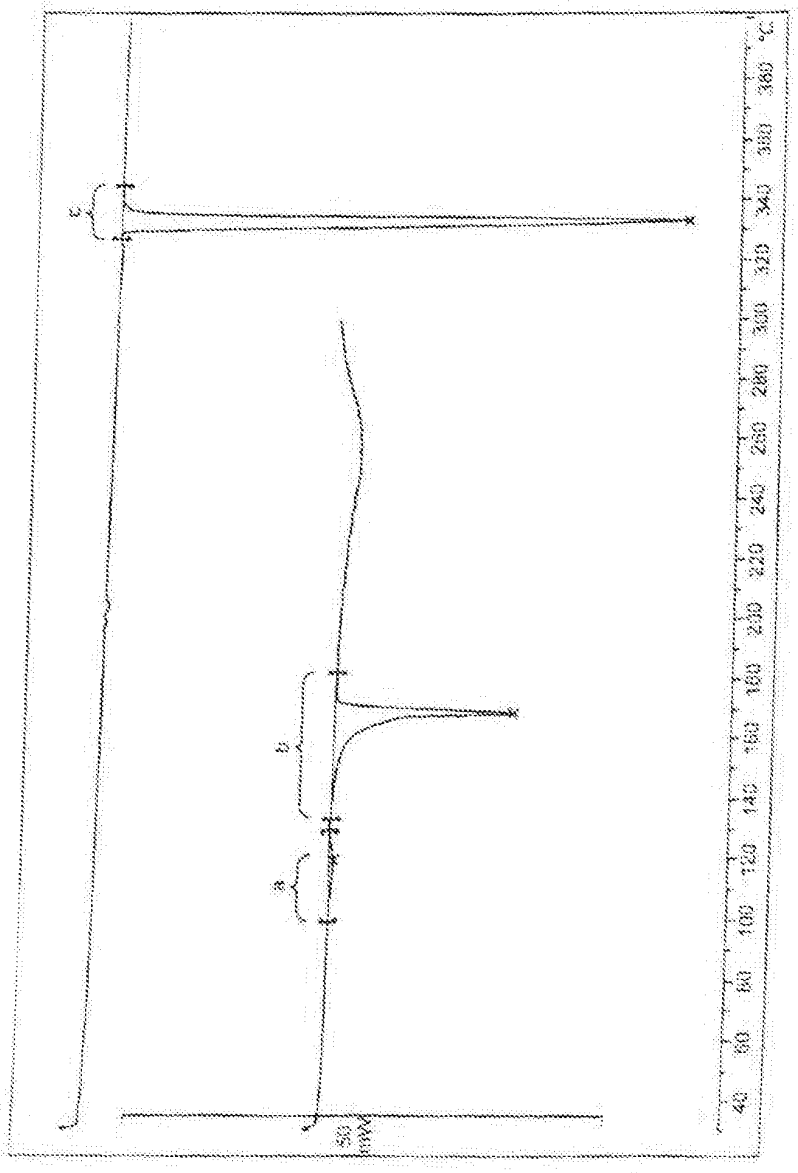
a
b
c
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
°C
50 mW

FIG. 11

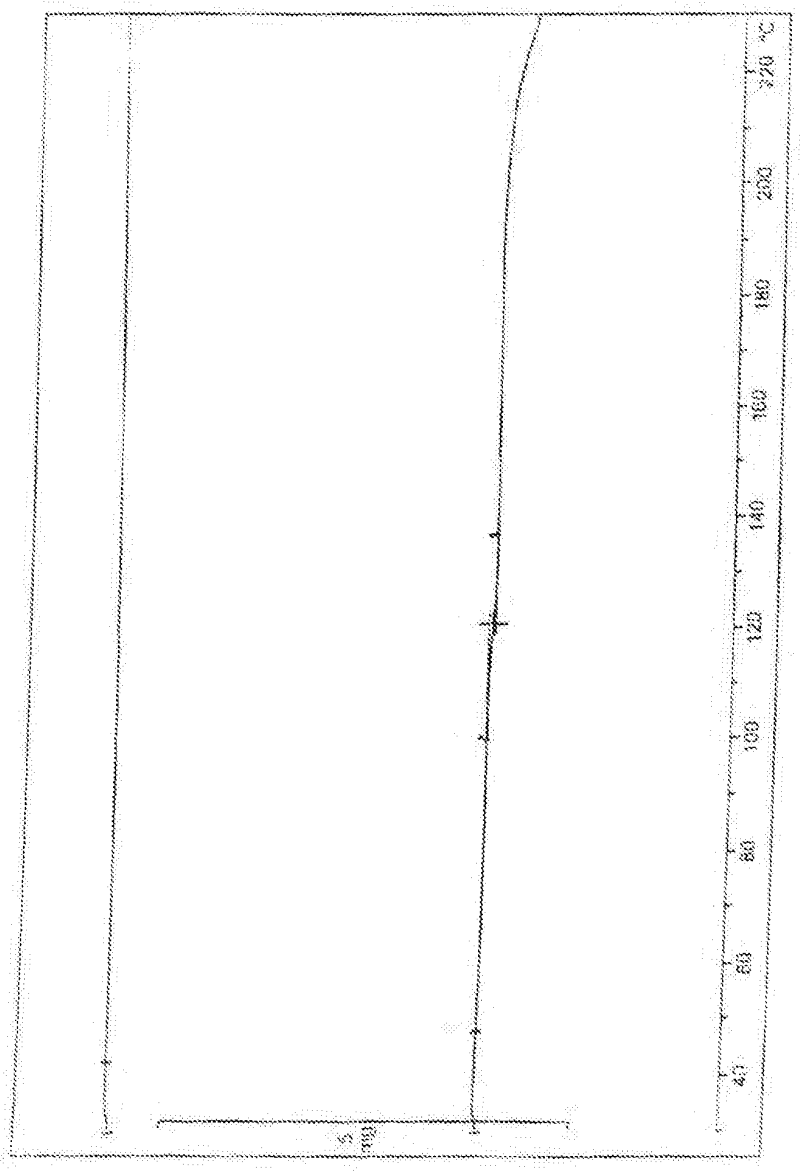

FIG. 12

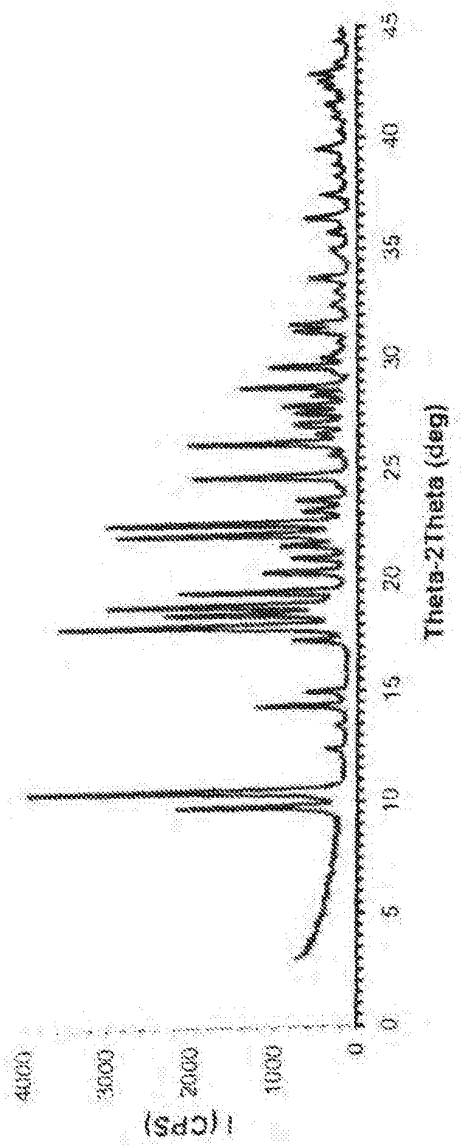
I (CPS)
4000
3000
2000
1000
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 13A

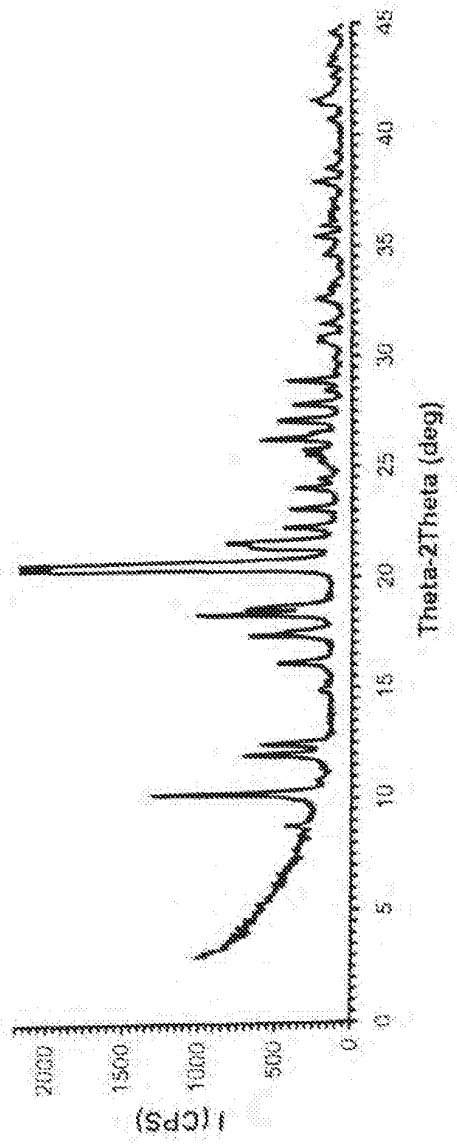
I (CPS)
2000
1500
1000
500
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 13B

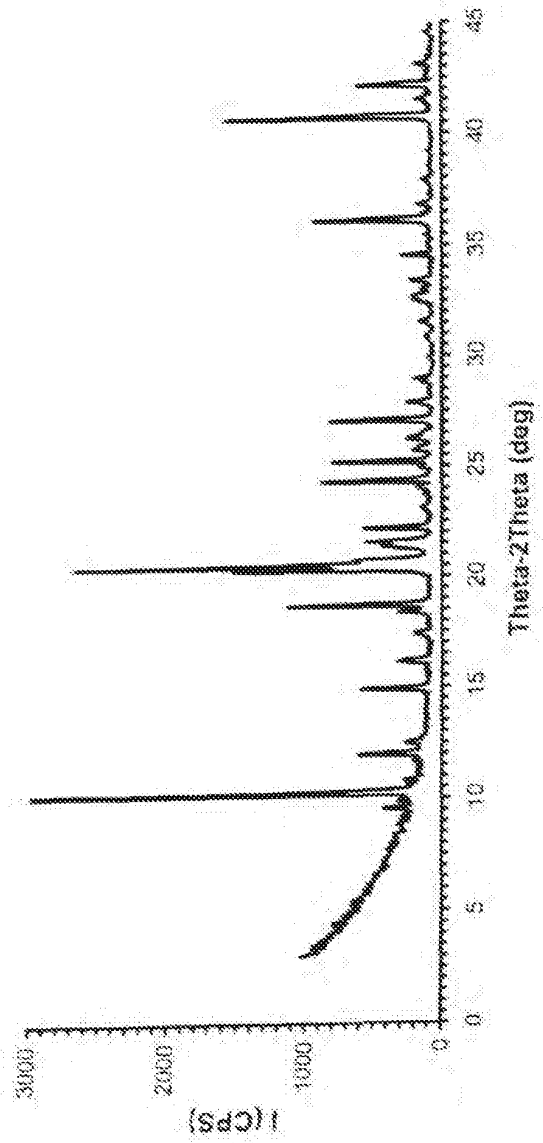

FIG. 13C

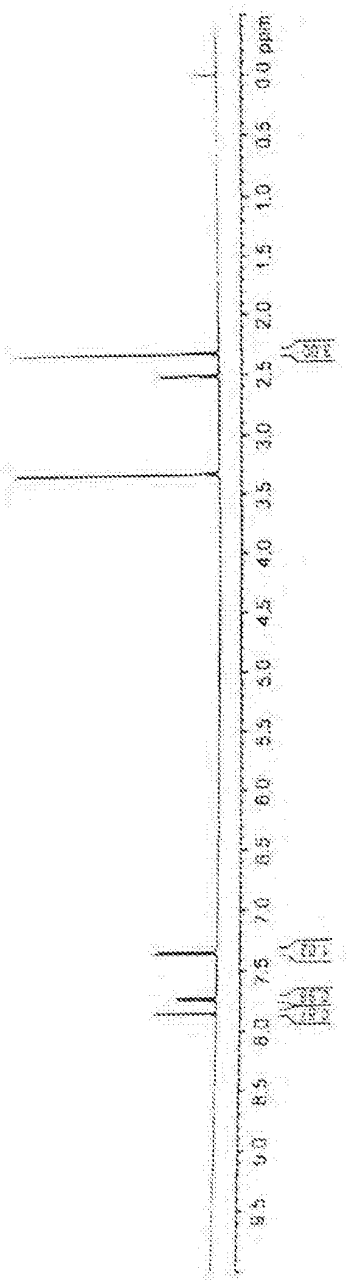

FIG. 14A

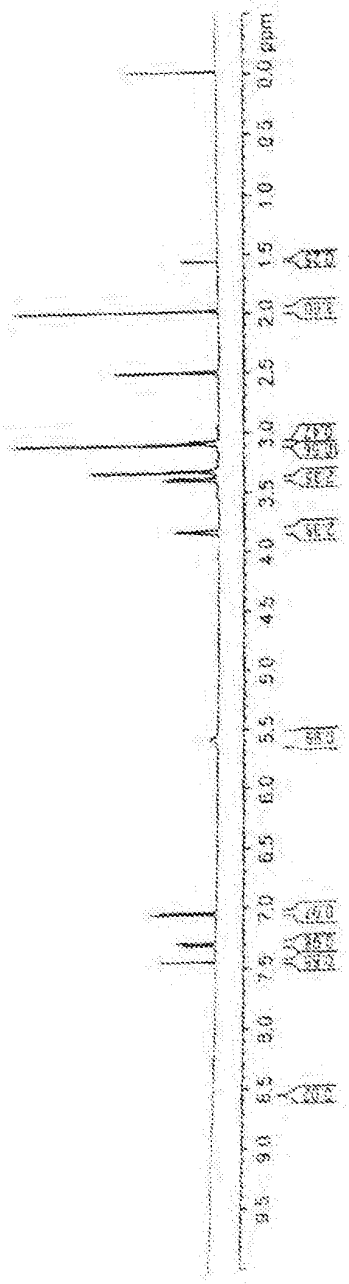

FIG. 14B

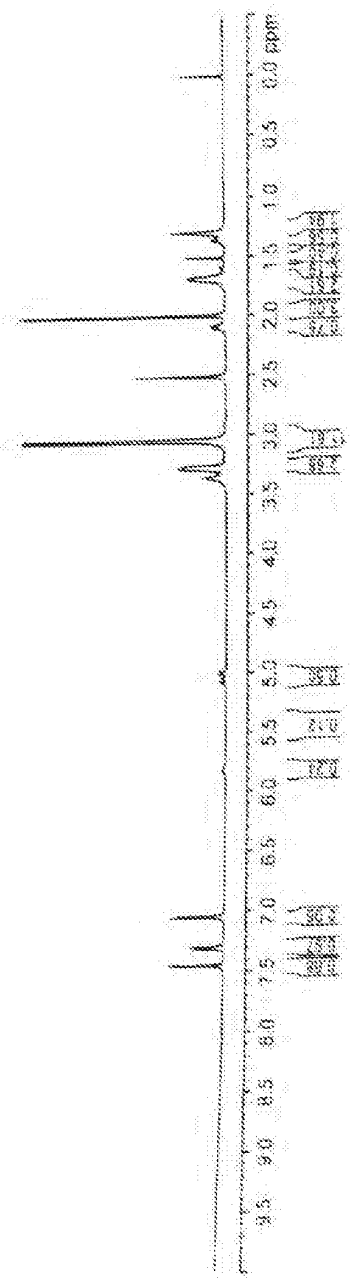

FIG. 14C

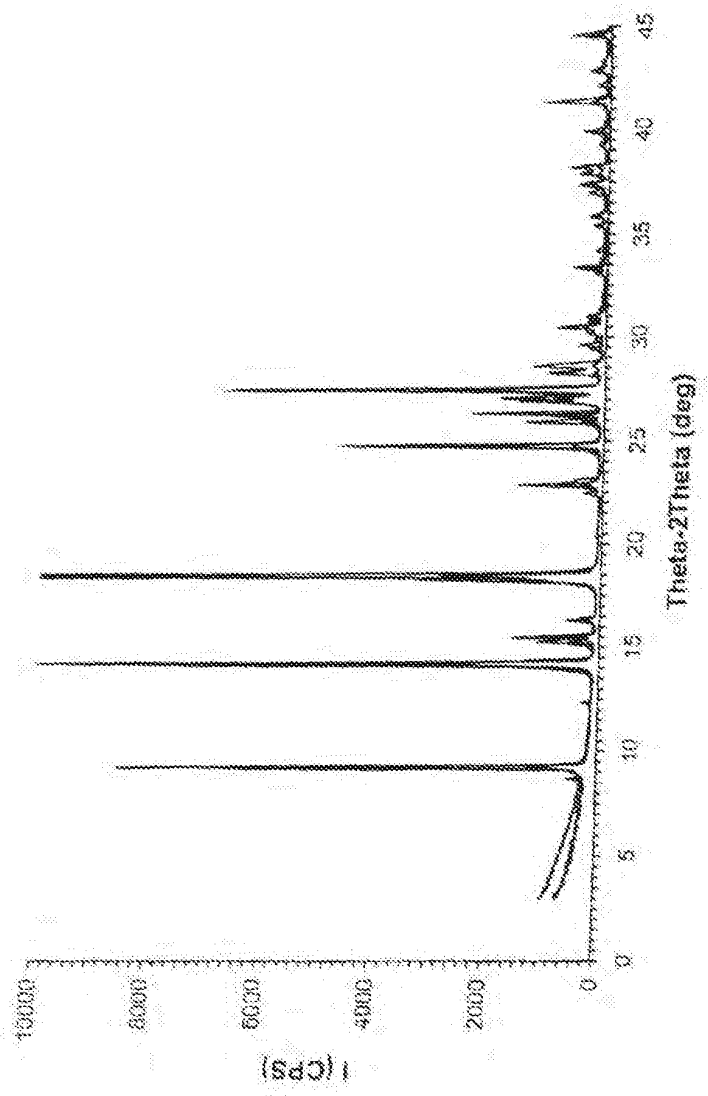
I (CPS)
10000
8000
6000
4000
2000
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 15A

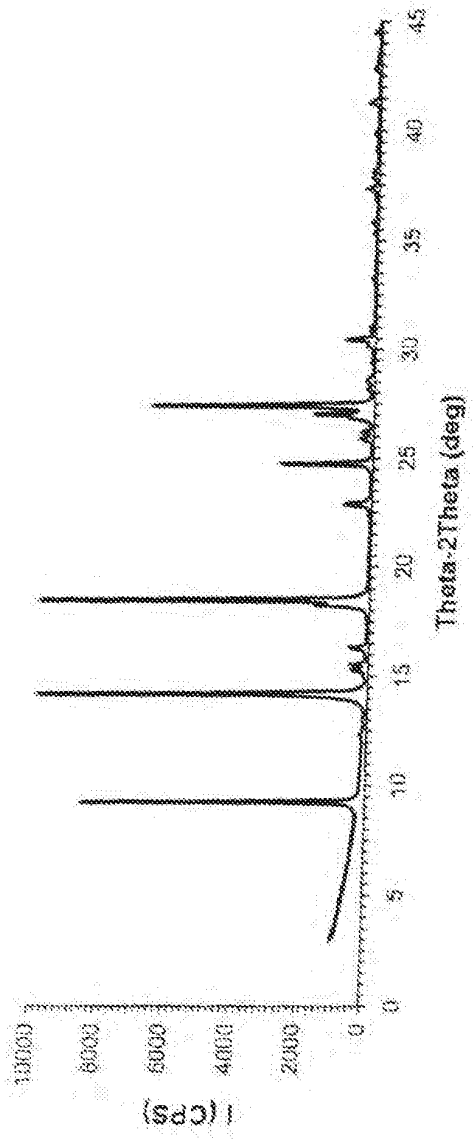
I (CPS)
10000
8000
6000
4000
2000
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 15B

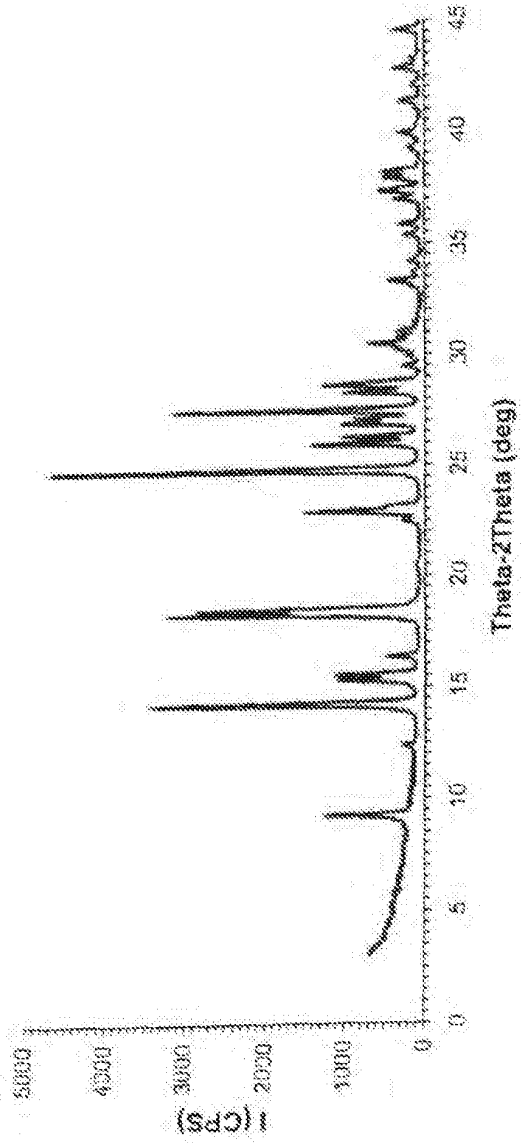
I (CPS)
5000
4000
3000
2000
1000
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 15C

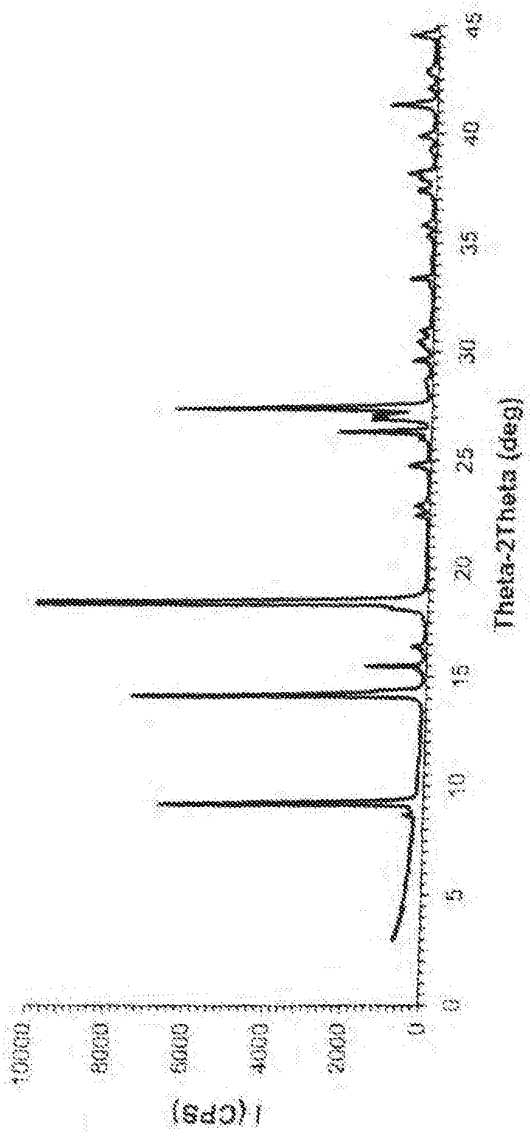
I (CPS)
10000
8000
6000
4000
2000
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 15D

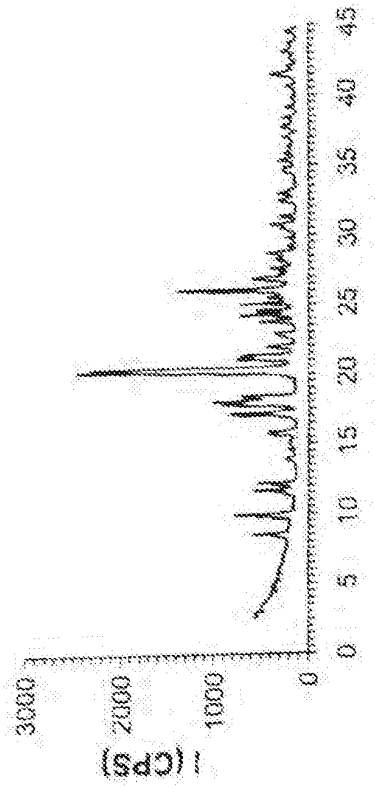

FIG. 16A

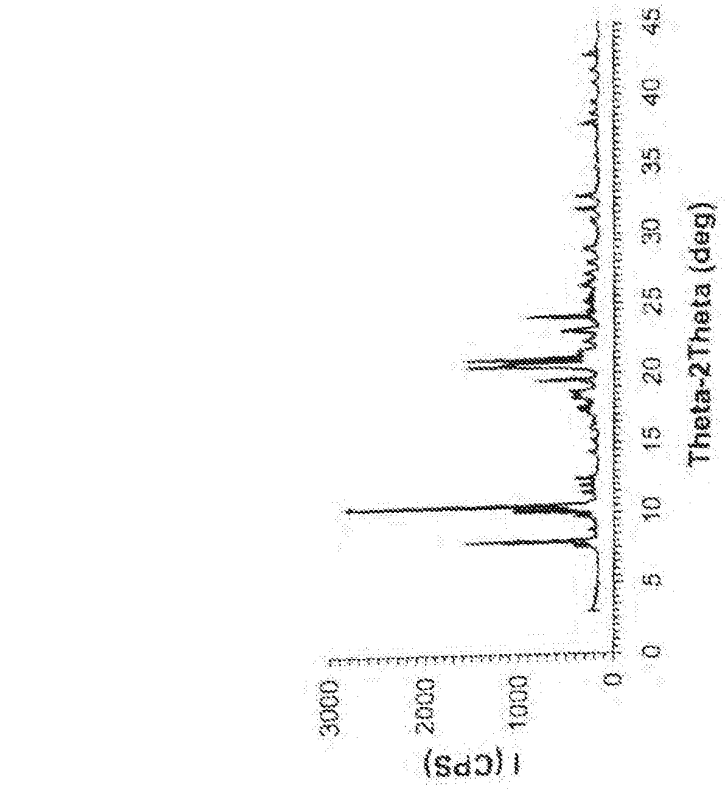

FIG. 16B

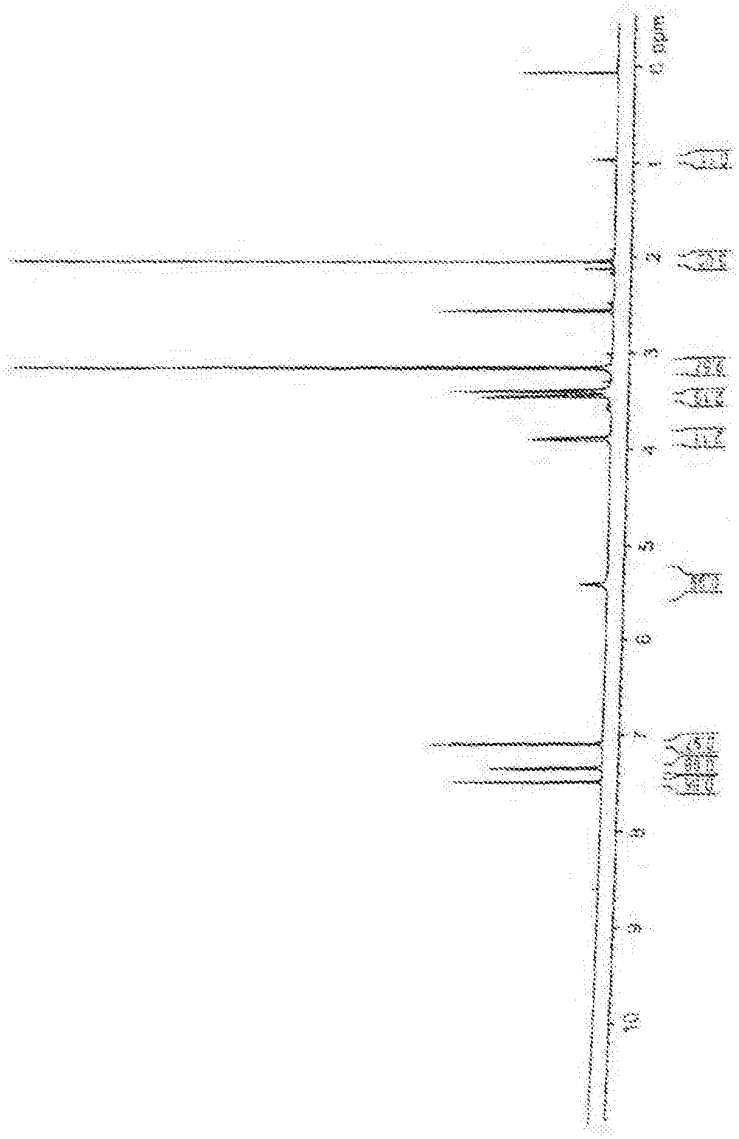

FIG. 17A

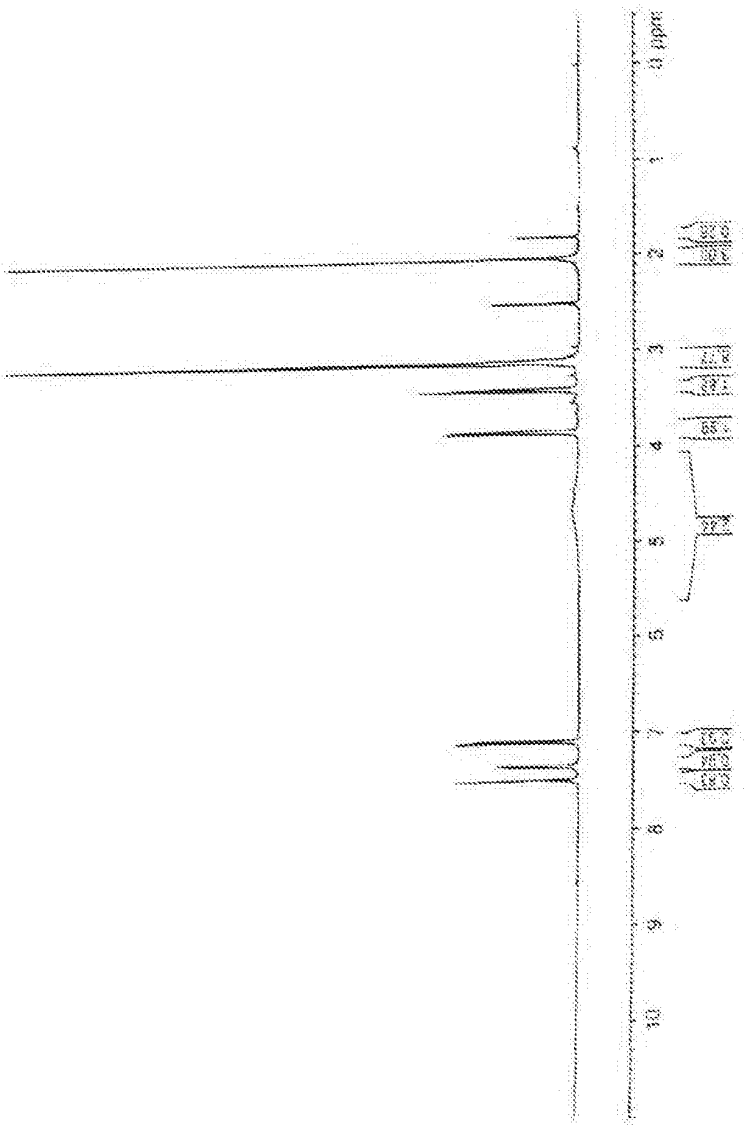

FIG. 17B

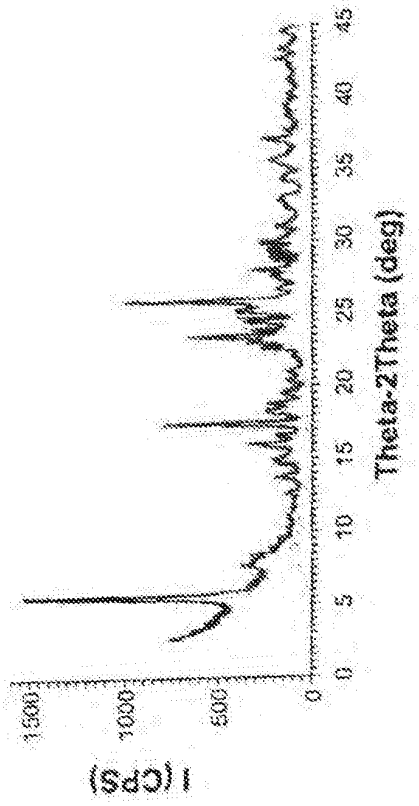

FIG. 18A

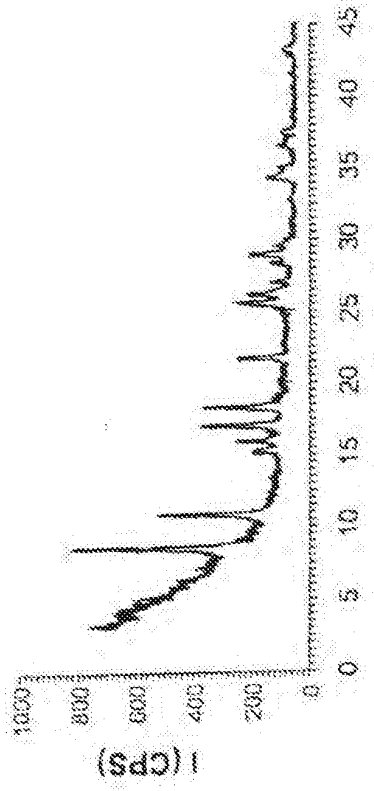
I (CPS)
1000
800
600
400
200
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 18B

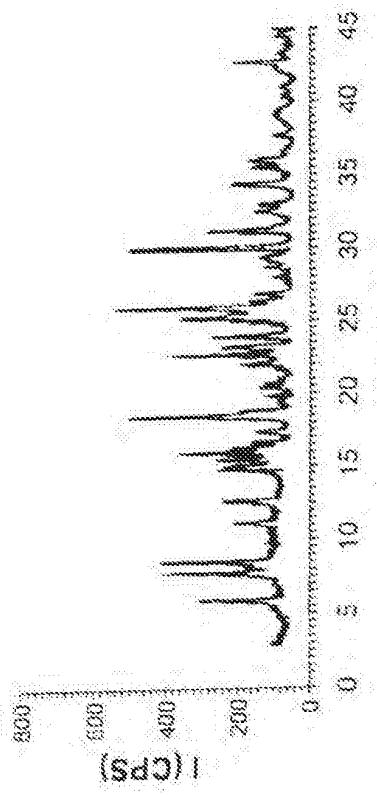

FIG. 18C

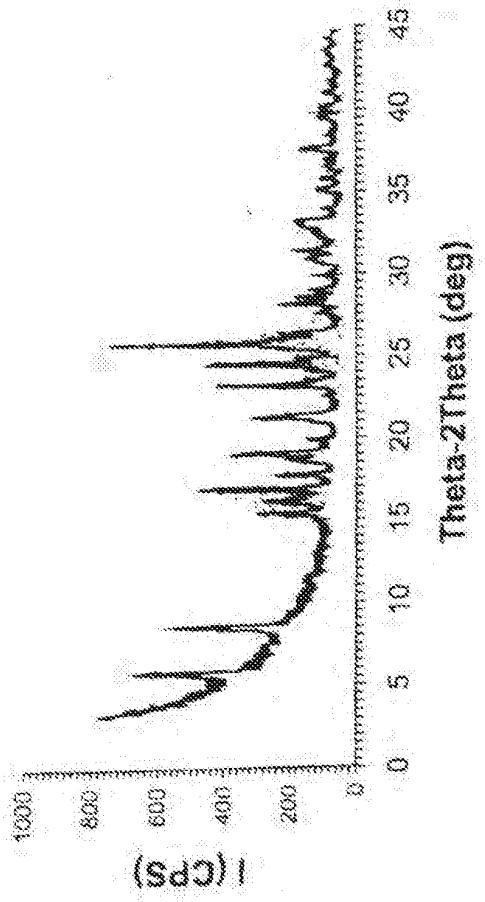
I (CPS)
1000
800
600
400
200
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 19A

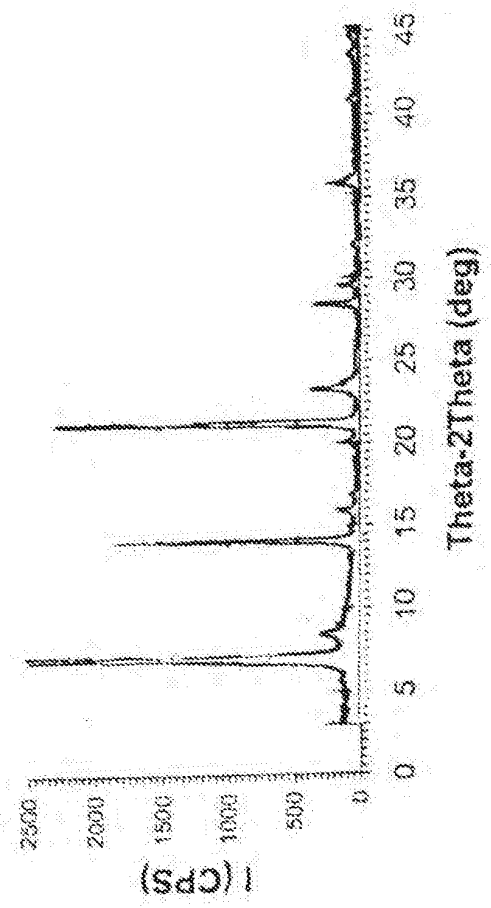
I (CPS)
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 19B

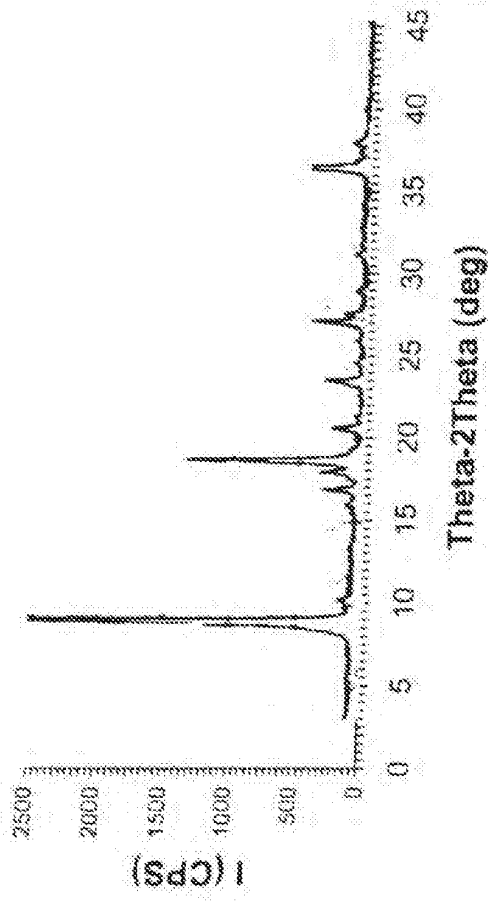
I (CPS)
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
35
40
45
Theta-2Theta (deg)

FIG. 19C

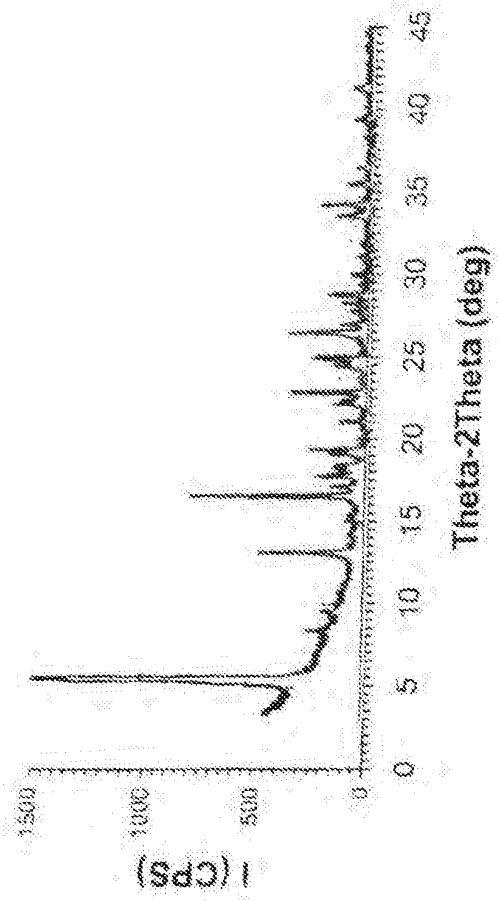

FIG. 19D

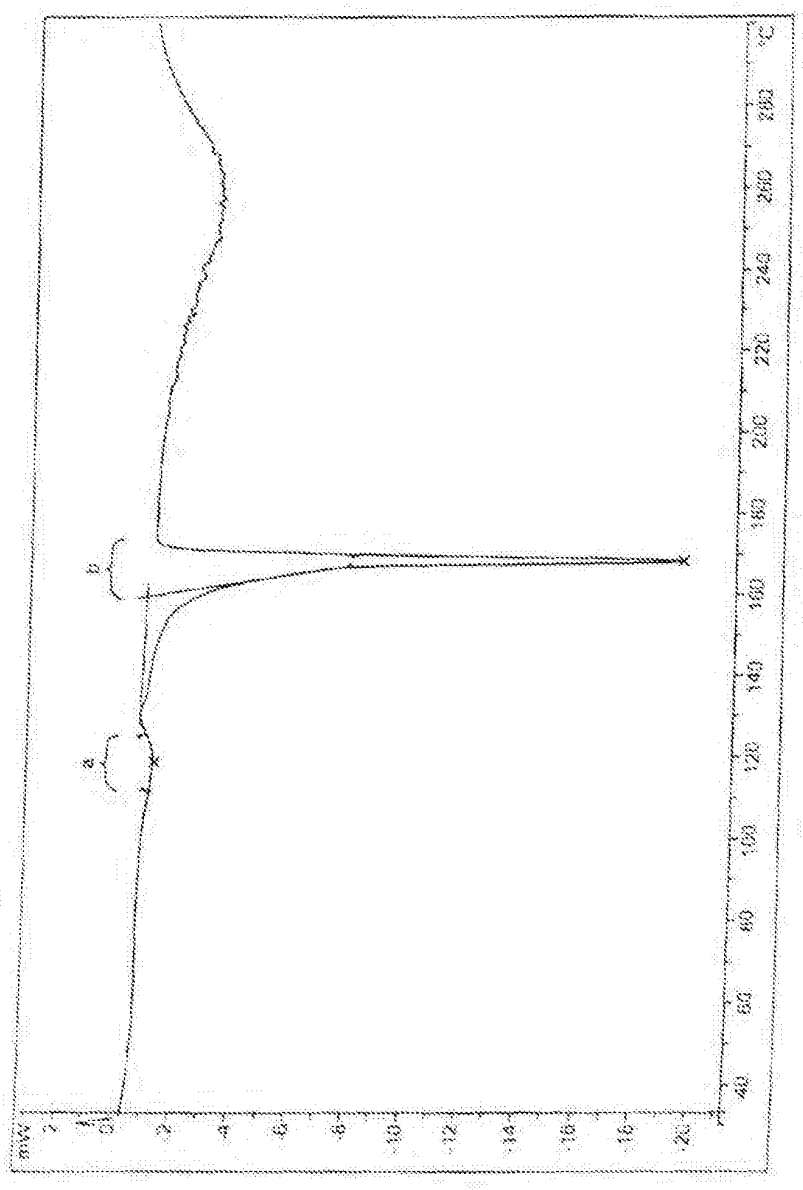

FIG. 20

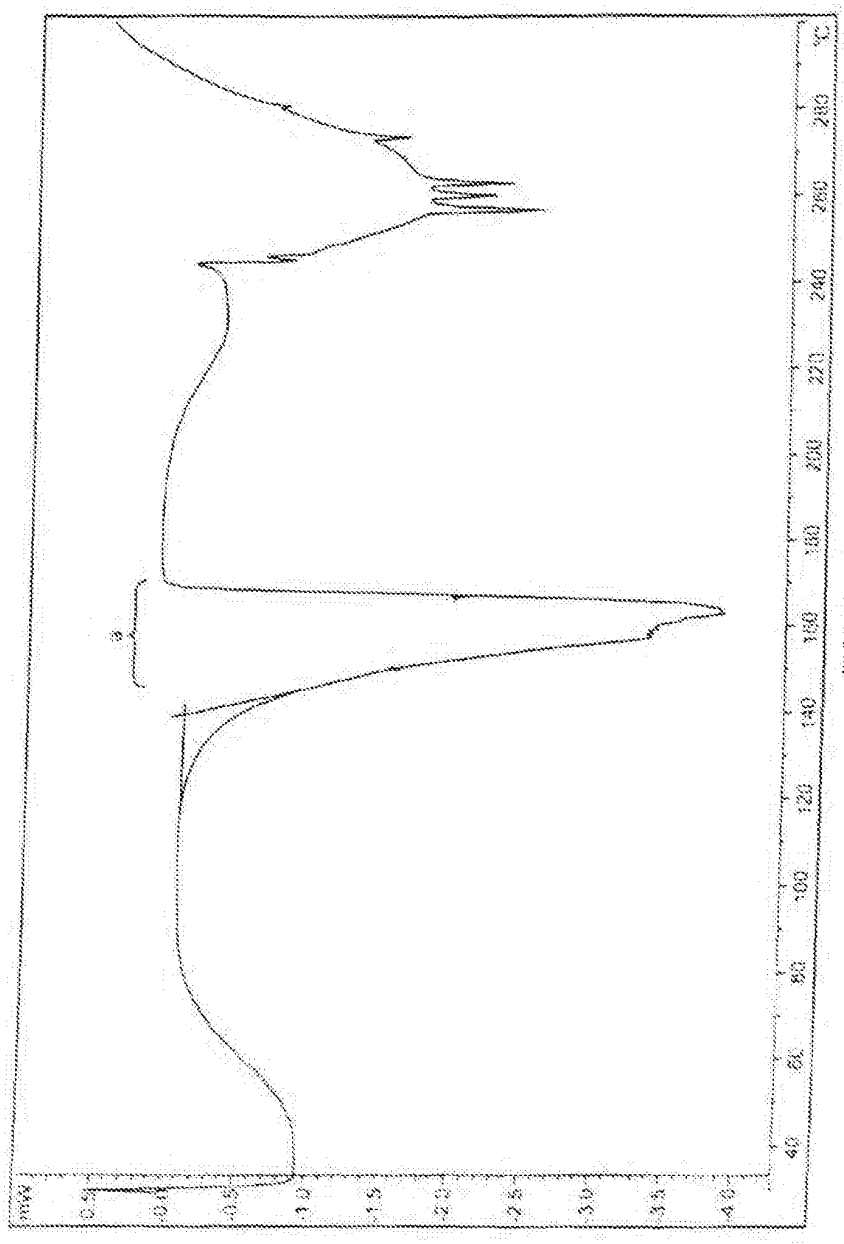
mW
°C
40
60
80
100
120
140
160
180
200
220
240
260
280
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0

FIG. 21

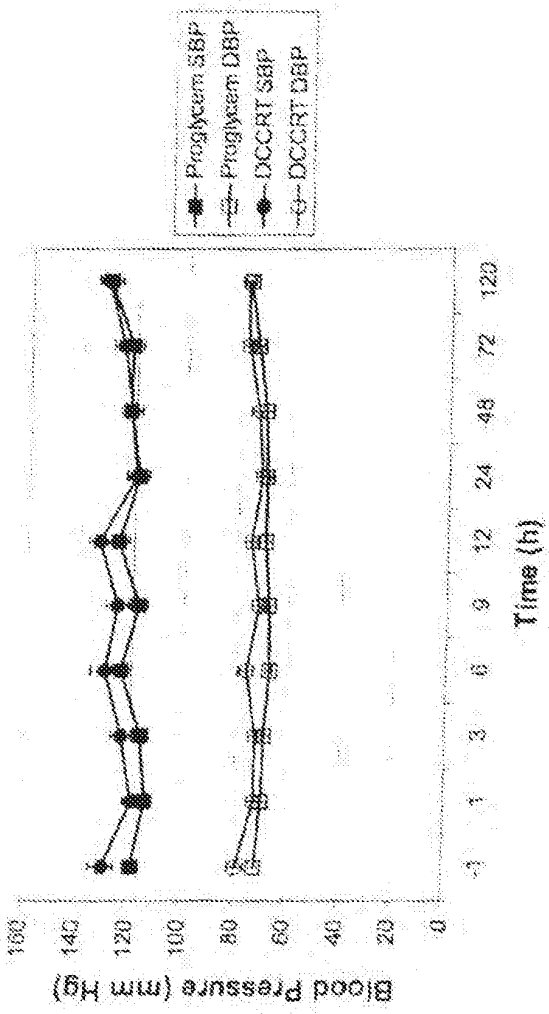
Proglycem SBP
Proglycem DBP
DCCRT SBP
DCCRT DBP
Blood Pressure (mm Hg)
160
140
120
100
80
60
40
20
0
-1
1
3
6
9
12
24
48
72
120
Time (h)

FIG. 22

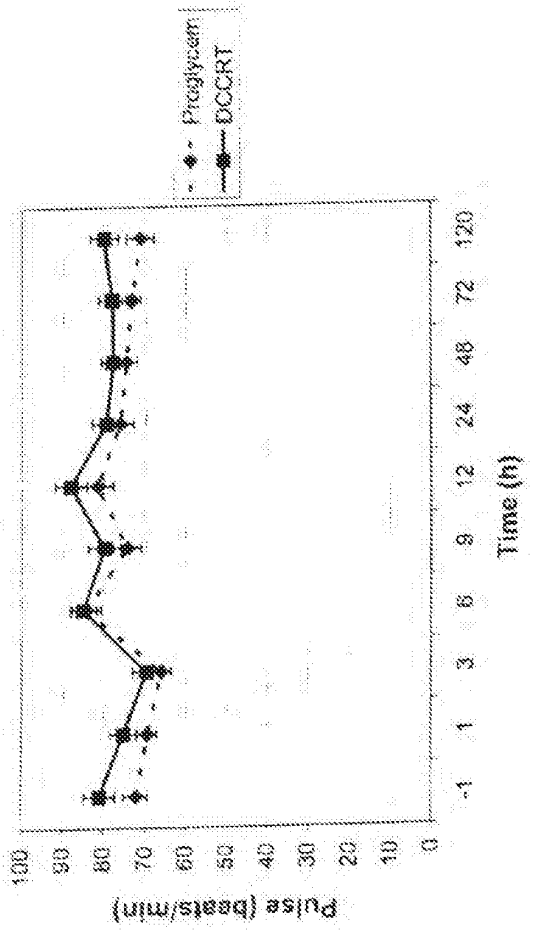
Proglycam
DCCRT
Pulse (beats/min)
100
90
80
70
60
50
40
30
20
10
0
-1
1
3
6
9
12
24
48
72
120
Time (h)

FIG. 23

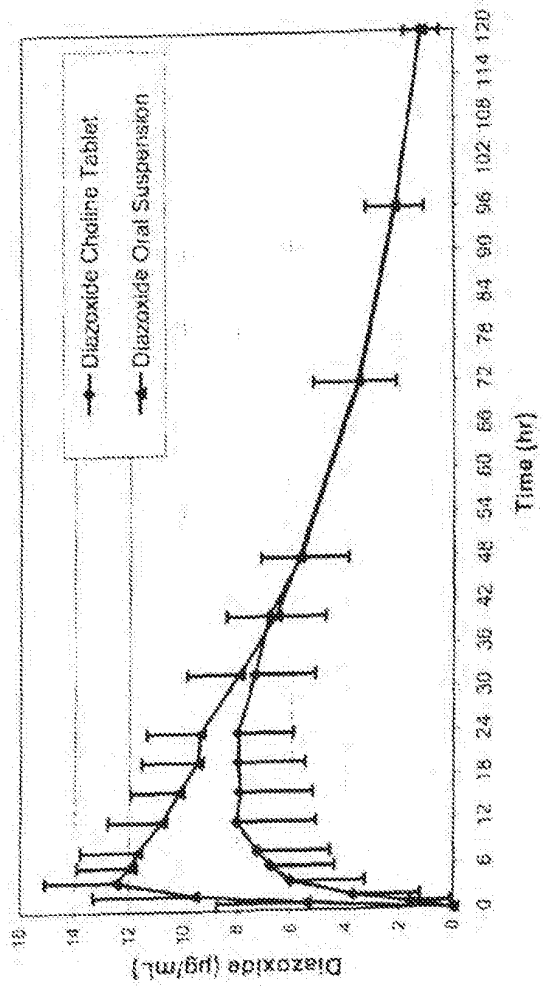
Diazoxide Choline Tablet
Diazoxide Oral Suspension
Diazoxide (µg/mL)
Time (hr)
0
6
12
18
24
30
36
42
48
54
60
66
72
78
84
90
96
102
108
114
120
0
2
4
6
8
10
12
14
16

FIG. 24

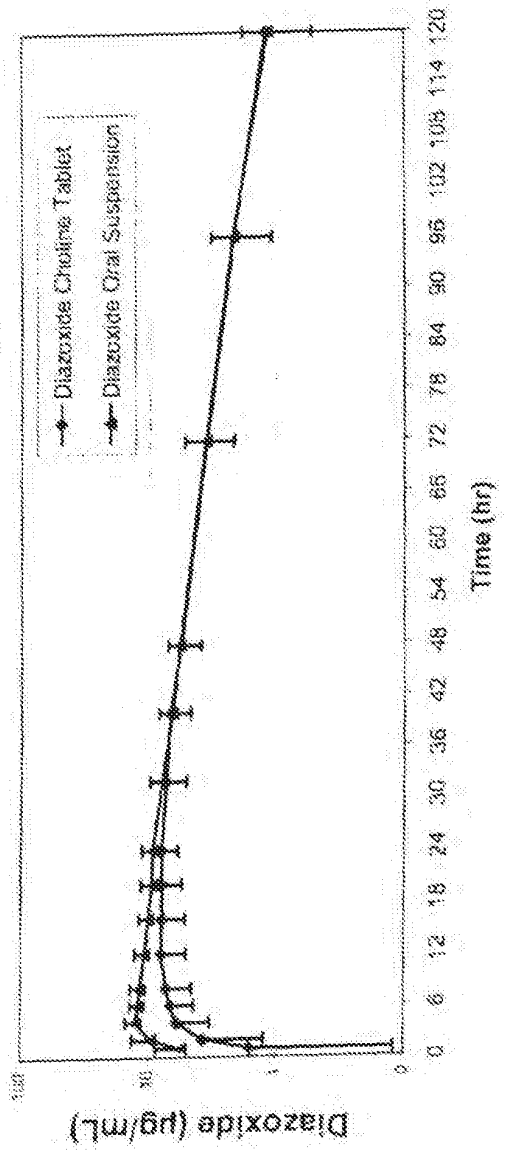
Diazoxide Choline Tablet
Diazoxide Oral Suspension
Diazoxide (µg/mL)
Time (hr)
0
6
12
18
24
30
36
42
48
54
60
66
72
78
84
90
96
102
108
114
120

FIG. 25

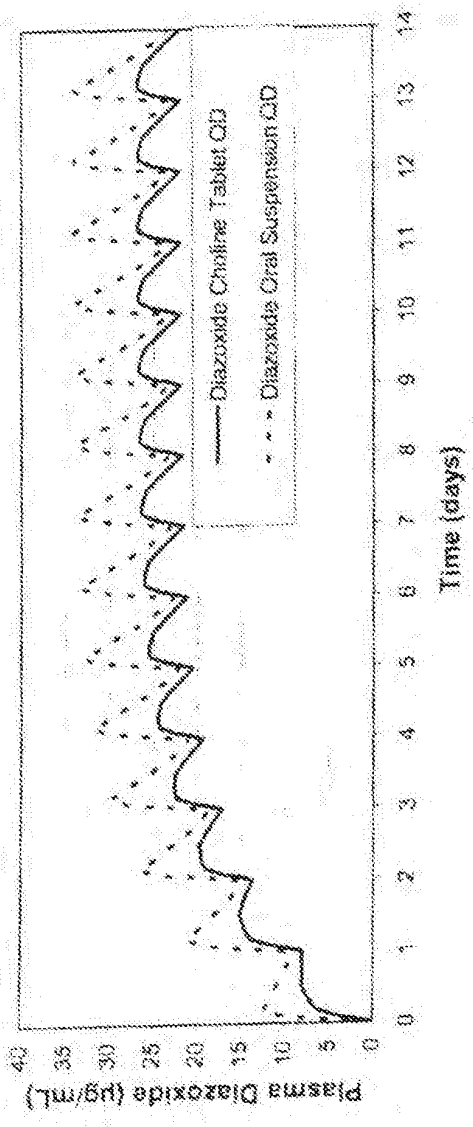
Diazoxide Choline Tablet QD
Diazoxide Oral Suspension QD
Time (days)
Plasma Diazoxide (µg/mL)
0
5
10
15
20
25
30
35
40
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14

FIG. 26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/66936

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/54 (2008.04)
USPC - 514/223.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/223.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Databases Searched: USPTO WEST (PGPUB, EPAB, JPAB, USPT), Google Patent, Google Scholar. Search Terms Used: benzothiadiazine, thyroid, pancreatitis or metab$, alkali metal, diazoxide choline, pharmac$ salt, channel opener

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 2006/026469 A2 (Cowen et al.) 09 March 2006 (09.03.2006) entire document especially/abstract; para [0021]-[0039], [0074], [0099], [0140], [0148], [0234], [0228], [0256]-[0257], [0274], [0279], [0398]	1-9, 12-14, 18, 20-38, 30-38, 40 and 42-75 --- 15-17, 19, 39 and 41
Y	US 6,140,343 A (DeNinno et al.) 31 October 2000 (31.10.2000) especially col 21, ln 23-33	15-16
Y	US 7,091,225 B2 (Sierra) 15 August 2006 ((15.08.2006) especially col 4, ln 06-15; col 7, ln 55-67	17, 19, 39 and 41

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 September 2008 (24.09.2008)	30 SEP 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/68936

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 10-11 and 29
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

[Continued on next page]

(54) Title: SALTS OF POTASSIUM ATP CHANNEL OPENERS AND USES THEREOF

(57) Abstract: Provided are immediate or prolonged administration of certain salts of KATP channel openers such as diazoxide to a subject to achieve novel pharmacodynamic, pharmacokinetic, therapeutic, physiological, metabolic and compositional outcomes in the treatment of diseases or conditions involving KATP channels. Also provided are pharmaceutical formulations, methods of administration and dosing of the salts that achieve these outcomes and reduce the incidence of adverse effects in treated individuals. Further provided are method of co-administering the salts with other drugs to treat diseases of humans and animals.

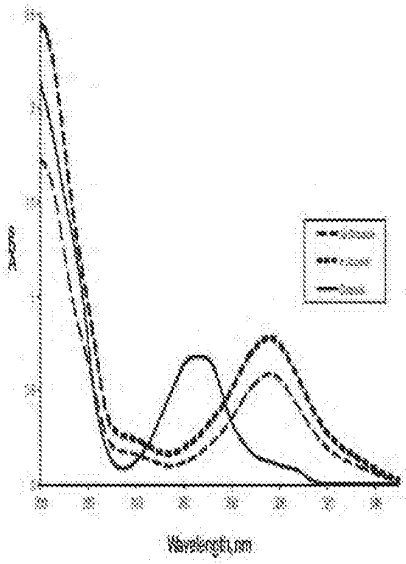

FIG. 1

WO 2013/130411 A1

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

SALTS OF POTASSIUM ATP CHANNEL OPENERS AND USES THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to salts of potassium ATP (K_{ATP}) channel openers, methods of preparing such salts, and methods of use thereof for treatment of a variety of diseases and conditions, including for example, type 1 and type 2 diabetes, hypertension, dyslipidemia, nonalcoholic steatohepatitis, pulmonary hypertension, myocardial infarction and arrhythmias following myocardical infarction and poly-cystic ovarian syndrome.

BACKGROUND OF THE INVENTION

[0002] The following description of the background of the invention is provided as an aid in understanding the invention and is not admitted to describe or constitute prior art to the invention.

[0003] ATP-sensitive potassium (K_{ATP}) channels play important roles in a variety of tissues by coupling cellular metabolism to electrical activity. The K_{ATP} channel has been identified as an octameric complex of two unrelated proteins, which assemble in a 4:4 stoichiometry. The first is a pore forming subunit, Kir6.x, which forms an inwardly rectifying K^+ channel; the second is an ABC (ATP binding cassette) transporter, also known as the sulfonylurea receptor (SURx) (Babenko et al., *Annu. Rev. Physiol.*, **60**:667-687 (1998)). The Kir6.x pore forming subunit is common for many types of K_{ATP} channels, and has two putative transmembrane domains (identified as TM1 and TM2), which are linked by a pore loop (H5). The subunit that comprises the SUR receptor includes multiple membrane-spanning domains and two nucleotide-binding folds.

[0004] According to their tissue localization, K_{ATP} channels exist in different isoforms or subspecies resulting from the assembly of the SUR and Kir subunits in multiple combinations. The combination of the SUR1 with the Kir6.2 subunits (SUR1/Kir6.2) typically forms the adipocyte and pancreatic β-cell type K_{ATP} channels, whereas the SUR2A/Kir6.2 and the SUR2B/Kir6.2 or Kir6.1 combinations typically form the cardiac type and the smooth muscle type K_{ATP} channels, respectively (Babenko et al., *Annu. Rev.*

Ex. 2002-0951

Physiol., **60**:667-687 (1998)). There is also evidence that the channel may include Kir2.x subunits. This class of potassium channels are inhibited by intracellular ATP and activated by intracellular nucleoside diphosphates. Such K_{ATP} channels link the metabolic status of the cells to the plasma membrane potential and in this way play a key role in regulating cellular activity. In most excitatory cells, K_{ATP} channels are closed under normal physiological conditions and open when the tissue is metabolically compromised (e.g. when the (ATP:ADP) ratio falls). This promotes K^+ efflux and cell hyperpolarization, thereby preventing voltage-dependent Ca^{2+} channels (VDCCs) from opening. (*Prog. Res Research*, (2001) **31**:77-80).

[0005] Potassium channel openers (PCOs or KCOs; also referred to as channel activators or channel agonists), are a structurally diverse group of compounds with no apparent common pharmacophore linking their ability to antagonize the inhibition of K_{ATP} channels by intracellular nucleotides. Diazoxide is a PCO that stimulates K_{ATP} channels in pancreatic β-cells (see Trube et al., *Pfluegers Arch Eur J Physiol*, 407, 493-99 (1986)). Pinacidil and chromakalim are PCOs that activate sarcolemmal potassium channels (see Escande et al., *Biochem Biophys Res Commun*, 154, 620-625 (1988); Babenko et al., *J Biol Chem*, 275(2), 717-720 (2000)). Responsiveness to diazoxide has been shown to reside in the 6th through 11th predicted transmembrane domains (TMD6-11) and the first nucleotide-binding fold (NBF1) of the SUR1 subunit.

[0006] Diazoxide, which is a nondiuretic benzothiadiazine derivative having the formula 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (empirical formula $C_8H_7ClN_2O_2S$), is commercialized in three distinct formulations to treat two different disease indications: (1) hypertensive emergencies and (2) hyperinsulinemic hypoglycemic conditions. Hypertensive emergencies are treated with Hyperstat IV, an aqueous formulation of diazoxide for intravenous use, adjusted to pH 11.6 with sodium hydroxide. Hyperstat IV is administered as a bolus dose into a peripheral vein to treat malignant hypertension or sulfonylurea overdose. In these uses, diazoxide acts to open potassium channels in vascular smooth muscle and pancreatic beta-cells, stabilizing the membrane potential at the resting level, resulting in vascular smooth muscle relaxation and suppression of insulin release, respectively.

Ex. 2002-0952

[0007] Hyperinsulinemic hypoglycemic conditions are treated with Proglycem®, an oral pharmaceutical version of diazoxide useful for administration to infants, children and adults. It is available as a chocolate mint flavored oral suspension, which includes 7.25% alcohol, sorbitol, chocolate cream flavor, propylene glycol, magnesium aluminum silicate, carboxymethylcellulose sodium, mint flavor, sodium benzoate, methylparaben, hydrochloric acid to adjust the pH, poloxamer 188, propylparaben and water. Diazoxide is also available as a capsule with 50 or 100 mg of diazoxide including lactose and magnesium stearate. In these uses, diazoxide activated K_{ATP} channels in insulin secreting cells thereby blunting the hypersecreting conditions.

[0008] Myocardial remodeling late after infarction is associated with increased incidence of fatal arrhythmias. Heterogeneous prolongation of the action potential in the surviving myocardium is one of the predominant causes. Sarcolemmal ATP-dependent potassium (K_{ATP}) channels are important metabolic sensors regulating electrical activity of cardiomyocytes and are capable of considerably shortening the action potential. Tavares et al. (Expression and function of ATP-dependent potassium channels in late post-infarction remodeling, *J Mol Cell Cardiol* 42:1016-1025 (2007)) studied the effect of diazoxide on late post infarction remodeling in rats. Cardiomyocytes were obtained from the infarct border zone, the septum and the right ventricle of rat hearts 10 weeks after coronary occlusion when rats developed signs of heart failure. Expression of the conductance subunit Kir6.1, but not Kir6.2, and of all SUR regulatory subunits was increased up to 3-fold in cardiomyocytes from the infarct border zone. Concomitantly, there was a prominent response of the K_{ATP} current to diazoxide that was not detectable in control cardiomyocytes. The action potential was prolonged in cardiomyocytes from the infarct border zone (74 ms) relative to sham (41 ms). However, activation of the K_{ATP} channels by diazoxide reduced action potential duration to 42 ms. In myocytes of the septum and right ventricle, expression of channel subunits, duration of action potential, and sensitivity to diazoxide were only slightly increased relative to shams. The authors suggested that drugs selectively activating diazoxide-sensitive sarcolemmal K_{ATP} channels should be considered in the prevention of arrhythmias in post-infarction heart failure.

Ex. 2002-0953

[0009] Schwartz et al. (Cardioprotection by multiple preconditioning cycles does not require mitochondrial KATP channels in pigs, *Am J Physiol Heart Circ Physiol* 283:H1538–H1544 (2002)) studied the effects of diazoxide preconditioning on infarct size in pigs. Diazoxide was administered 3.5 mg/kg, 1 ml/min IV to in barbital-anesthetized open-chest pigs subjected to 30 min of complete occlusion of the left anterior descending coronary artery and 3 h of reflow. Infarct size (percentage of the area at risk) after 30 min of ischemia in controls was 35.1 ± 9.9% (n =7). Diazoxide infusion significantly limited infarct size (14.6 ± 7.4%, n =7). Similar results have been demonstrated in rat and rabbit models.

[0010] Diazoxide administered either as an IV bolus or orally has been used to treat pulmonary hypertension. For example, Chan et al. (Reversibility of primary pulmonary hypertension during six years of treatment with oral diazoxide, *Br Heart J* 57(2):207-209 (1987)) reported the successful treatment of a 32 year old woman with pulmonary hypertension. Her symptoms resolved completely with oral diazoxide and the pulmonary arterial pressure was reduced to normal levels over a period of six years. When diazoxide was discontinued on two separate occasions pulmonary hypertension recurred. Squarcia et al. (Primary pulmonary hypertension in childhood: familial aspects, *Pediatr Med Chir* 3(6):467-472 (1981)) suggested that among alternative vasodilators available for the experimental treatment of pulmonary hypertension diazoxide appears to have some advantages because it reduces not only pulmonary arteriolar resistance, but also pulmonary artery pressure, without producing tachycardia.

[0011] Honey et al. (Clinical and hemodynamic effects of diazoxide in primary pulmonary hypertension, *Thorax* 35(4):269-276 (1980)) studied the effects of IV and oral diazoxide on primary pulmonary hypertension. In their study diazoxide was injected into the pulmonary artery in nine patients with primary pulmonary hypertension. There was no significant change in pulmonary artery pressure, which fell by more than 10 mmHg in only two patients. The pulmonary blood flow increased in all patients as a result of a fall in pulmonary vascular resistance (by 4 to 17 units). Systematic vascular resistance also fell as expected in all patients. Oral diazoxide was given to seven patients, two of whom showed sustained clinical improvement while remaining on treatment (400 to 600 mg daily). Five patients were unable to tolerate the drug, because of nausea and sickness

Ex. 2002-0954

(two), peripheral edema requiring large doses of diuretics (four), diabetes (three), and postural hypotension (one). Hirsutism was troublesome in the two patients remaining on treatment. They concluded that diazoxide may be useful in the management of some patients with primary pulmonary hypertension, but its use is limited by the frequency of side effects.

[0012] Several experimental formulations of diazoxide have been tested in humans and animals. These include an oral solution tested in pharmacodynamic and pharmacokinetic studies and a tablet formulation under development in the early 1960's as an anti-hypertensive, but never commercialized (see Calesnick et al., *J. Pharm. Sci.* **54**:1277-1280 (1965); Reddy et al., *AAPS Pharm Sci Tech* **4**(4):1-98, 9 (2003); US Patent No. 6,361,795).

[0013] Current oral formulations of diazoxide are labeled for dosing two or three times per day at 8 or 12 hour intervals. Most subjects receiving diazoxide are dosed three times per day. Commercial and experimental formulations of diazoxide are characterized by rapid drug release following ingestion with complete release in approximately 2 hours. Unless indicated differently, the term "approximately" when used in the context of a numeric value, refer to the stated numeric value +/- 10%. In the context of two-theta angles from XRPD studies, the term approximately refers to +/- 5% of the stated numeric value.

[0014] Current oral formulations of diazoxide in therapeutic use result in a range of adverse side effects including dyspepsia, nausea, diarrhea, fluid retention, edema, reduced rates of excretion of sodium, chloride, and uric acid, hyperglycemia, vomiting, abdominal pain, ileus, tachycardia, palpitations, and headache. (See e.g., current packaging insert for Proglycem®). Oral treatment with diazoxide is used in individuals experiencing serious disease where failure to treat results in significant morbidity and mortality. The adverse side effects from oral administration are tolerated because the benefits of treatment are substantial. The adverse side effects profile of oral diazoxide limit the utility of the drug in treating obese subjects at doses within the labeled range of 3 to 8 mg/kg per day.

[0015] The effect of diazoxide in animal models of diabetes and obesity (e.g. obese and lean Zucker rats) has been previously reported. See e.g. Alemzadeh et al.,

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Endocrinology **133**:705-712 (1993); Alemzadeh et al., *Metabolism* **45**:334-341 (1996); Alemzadeh et al., *Endocrinology* **140**:3197-3202 (1999); Stanridge et al., *FASEB J* **14**:455-460 (2000); Alemzadeh et al., *Med Sci Monit* **10**(3): BR53-60 (2004); Alemzadeh et al., *Endocrinology* **145**(12):3476-3484 (2004); Aizawa et al., *J of Pharma Exp Ther* **275**(1): 194-199 (1995); and Surwit et al., *Endocrinology* **141**:3630-3637 (2000).

[0016] The effect of diazoxide in humans with obesity or diabetes has been previously reported. See e.g., Wigand et al., *Diabetes* **28**(4):287-291 (1979), evaluation of diazoxide on insulin receptors; Ratzmann et al., *Int J Obesity* **7**(5):453-458 (1983), glucose tolerance and insulin sensitivity in moderately obese patients; Marugo et al., *Boll Spec It Biol Sper* **53**:1860-1866 (1977), moderate dose diazoxide treatment on weight loss in obese patients; Alemzadeh et al., *J Clin Endocr Metab* **83**:1911-1915 (1998), low dose diazoxide treatment on weight loss in obese hyperinsulinemic patients; Guldstrand et al., *Diabetes and Metabolism* **28**:448-456 (2002), diazoxide in obese type II diabetic patients; Ortqvist et al., *Diabetes Care* **27**(9):2191-2197 (2004), beta-cell function measured by circulating C-peptide in children at clinical onset of type 1 diabetes; Bjork et al., *Diabetes Care* **21**(3):427-430 (1998), effect of diazoxide on residual insulin secretion in adult type 1 diabetes patients; and Qvigstad et al., *Diabetic Medicine* **21**:73-76 (2004).

[0017] The effect of potassium channel openers on lipid levels has been reported. Gutman et al. (Horm Metab Res 1985 17(10):491-494) studied the effect of diazoxide on an animal model with elevated triglycerides. Normal Wistar rats fed an isocaloric, sucrose-rich (63%) diet (SRD), were reported to develop glucose intolerance and elevated triglyceride levels in plasma (P) as well as in heart (H) and liver (L) tissue. This metabolic state was reported to be accompanied by hyperinsulinism both in vivo and in vitro, consistent with a state of insulin resistance. Gutman et al., administered diazoxide (120 mg/kg/day) together with the diet (SRD + DZX) for 22 days. Control groups fed a standard chow (STD) or the STD plus diazoxide (STD + DZX) were included in the study. Gutman et al., suggested that diazoxide could prevent the development of hyperinsulinism, glucose intolerance and elevated levels of triacylglycerol in plasma, heart and liver present in animals fed on a sucrose rich diet.

[0018] Yokoyama et al. (Gen Pharmacol 1998 30(2):233-237) studied the effects of KRN4884 on lipid metabolism in hyperlipidemic rats. KRN4884 is a novel

Ex. 2002-0956

pyridinecarboxamidine type potassium channel opener. Oral administration of KRN4884 (1-10 mg/kg/day) for 14 days was reported to dose dependently reduce serum triglyceride levels in Zucker rats. The reductions in serum triglyceride were associated with reductions in triglyceride in chylomicron and very low density lipoprotein. KRN4884 produced no change in serum insulin and glucose levels in Zucker rats. KRN4884 exhibited a similar triglyceride lowering effect in diet-induced hyperlipidemic rats. In a second study with KRN4884 (J Cardiovasc Pharmacol 2000 35(2):287-293), these authors used high-fructose diet rats which developed hypertension, hypertriglyceridemia, increased total cholesterol/HDL (high-density lipoprotein)-cholesterol ratio, and hyperinsulinemia, and reported that KRN4884 treatment significantly increased lipoprotein lipase (LPL) activity in muscle and tended to increase LPL activity in adipose tissue. Hepatic triglyceride lipase activity was not affected by KRN4884 administration.

[0019] Matzno et al. (J Pharmacol Exp Ther 1994 271(3):1666-71) studied the effect of (+)-N-(6-amino-3-pyridil)-N'-[(1S,2R,4R)-bicyclo-[2.2.1]hept-2-yl] -N"-cyanoguanidine hydrochloride (AL0671), a cyanoguanidine-derivative potassium channel opener, on serum lipid and lipoprotein levels in obese Zucker rats. Serial administration (for 1 or 2 weeks) of AL0671 (5 mg/kg/day) was reported to significantly decrease serum total triglyceride, chylomicron and very-low-density lipoprotein levels with increasing high-density lipoprotein cholesterol, whereas low-density lipoprotein levels did not change. AL0671 (5 mg/kg/day) also was reported to increase lipoprotein lipase activities 4-fold and hepatic triglyceride lipase activities 3-fold in postheparin plasma. The authors suggested that AL0671 activates both lipoprotein lipase and hepatic triglyceride lipase activities through its potassium channel-opening activity followed by decreasing triglyceride-rich lipoproteins in genetically obese hyperlipemic rats.

[0020] Alemzadeh and Tushaus (Med Sci Monit, 2005; 11(12): BR439-448) studied the effect of 8 weeks of diazoxide treatment (150 mg/kg/day) on triglyceride biosynthesis in Zucker Diabetic Fatty (ZDF) rats. They reported that diazoxide treatment significantly reduced expression of sterol regulatory element-binding protein-1c, fatty acid synthase, acetyl CoA carboxylase, hormone-sensitive lipase, and peroxisome proliferator agonist receptor-γ, without altering expressions of acyl CoA oxidase, peroxisome proliferator

Ex. 2002-0957

receptor- α, and carnitine palmitoyl transferase-1. Also reported was that diazoxide treatment decreased hepatic triglycerides, long chain acyl-CoA and cholesterol contents.

[0021] U.S. Patent No. 5,284,845 describes a method for normalizing blood glucose and insulin levels in an individual exhibiting normal fasting blood glucose and insulin levels and exhibiting in an oral glucose tolerance test, elevated glucose levels and at least one insulin level abnormality selected from the group consisting of a delayed insulin peak, an exaggerated insulin peak and a secondary elevated insulin peak. According to this reference, the method includes administering diazoxide in an amount from about 0.4 to about 0.8 mg/kg body weight before each meal in an amount effective to normalize the blood glucose and insulin levels.

[0022] U.S. Patent No. 6,197,765 describes administration of diazoxide for treatment for syndrome-X, and resulting complications, that include hyperlipidemia, hypertension, central obesity, hyperinsulinemia and impaired glucose tolerance. According to this reference, diazoxide interferes with pancreatic islet function by ablating endogenous insulin secretion resulting in a state of insulin deficiency and high blood glucose levels equivalent to that of diabetic patients that depend on exogenous insulin administration for normalization of their blood glucose levels.

[0023] U.S. Patent No. 2,986,573 describes the preparation of diazoxide and its use for the treatment of hypertension. The patent asserts that alkali metal salts may be prepared by methods well-known in the art for the preparation of a salt of a strong base with a weak acid. It also alleges a specific method for making a sodium salt of diazoxide. This patent does not provide any evidence to support the formation of any salt of diazoxide.

[0024] U.S. Patent No. 5,629,045 describes diazoxide for topical ophthalmic administration.

[0025] WO 98/10786 describes use of diazoxide in the treatment of X-syndrome including obesity associated therewith.

[0026] U.S. Patent publication no. 2003/0035106 describes diazoxide containing compounds for reducing the consumption of fat-containing foods.

[0027] U.S. Patent Publication No. 2004/0204472 describes the use of a Cox-2 inhibitor plus diazoxide in the treatment of obesity. Also described therein is the use of a Cox-2 inhibitor plus a pharmaceutically acceptable salt of diazoxide, wherein acceptable cations include alkali metals and alkaline earth metals.

[0028] U.S. Patent Publication No. 2002/0035106 describes use of K_{ATP} channel agonists for reducing the consumption of fat containing food. This application mentions pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts and optionally alkylated ammonium salts, but does not disclose or describe how to prepare any such salts. This patent also does not provide any evidence to support the formation of any salt of a K_{ATP} channel agonist.

[0029] U.K. Patent GB982072 describes the preparation and use of diazoxide and derivatives for the treatment of hypertension and peripheral vascular disorders. This patent mentions non-toxic alkali metals salts but does not disclose or describe how to prepare any such salts. This patent does not provide any evidence to support the formation of any salt of diazoxide or its derivatives.

SUMMARY OF THE INVENTION

[0030] The current invention relates to methods of preparation and use of formulations that include alkali metal, tertiary amine and ammonium salts of diazoxide and diazoxide derivatives. It has been surprisingly found that it is difficult to produce salts of diazoxide and derivatives. In particular, the inventors have been unable to reproduce formation of a diazoxide salt using the method asserted in U.S. Patent No. 2,986,573. Contrary to what is reported in the literature, salt formation with diazoxide and derivatives depends on a proper selection of solvent and counter-ion.

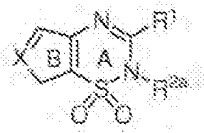
[0031] Provided herein are pharmaceutical formulations of K_{ATP} channel openers and their use for treatment of various diseases and conditions including but not limited to type 1 and type 2 diabetes, hypertension, dyslipidemia, nonalcoholic steatohepatitis (NASH) pulmonary hypertension, myocardial infarction and arrhythmias following myocardical infarction, and poly-cystic ovarian syndrome. Such formulations are characterized as being bioavailable. A K_{ATP} channel opener as used herein has any one or more of the following properties: (1) opening SURx/Kir6.y potassium channels, where x = 1, 2A or

Ex. 2002-0959

2B and y= 1 or 2; (2) binding to the SURx subunit of K_{ATP} channels; and (3) inhibiting glucose induced release of insulin following administration of the compound *in vivo*. Preferably, K_{ATP} channel openers are K_{ATP} channel openers with all three properties. K_{ATP} channel openers as defined herein are preferably salts prepared from the compounds of Formulae I-VIII, as set forth below.

[0032] In another aspect, the present invention also provides salts of the compounds defined by Formulae I – VIII. Salts of Formulae I – IV provided herein include monovalent alkali metal salts and monovalent and divalent salts of organic compounds, preferably organic compounds which include an ammonium moiety. Salts of Formulae V – VIII are also provided herein, preferably prepared with monovalent and divalent counter-ions.

[0033] K_{ATP} channel openers defined by Formula I are as follows:



Formula I

wherein;

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, and substituted cycloalkyl provided however that when R^1 is a substituted lower alkyl or a substituted cycloalkyl, then the substituent does not include an amino group;

R^{2a} is hydrogen;

X is a 1, 2 or 3 atom chain, wherein each atom is independently selected from carbon, sulfur and nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy, cycloalkyl, substituted cycloalkyl, or substituted lower alkoxy, provided however that when an atom of the chain is substituted with substituted lower alkyl, substituted lower alkoxy or substituted cycloalkyl, then the substituent does not include an amino group;

wherein ring B is saturated, monounsaturated, polyunsaturated or aromatic;

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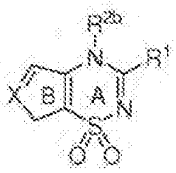
and all bioequivalents including salts, prodrugs and isomers thereof.

[0034] In particular embodiments of Formula I, X is $C(R^a)C(R^b)$, wherein R^a and R^b are independently selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, lower alkoxy, substituted lower alkoxy, sulfonyl, and the like. In further embodiments, R^a and R^b are independently selected from the group consisting of hydroxyl, substituted oxy, substituted thiol, alkylthio, substituted alkylthio, sulfinyl, sulfonyl, substituted sulfinyl, substituted sulfonylalkylsulfinyl, alkylsulfonyl, and the like. In a preferred embodiment, Ring B does not include any heteroatoms.

[0035] Salts of embodiments of the channel openers defined by Formula I may be prepared from the following: (a) metal hydroxides, preferably alkali metal hydroxides (e.g., NaOH and KOH) and (b) organic hydroxides , preferably organic compounds which include at least one tertiary amine or at least one quaternary ammonium ion (e.g., diethylaminoethanol, triethylamine, hydroxyethylpyrrolidine, choline and hexamethylhexamethylenediammonium, and the like).

[0036] K_{ATP} channel openers defined by Formula II are as follows:



Formula II

wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, and substituted cycloalkyl provided however that when R^1 is a substituted lower alkyl or a substituted cycloalkyl, then the substituent does not include an amino group;

R^{2b} is hydrogen;

X is a 1, 2 or 3 atom chain, wherein each atom is independently selected from carbon, sulfur and nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy,

Ex. 2002-0961

cycloalkyl, substituted cycloalkyl, or substituted lower alkoxy, provided however that when an atom of the chain is substituted with substituted lower alkyl, substituted cycloalkyl or substituted lower alkoxy, then the substituent does not include an amino group;

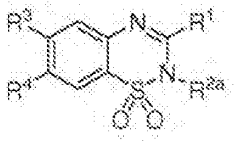
wherein ring B is saturated, monounsaturated, polyunsaturated or aromatic;

and all bioequivalents including salts, prodrugs and isomers thereof.

[0037] In particular embodiments of Formula II, X is $C(R^a)C(R^b)$, wherein R^a and R^b are independently selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, lower alkoxy, substituted lower alkoxy, sulfonyl, and the like. In further embodiments, R^a and R^b are independently selected from the group consisting of hydroxyl, substituted oxy, substituted thiol, alkylthio, substituted alkylthio, sulfinyl, sulfonyl, substituted sulfinyl, substituted sulfonyl, alkylsulfinyl, alkylsulfonyl, nitro and the like. In preferred embodiment, Ring B does not include any heteroatoms.

[0038] Salts of embodiments of the channel openers defined by Formula II may be prepared from the following: (a) metal hydroxides, preferably alkali metal hydroxides (e.g., NaOH and KOH) and (b) organic hydroxides , preferably organic compounds which include at least one tertiary amine or at least one quaternary ammonium ion (e.g., diethylaminoethanol, triethylamine, hydroxyethylpyrrolidine, choline and hexamethylhexamethylenediammonium, and the like).

[0039] K_{ATP} channel openers defined by Formula III are as follows:



Formula III

wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, and cycloalkyl provided however that when R^1 is a substituted lower alkyl, then the substituent does not include an amino group;

Ex. 2002-0962

R^{2a} is hydrogen;

R^3 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl and substituted cycloalkyl provided however that when R^3 is a substituted lower alkyl, then the substituent does not include an amino group;

R^4 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl and substituted cycloalkyl provided however that when R^4 is a substituted lower alkyl, then the substituent does not include an amino group;

and all bioequivalents including salts, prodrugs and isomers thereof.

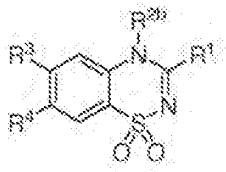
[0040] In particular embodiments of Formula III, R^1 is a lower alkyl, (preferably ethyl or methyl); R^{2a} is hydrogen; and R^3 and R^4 are each independently halogen.

[0041] In another embodiment of Formula III, R^1 is methyl; R^{2a} is hydrogen; R^3 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl, and substituted cycloalkyl; and R^4 is chlorine.

[0042] Salts of embodiments of the channel openers defined by Formula III may be prepared from the following: (a) metal hydroxides, preferably alkali metal hydroxides (e.g., NaOH and KOH) and (b) organic hydroxides, preferably organic compounds which include at least one tertiary amine or at least one quaternary ammonium ion (e.g., diethylaminoethanol, triethylamine, hydroxyethylpyrrolidine, choline and hexamethylhexamethylenediammonium, and the like).

Ex. 2002-0963

[0043] K_{ATP} channel openers defined by Formula IV are as follows:



Formula IV

wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, and cycloalkyl provided however that when R^1 is a substituted lower alkyl, then the substituent does not include an amino group;

R^{2b} is hydrogen;

R^3 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl and substituted cycloalkyl provided however that when R^3 is a substituted lower alkyl, then the substituent does not include an amino group;

R^4 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl and substituted cycloalkyl provided however that when R^4 is a substituted lower alkyl, then the substituent does not include an amino group;

and all bioequivalents including salts, prodrugs and isomers thereof.

[0044] In particular embodiments of Formula IV, R^1 is a lower alkyl, (preferably ethyl or methyl); R^{2b} is hydrogen; and R^3 and R^4 are each independently halogen.

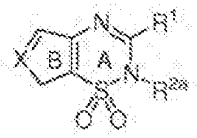
[0045] In another embodiment of Formula IV, R^1 is methyl; R^{2b} is hydrogen; R^3 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl, and substituted cycloalkyl; and R^4 is chlorine.

[0046] Salts of embodiments of the channel openers defined by Formula IV may be prepared from the following: (a) metal hydroxides, preferably alkali metal hydroxides (e.g., NaOH and KOH) and (b) organic hydroxides, preferably organic compounds which include at least one tertiary amine or at least one quaternary ammonium ion (e.g.,

Ex. 2002-0964

diethylaminoethanol, triethylamine, hydroxyethylpyrrolidine, choline and hexamethylhexamethylenediammonium, and the like).

[0047] K_{ATP} channel openers defined by Formula V are as follows:



Formula V

wherein:

R^1 is selected from the group consisting of optionally substituted amino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

R^{2a} is selected from the group consisting of hydrogen, and lower alkyl;

X is a 1, 2 or 3 atom chain, wherein each atom is independently selected from carbon, sulfur and nitrogen, and each atom is optionally substituted with halogen, hydroxyl, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted cycloalkyl, or optionally substituted amino;

wherein ring B is saturated, monounsaturated, polyunsaturated or aromatic;

wherein at least one of R^1 or a substituent of X includes an amino group;

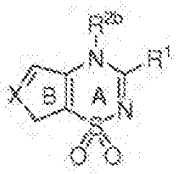
and all bioequivalents including salts, prodrugs and isomers thereof.

[0048] In particular embodiments of Formula V, X is $C(R^a)C(R^b)$, wherein R^a and R^b are independently selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkoxy, amino, sulfonylamino, aminosulfonyl, sulfonyl, and the like. Preferably R^1 includes at least one substituent containing an amino group. In further embodiments, R^a and R^b are independently selected from the group consisting of hydroxyl, substituted oxy, substituted thiol, alkylthio, substituted alkylthio, sulfinyl, sulfonyl, substituted sulfinyl, substituted sulfonyl, substituted sulfonylamino, substituted amino, substituted amine,

Ex. 2002-0965

alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, and the like. In a preferred embodiment, Ring B does not include any heteroatoms.

[0049] K_{ATP} channel openers defined by Formula VI are as follows:



Formula VI

wherein:

R^1 is selected from the group consisting of optionally substituted amino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

R^{2b} is selected from the group consisting of hydrogen and lower alkyl;

X is a 1, 2 or 3 atom chain, wherein each atom is independently selected from carbon, sulfur and nitrogen, and each atom is optionally substituted with halogen, hydroxyl, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted cycloalkyl, or optionally substituted amino;

wherein ring B is saturated, monounsaturated, polyunsaturated or aromatic;

wherein at least one of R^1 or a substituent of X includes an amino group;

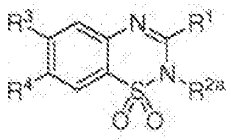
and all bioequivalents including salts, prodrugs and isomers thereof.

[0050] In particular embodiments of Formula VI, X is $C(R^a)C(R^b)$, wherein R^a and R^b are independently selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, lower alkoxy, substituted lower alkoxy, amino, sulfonylamino, aminosulfonyl, sulfonyl, and the like. In further embodiments, R^a and R^b are independently selected from the group consisting of hydroxyl, substituted oxy, substituted thiol, alkylthio, substituted alkylthio, sulfinyl, sulfonyl, substituted sulfinyl, substituted sulfonyl, substituted sulfonylamino, substituted

Ex. 2002-0966

amino, substituted amine, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, and the like. Preferably R^1 includes at least one substituent containing an amino group. In a preferred embodiment, Ring B does not include any heteroatoms.

[0051] K_{ATP} channel openers defined by Formula VII are as follows:



Formula VII

wherein:

R^1 is selected from the group consisting of optionally substituted amino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

R^{2a} is selected from the group consisting of hydrogen, lower alkyl, and substituted lower alkyl;

R^3 is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted amino, optionally substituted cycloalkyl and optionally substituted aryl;

R^4 is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted amino, optionally substituted cycloalkyl and optionally substituted aryl;

wherein at least one of R^1, R^3 and R^4 includes a substituent containing an amino group;

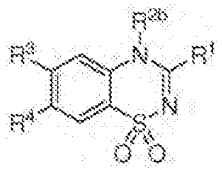
and all bioequivalents including salts, prodrugs and isomers thereof.

[0052] Preferably, R^1 includes a substituent containing an amino group. In particular embodiments of Formula VII; R^1 includes an amino substituent, R^{2a} is hydrogen; and R^3 and R^4 are each independently halogen.

Ex. 2002-0967

[0053] In another embodiment of Formula VII, R^{2a} is hydrogen; R^3 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, substituted amino, cycloalkyl, and substituted cycloalkyl; and R^4 is chlorine.

[0054] K_{ATP} channel openers defined by Formula VIII are as follows:



Formula VIII

wherein;

R^1 is selected from the group consisting of optionally substituted amino, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heteroarylalkyl;

R^{2b} is selected from the group consisting of hydrogen, lower alkyl, and substituted lower alkyl;

R^3 is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted amino, optionally substituted cycloalkyl and optionally substituted aryl;

R^4 is selected from the group consisting of hydrogen, halogen, optionally substituted lower alkyl, optionally substituted amino, optionally substituted cycloalkyl and optionally substituted aryl;

wherein at least one of R^1, R^3 and R^4 includes a substituent containing an amino group;

and all bioequivalents including salts, prodrugs and isomers thereof.

[0055] Preferably R^1 includes a substituent containing an amino group. In particular embodiments of Formula VIII, R^{2b} is hydrogen; and R^3 and R^4 are each independently halogen.

Ex. 2002-0968

[0056] In another embodiment of Formula VIII, R^{2b} is hydrogen; R^3 is selected from the group consisting of hydrogen, halogen, lower alkyl, optionally substituted lower alkyl, optionally substituted amino, and optionally substituted cycloalkyl; and R^4 is chlorine.

[0057] Unless otherwise indicated, reference in this application to K_{ATP} channel openers should be understood to refer to K_{ATP} channel openers based upon a salt of one of the compounds described by Formulae I-VIII and having one or more, and preferably all three, of the following properties: (1) opening SURx/Kir6.y potassium channels, wherein x = 1, 2A or 2B and y = 1 or 2; (2) binding to the SURx subunit of K_{ATP} channels; and (3) inhibiting glucose induced release of insulin following administration of the compound *in vivo*. Such K_{ATP} channel openers preferably have the structure of any of the compounds of Formula I-VIII, or more preferably Formula III-IV where ring B or its equivalent does not include any heteroatoms. More preferably, the structure is diazoxide. Structural variants or bioequivalents of any of the compounds defined by Formulae I-VIII, such as derivatives, salts, prodrugs or isomers, are also contemplated herein. Specifically, salts of compounds of Formula I-IV wherein the cation is selected from a cation of an alkali metal or an organic compound which includes a tertiary amine or a quaternary ammonium ion. Preferably, when the salt includes an anion of diazoxide and a sodium cation, the salt is not in a form suitable for intravenous use. In other embodiments, when the anion is diazoxide in a solution suitable for intravenous use, the cation is not sodium. In alternate embodiments, in solutions suitable for intravenous use, when the cation is sodium, the anion is not an anion of diazoxide. In certain embodiments, when the salt includes an anion of diazoxide and a sodium cation, the salt is not in liquid form. More preferably, K_{ATP} channel openers contemplated herein are salts of compounds of Formulae III and IV wherein the cation is selected from sodium, potassium, choline or hexamethyl hexamethylene diammonium. Other K_{ATP} channel openers that are contemplated for use herein include BPDZ 62, BPDZ 73, NN414, BPDZ 154.

[0058] Also provided herein are salts of compounds of Formula V - VIII, wherein at least one substituent of the compound of Formulae V – VIII includes an amino group. In another embodiment, the compound of Formula V-VIII forms the anion of the salt and a monovalent or divalent metal forms the cation. In other embodiments, the cation includes a tertiary amino or quaternary ammonium group.

Ex. 2002-0969

[0059] *In vitro* analysis of glucose induced release of insulin via K_{ATP} channel openers can be determined using rat islets as provided by De Tullio et al., *J. Med. Chem.*, **46**:3342-3353 (2003), or by using human islets as provided by Björklund et al., *Diabetes*, **49**:1840-1848 (2000).

[0060] Provided herein are formulations, such as controlled release pharmaceutical formulations, of K_{ATP} channel openers and bioequivalents thereof, which include salts of the compounds of Formulae I – VIII. In one embodiment, the salt can be formulated for controlled release following oral administration. Such formulations contain in a single administration dosage between 10 and 100 mg, between 25 and 100 mg, between 100 and 200 mg, between 200 and 300 mg, between 300 and 500 mg or between 500 and 2000 mg of the salt of the K_{ATP} channel openers provided in Formulae I – VIII. In certain embodiments, the dosage of the K_{ATP} channel openers contained in a formulation may be determined based on the weight of the subject for which it is to be administered, *i.e.*, the formulation may contain in a single administration dosage between 0.1-20 mg of the K_{ATP} channel opener per kg of the subject's body weight, or between 0.1-0.5 mg of the K_{ATP} channel opener per kg of the subject's body weight; or between 0.5-1 mg of the K_{ATP} channel opener per kg of the subject's body weight; or between 1-2 mg of the K_{ATP} channel opener per kg of the subject's body weight, or between 2-5 mg of the K_{ATP} channel opener per kg of the subject's body weight, or between 5-10 mg of the K_{ATP} channel opener per kg of the subject's body weight, or between 10-15 mg of the K_{ATP} channel opener per kg of the subject's body weight, or between 15-20 mg of the K_{ATP} channel opener per kg of the subject's body weight.

[0061] Also provided herein are controlled release pharmaceutical formulations containing K_{ATP} channel openers selected from salts of Formulae I –VIII, which can be obtained by at least one of the following: (a) particle size reduction involving comminution, spray drying, or other micronising techniques, (b) use of an ion exchange resin, (c) use of inclusion complexes, for example cyclodextrin, (d) compaction of the K_{ATP} channel opener with a solubilizing agent including a low viscosity hypromellose, low viscosity methylcellulose or similarly functioning excipient or combinations thereof, (e) associating the K_{ATP} channel opener with a salt prior to formulation, (f) use of a solid dispersion of the K_{ATP} channel opener, (g) use of a self emulsifying system, (h) addition

Ex. 2002-0970

of one or more surfactants to the formulation, (i) use of nanoparticles, or (j) combinations of these approaches.

[0062] Further provided herein are controlled release pharmaceutical formulations containing K_{ATP} channel openers selected from salts of the compounds defined by Formulae I – VIII, which include at least one component that substantially inhibits release of the K_{ATP} channel activator from the formulation until after gastric transit. As used herein, "substantially inhibits" means less than 15% release, more preferably at least less than 10% release, or even more preferably at least less than 5% release of the drug from the formulation during gastric transport. Release can be measured in a standard USP based in-vitro gastric dissolution assay in a calibrated dissolution apparatus. See e.g., U.S. Pharmacopeia, Chapter 711 (2005).

[0063] Also provided are oral pharmaceutical formulations of the K_{ATP} channel openers selected from the salts of the compounds of Formulae I – VIII, which include at least one component that substantially inhibits release of the K_{ATP} channel opener from the formulation until after gastric transit. Substantial inhibition of drug release during gastric transit is achieved by inclusion of a component in the formulation selected from the group consisting of: (a) a pH sensitive polymer or co-polymer applied as a compression coating on a tablet, (b) a pH sensitive polymer or co-polymer applied as a thin film on a tablet, (c) a pH sensitive polymer or co-polymer applied as a thin film to an encapsulation system, (d) a pH sensitive polymer or co-polymer applied to encapsulated microparticles, (e) a non-aqueous-soluble polymer or copolymer applied as a compression coating on a tablet, (f) a non-aqueous-soluble polymer or co-polymer applied as a thin film on a tablet, (g) a non-aqueous soluble polymer applied as a thin film to an encapsulation system, and (h) a non-aqueous soluble polymer applied to microparticles, wherein the pH sensitive polymer or co-polymer is resistant to degradation under acid conditions. Alternatively, substantial inhibition of drug release during gastric transport can also be achieved by incorporation of the formulation in an osmotic pump system, by use of systems controlled by ion exchange resins, or by combinations of any of the above approaches.

[0064] Also provided herein are controlled release pharmaceutical formulations of K_{ATP} channel openers selected from salts of the compounds of Formulae I – VIII, wherein

Ex. 2002-0971

the formulation includes at least one component that contributes to sustained release of a K_{ATP} channel opener over an extended period, e.g., over a period of 2-24 hours following administration, or over a period of 2-4 hours following administration, or over a period of 4-8 hours following administration, or over a period of more than 8-24 hours following administration. These formulations are characterized in having one of the following components: (a) a pH sensitive polymeric coating, (b) a hydrogel coating, (c) a film coating that controls the rate of diffusion of the drug from a coated matrix, (d) an erodable matrix that controls rate of drug release, (e) polymer coated pellets, granules or microparticles of drug which can be further encapsulated or compressed into a tablet, (f) an osmotic pump system containing the drug, (g) a compression coated tablet form of the drug, or (h) combinations of any of the approaches of (a) – (f) above.

[0065] As used herein, an erodable matrix is the core of a tablet formulation that, upon exposure to a suitable aqueous environment, begins a process of disintegration which facilitates the release of drug from the matrix. The rate of release of drug from the tablet is controlled both by the solubility of the drug and the rate of disintegration of the matrix.

[0066] The above formulations may further comprise one or more additional pharmaceutically active agents (other than K_{ATP} channel openers selected from the salts of the compounds of Formulae I – VIII) useful for the treatment of a condition selected from the group consisting of obesity, prediabetes, diabetes, hypertension, depression, elevated cholesterol, fluid retention, other obesity associated co-morbidities, ischemic and reperfusion injury, epilepsy, cognitive impairment, schizophrenia, mania, other psychotic diseases, and the like.

[0067] Further provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII wherein administration to an obese, overweight or obesity prone subject results in at least one of the following: (a) inhibition of fasting insulin secretion, (b) inhibition of stimulated insulin secretion, (c) elevation of energy expenditure, (d) elevation of beta oxidation of fat, or (e) inhibition of hyperphagia for about 24 hours.

Ex. 2002-0972

[0068] Additionally provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII wherein administration to an obese, overweight or obesity prone subject results in at least one of the following: (a) inhibition of fasting insulin secretion, (b) inhibition of glucose stimulated insulin secretion, (c) elevation of energy expenditure, (d) elevation of beta oxidation of fat, or (e) inhibition of hyperphagia for about 18 hours.

[0069] Still further provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII which upon administration to an obese, overweight or obesity prone subject results in at least one of the following: (a) inhibition of fasting insulin secretion, (b) inhibition of glucose stimulated insulin secretion, (c) elevation of energy expenditure, (d) elevation of beta oxidation of fat, or (e) inhibition of hyperphagia for about 24 hours.

[0070] Additionally provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII that upon administration to an obese, overweight or obesity prone subject results in at least one of the following: (a) inhibition of fasting insulin secretion, (b) inhibition of glucose stimulated insulin secretion, (c) elevation of energy expenditure, (d) elevation of beta oxidation of fat, or (e) inhibition of hyperphagia for about 18 hours.

[0071] In other embodiments of the invention there are provided formulation comprising diazoxide choline and about 1% to about 55% by weight of a polymer as described herein. For example, the polymer may be selected from the group consisting of polyethylene oxide and cellulose. Cellulose suitable for use in such formulations may be selected from hydroxypropylmethyl cellulose, hydroxypropylcellulose, ethylcellulose, methylcellulose, carboxymethylcellulose, and a mixture of any two or more thereof. Various polyethylene oxides may be used in the formulations, including those selected from PEO N750, PEO 303 or a mixture thereof.

[0072] Provided herein are methods of using any of the salts of the compounds of Formulae I – VIII and formulations thereof. For example, provided herein is a method of treating hypoglycemia, the method comprising orally administering to a subject in need

Ex. 2002-0973

thereof, a controlled release formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII.

[0073] Further provided herein is a method of treating obesity associated co-morbidities in an obese, overweight or obesity prone subject, the method comprising administering a therapeutically effective amount of a solid oral dosage form of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII, or controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0074] Yet further provided herein is a method of achieving weight loss in an obese overweight, or obesity prone subject, the method comprising administering a therapeutically effective amount of a solid oral dosage form of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII or controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. The daily dosage administered is preferably between 50 and 180 mg. In certain embodiments, the obese subject has a body mass index greater than 30 kg/m^2, or greater than 35 kg/m^2, or greater than 40 kg/m^2, or greater than 50 kg/m^2, or greater than 60 kg/m^2 at the time the method commences.

[0075] Also provided is a method of maintaining a weight loss in an obese overweight, or obesity prone subject, the method comprising administering a therapeutically effective amount of a solid oral dosage form of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII or controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. 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 preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0076] Also provided is a method of treating obesity or type 1 or type 2 diabetes with a salt of KATP channel opener which minimizes a range of adverse events including but

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not limited to headaches, fluid retention, edema, hyperglycemia, and tachycardia. In accordance with this method, the initial dose is chosen to provide for elevations in supine heart rate that on average are not greater than 5 beats per minute, followed by tolerization and a return to baseline heart rate by the time steady state circulating K_{ATP} channel opener levels are reached. This starting dose is preferably between 10 and 200 mg of K_{ATP} channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Preferably, the K_{ATP} channel opener is diazoxide. The starting dose is given to the patient daily for days or a few weeks. In further embodiments, the method includes escalating the dose which is administered when after supine heart rates return to baseline. An initial escalating dose is established using the same criteria as the initial dose. The initial escalating dose is given to the patient daily for days or a few weeks. The increment in dose is preferentially 25 to 150 mg of K_{ATP} channel opener or the equivalent based on relative bioavailability and potency compared to diazoxide. Further rounds of this dose escalation would continue until the therapeutically effective dose is reached. Alternatively, standing heart rate may be utilized where the average increase is not greater than 10 beats per minute.

[0077] Further provided is a method of treating subjects with type 1 or type 2 diabetes suffering from hypoglycemia associated autonomic failure involving the administration of an agent that either stimulates glucagon release from pancreatic alpha cells via interaction with K_{ATP} channels and/or stimulates hypothalamic neurons resulting in an amplification of or restoration of the counter regulatory hormonal response to hypoglycemia, via activation of K_{ATP} channels. In a preferred embodiment, the agent is a therapeutically effective amount of a formulation selected from the group consisting of:

i) a formulation comprising a salt, wherein the salt comprises an anion of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group;

ii) a formulation comprising a salt, wherein the salt comprises an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and

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iii) a formulation comprising a salt, wherein the salt comprises an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent of the compound of Formulae V–VIII includes an amino group. In another embodiment, the compound of Formula V-VIII forms the anion of the salt and a monovalent or divalent metal forms the cation. In other embodiments, the cation includes a tertiary amino or quaternary ammonium group.

[0078] Further provided is a method of elevating energy expenditure in an overweight, obese or obesity prone subject, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII or controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. In certain embodiments, the subject has a body mass index greater than 20 kg/m^2, or greater than 25 kg/m^2, or greater than 30 kg/m^2, or greater than 35 kg/m^2, or greater than 40 kg/m^2, or greater than 50 kg/m^2, or greater than 60 kg/m^2 at the time the method commences.

[0079] Additionally provided is a method of elevating beta oxidation of fat in an overweight, obese or obesity prone subject, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII or controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. In certain embodiments, the subject has a body mass index greater than 20 kg/m^2, or greater than 25 kg/m^2, or greater than 30 kg/m^2, or greater than 35 kg/m^2, or greater than 40 kg/m^2, or greater than 50 kg/m^2, or greater than 60 kg/m^2 at the time the method commences.

[0080] Yet further provided is a method of reducing visceral fat in an overweight, obese or obesity prone subject, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII or controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. In a

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preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0081] Still further provided is a method of delaying or preventing the transition to diabetes of a prediabetic subject comprising administering an effective amount of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII or controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0082] Additionally provided is a method of restoring normal glucose tolerance in a prediabetic subject comprising administering an effective amount of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII or controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0083] Further provided is a method of restoring normal glucose tolerance in a diabetic subject comprising administering an effective amount of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII or controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0084] Still further provided is a method of delaying or preventing progression of diabetes in an subject comprising administering an effective amount of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII or controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0085] Also provided is a method to prevent or treat weight gain, impaired glucose tolerance or dyslipidemia associated with the administration of anti-psychotics to a subject, said method including the co-administration of an effective amount of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII or

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controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0086] Further provided is a method to treat obesity, or hyperphagia in a Prader-Willi Syndrome patient, a Froelich's Syndrome patient, in a Cohen Syndrome patient, in a Summit Syndrome patient, in an Alstrom Syndrome patient, in a Borjeson Syndrome patient or in a Bardet-Biedl Syndrome patient comprising the administration of an effective amount of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII or controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0087] Still further provided is a method to treat obesity or elevated triglycerides in a patient suffering hyperlipoproteinemia type I, type II, type III or type IV comprising administering an effective amount of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII or controlled release pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0088] Also provided is a method of reducing the incidence of adverse effects from administration of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII in the treatment of diseases of a subject achieved by any of the following: (a) use of a dosage form that on administration reduces C_{max} relative to the current Proglycem® oral suspension or capsule products in order to reduce the incidence of adverse side effects that are associated with peak drug levels, (b) use of a dosage form that delays release until gastric transit is complete in order to reduce the incidence of adverse side effects that are associated with the release of drug in the stomach, (c) initiating dosing at subtherapeutic levels and in a stepwise manner increasing dose daily until the therapeutic dose is achieved wherein the number of steps is 2 to 10 to reduce the incidence of adverse side effects that occur transiently at the initiation of treatment, (d) use of the lowest effective dose to achieve the desired therapeutic effect in order to reduce

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the incidence of adverse side effects that are dose dependent, or (e) optimizing the timing of administration of dose within the day and relative to meals.

[0089] Further provided is a method of reducing the incidence of adverse effects from administration of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII without substantially impacting the pharmacokinetic profile of said administered K_{ATP} channel opener, comprising administering to a subject said K_{ATP} channel opener orally in conjunction with a meal which includes solid food. As used herein, in administration of the opener in conjunction with a meal means that the two are ingested within 15 minutes of each other. Accordingly, there is provided a method of reducing the incidence of adverse effects resulting from orally administering a salt of a K_{ATP} channel opener comprising, causing to be orally ingested a formulation selected from the group consisting of:

i) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group;

ii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and

iii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group; and,

a meal containing one or more solid food items sufficient to reduce the incidence of adverse effects resulting from the orally ingested salt of a K_{ATP} channel opener. In a preferred embodiment, the formulation and the meal are taken within 15 minutes or less of each other.

[0090] Further provided is a method of preventing weight gain, dyslipidemia or impaired glucose tolerance in a subject treated with an anti-psychotic drug, the method comprising administering a pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII.

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[0091] Yet further provided is a method of treating weight gain, dyslipidemia or impaired glucose tolerance in a subject treated with an anti-psychotic drug, the method comprising administering a pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII.

[0092] Also provided is a method of treating diseases characterized by obesity, hyperphagia, dyslipidemia, or decreased energy expenditure including (a) Prader-Willi Syndrome, (b) Froelich's syndrome, (c) Cohen syndrome, (d) Summit Syndrome, (e) Alstrom Syndrome, (f) Borjesen Syndrome, (g) Bardet-Biedl Syndrome, or (h) hyperlipoproteinemia type I, II, III, and IV comprising administering a pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII.

[0093] Further provided is a pharmaceutical formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII further comprising a pharmaceutically active agent other than the K_{ATP} channel opener. In this formulation, 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, or other obesity associated co-morbidities, ischemic and reperfusion injury, epilepsy, cognitive impairment, schizophrenia, mania, and other psychotic condition.

[0094] The formulations containing K_{ATP} channel openers selected from the salts of the compounds of Formulae I – VIII described herein provide for improved compliance, efficacy and safety, and for co-formulations with other agents. Included are co-formulations of K_{ATP} channel openers selected from the salts of the compounds of Formulae I – VIII with one or more additional pharmaceutically active agents that have complementary or similar activities or targets. Other pharmaceutically active agents that can be combined with K_{ATP} channel openers selected from the salts of the compounds of Formulae I – VIII to treat obesity or to maintain weight loss in an obesity prone subject include, but are not limited to: sibutramine, orlistat, phentermine, rimonabant, a diuretic, an antiepileptic, or other pharmaceutical active whose therapeutic utility includes weight loss. It is preferable to maintain weight in an obese subject once some weight loss has occurred when the alternative is to regain weight. Other pharmaceutically active agents

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that may be combined with K_{ATP} channel openers selected from the salts of the compounds of Formulae I – VIII to treat type II diabetes, or prediabetes include acarbose, miglitol, metformin, repaglinide, nateglinide, rosiglitazone, proglitazone, ramipril, metaglidasen, or any other pharmaceutical active that improves insulin sensitivity or glucose utilization or glycemic control where the mode of action is not enhanced insulin secretion. Other pharmaceutical active agent that can be combined with K_{ATP} channel openers selected from the salts of the compounds of Formulae I – VIII to treat obesity associated co-morbidities include a drug active used to lower cholesterol, a drug active used to lower blood pressure, an anti-inflammatory drug that is not a cox-2 inhibitor, a drug that is an antidepressant, a drug used to treat urinary incontinence, or other drug routinely used to treat disease conditions the incidence of which is elevated in overweight or obese patients as compared to normal weight subjects including, but not limited to, drugs to treat atherosclerosis, osteoarthritis, disc herniation, degeneration of knees and hips, breast, endometrium, cervical, colon, leukemia and prostate cancers, hyperlipidemia, asthma/reactive airway disease, gallstones, GERD, obstructive sleep apnea, obesity hypoventilation syndrome, recurrent ventral hernias, menstrual irregularity and infertility.

[0095] Also provided herein are methods for treating obesity or obesity associated co-morbidities or other diseases or conditions involving K_{ATP} channels by co-administration to a subject in need thereof of an effective amount of any of the compounds according to Formulae I-VIII, or a salt of any of the compounds according to Formulae I-VIII or pharmaceutical formulation thereof, and a drug selected from the group consisting of an amphetamine or amphetamine mixture, Sibutramine, Orlistat, Rimonabant, a CB-1 antagonist, a $5HT_{2c}$ receptor agonist, a drug used to treat addiction, a beta adrenergic receptor agonist, an ACC inhibitor, leptin, a leptin analogue, a leptin agonist, a somatostatin agonist, an adiponectin agonist or secretagogue, Amylin, PYY or a PYY analogue, a ghrelin antagonist, a drug that inhibits gastrointestinal lipases or other digestive enzymes, a de-novo lipogenesis inhibitor, a drug that blocks absorption of dietary fat, growth hormone or a growth hormone analogue, a growth hormone secretagogue, a CCK agonist, an oleoylethanolamine receptor agonist, a fatty acid synthase inhibitor, a thyroid receptor agonist, a selective androgen receptor modulator, a PPAR agonist, a Beta hydroxysteroid Dehydrogenase-2 inhibitor, oxyntomodulin, oleoylestrone, a NPY2 receptor antagonist, a NPY5 receptor antagonist, a NPY agonist, a

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monoamine uptake inhibitor, a MTP inhibitor, a MC4 receptor agonist, a MCH1 receptor antagonist, a 5HT-6 antagonist, a histamine-3 antagonist, a glycine analog, a fgf1 inhibitor, a DGAT-1 inhibitor, a carboxypeptidase inhibitor, 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 improves insulin sensitivity, a drug that improves glucose utilization or uptake, 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, a drug that is used to induce weight loss in an overweight or obese individual, and pharmaceutically acceptable salts thereof.

[0096] Provided herein are methods of (a) inhibiting or preventing the progression of type I diabetes, (b) reducing insulin dosing, (c) increasing glycemic control, or (d) delaying the loss of residual insulin secretion in a subject suffering from type I diabetes, comprising administering to said subject a therapeutically effective amount of a formulation of a K_{ATP} channel opener selected from the salts of the compounds of Formulae I – VIII. For example, the formulation may be selected from the group consisting of: i) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group; ii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and iii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline.

[0097] As noted above, the methods described herein can be used to inhibit or prevent the progression of Type I diabetes. In some such methods, the rate of beta cell loss is decreased by, e.g., about 5% to about 95% compared to the subject prior to administration of the formulations of the present invention. In other instances, the rate of beta cell loss is

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decreased by at least about 5%, 10%, 15%, 20%, 25%, 30% 40%, 50%, 60%, 70%, 80%, 90%, or 95% compared to the subject prior to administration of the formulations of the present invention, or prior to administration of a combination of the formulation as described herein and additional therapeutic agent(s).

[0098] The methods described herein can be used to reduce insulin dosing as described above. In some instance of the methods, the insulin dosing is decreased by about 5% to about 95% in a subject, compared to the subject's insulin dose prior to being administered the formulations of the present invention, or prior to administration of a combination of the formulation as described herein and additional therapeutic agent(s). In other instances of the methods, the insulin dosing is decreased by at least about 5%, 10%, 20%, 30%, or 50%.

[0099] As described above, the methods described herein can be used to increase glycemic control. "Glycemic control" refers to attempts to reproduce natural physiological glucose homeostasis. Accordingly, glycemic control is increased in a subject when the natural physiological glucose homeostasis is attained more often in a subject administered the formulations of the present invention compared to the subject prior to administration of the formulations.

[00100] The methods described herein can be used to delay the loss of residual insulin secretion. Residual insulin secretion refers to the partial preservation of islet beta-cell function, as demonstrated by preserved insulin production in subjects having Type I diabetes. Although not sufficient for the needs of the individual, residual insulin secretion is important for metabolic control, for avoidance of hypoglycemic episodes, and for protection against diabetic complications. To retain residual insulin secretion in type I diabetes is highly desirable. As used herein, the term "residual insulin secretion" refers to a level of insulin production by islet beta cells that is least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, or 60% of the level produced by a subject not diagnosed with Type I diabetes. In one instance, the methods provide that the loss of residual insulin secretion is delayed by at least about 3 months, 6 months, 12 months, 15 months, 18 months, 21 months, or up to 48 months compared to a subject not administered the formulations of the present invention.

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[00101] Further provided herein are methods of increasing insulin sensitivity in a subject suffering from type II diabetes, comprising administering to said subject a therapeutically effective amount of a formulation of a KATP channel opener selected from the salts of the compounds of Formulae I – VIII. For example, the formulation may be selected from the group consisting of: i) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group; ii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and iii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. In the methods, the therapeutically effective amount of the formulation may range from about 15 mg/day to about 500 mg/day. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline.

[00102] The methods described herein can be used to increase insulin sensitivity in a subject by, e.g., about 10% to about 95% or more. In one instance, the insulin sensitivity is increased in a subject by at least about 30% compared to the subject prior to administration of the formulations of the present invention. In other instances, the insulin sensitivity is increased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70%, 80% or 90% compared to the subject prior to administration of the formulations of the present invention, or prior to administration of a combination of the formulation as described herein and additional therapeutic agent(s). Insulin sensitivity is indicated, for example, by reductions in the homeostasis model assessment-insulin resistance (HOMA-IR) index.

[00103] Still further provided are methods of treating a subject suffering from type II diabetes, comprising co-administering to said subject a therapeutically effective amount of a formulation and an anti-diabetic drug that either stimulates insulin secretion or is a short acting anti-diabetic drug, wherein the formulation is selected from the group

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consisting of : i) a formulation comprising a KATP channel opener selected from the group consisting of Formulae I – VIII; ii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group; iii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and iv) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. In related embodiments of the above method, the anti-diabetic drug stimulates insulin secretion in a meal dependent fashion or is a short acting anti-diabetic drug with a circulating half life less than 5 hours. In the methods, the formulation and the anti-diabetic drug may be co-administered separately, sequentially or simultaneously. Suitable anti-diabetic drugs include but are not limited to exenatide, natiglinide, mitglinide, repaglinide, a DPP-IV inhibitor (for example vildagliptin, sitagliptin and saxagliptin) , a PPAR agonist or partial agonist, a GLP-1 analog (e.g., liraglutide) or mimetic (e.g., modified exendin-4 analogue) or agonist, a thiazolidinedione, a disaccharidase inhibitor, a fructose-1, 6-bisphosphatase inhibitor, a sulfonylurea receptor antagonist such as meglitinides and pharmaceutically acceptable salts thereof .

[00104] In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline.

[00105] In some embodiments of treating type II diabetes, the anti-diabetic drug may be one or more agents selected from the group consisting of a GLP-1 analog or mimetic, and a sulfonylurea receptor antagonist such as meglitinides.

[00106] Suitable sulfonylurea receptor antagonists for use in methods described herein include one or more agents selected from the group consisting of, but not limited to nateglinide, mitglinide, repaglinide and pharmaceutically acceptable salts thereof.

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[00107] Suitable DPP-IV inhibitors for use in the present methods include one or more agents selected from the group consisting of, but limited to sitagliptin, saxagliptin, vildagliptin, and pharmaceutically acceptable salts thereof.

[00108] GLP-1 analogs or mimetics that may be used in the present methods include one or more agents selected from the group consisting of exenatide, liraglutide, albugon, exendin-4 analogs and conjugates, and pharmaceutically acceptable salts and conjugates thereof.

[00109] Suitable meglitinides for use in the present methods include one or more agents selected from the group consisting of, but not limited to repaglinide, nateglinide, mitiglinide and pharmaceutically acceptable salts thereof.

[00110] Likewise suitable thiazolidinediones, PPAR agonists or partial agonists that may be used in the methods described herein include one or more agents selected from the group consisting of, but not limited to pioglitazone, rosiglitazone, troglizazone, tesaglitazar, muraglitazar, netoglitazar, LY518674, ragaglitazar, sipoglitazar, and pharmaceutically acceptable salts thereof.

[00111] Exemplary disaccharidase inhibitor for use in the present methods include one or more agents selected from the group consisting of, but not limited to acarbose, AO-128, and pharmaceutically acceptable salts thereof.

[00112] Fructose-1,6-bisphosphatase inhibitors suitable for use in the present methods include one or more agents selected from the group consisting of, but not limited to phenyl phosphonates, benzimidazoles, CS-917, anilinoquinazolones, and benzoxaozole benzenesulfonamides, and pharmaceutically acceptable salts thereof.

[00113] The formulation and anti-diabetic may be combined in a single pharmaceutical composition. For example, the formulation and anti-diabetic may be combined in a controlled release pharmaceutical composition comprising 50 to 500 mg of diazoxide choline and 20 to 100 mg of sitagliptin. While typically such controlled release pharmaceutical compositions are administered once per 24 hours, other dosing regimens are contemplated including two or three times a day or every other day.

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[00114] Exemplary anti-diabetic drug for use in the present methods include one or more agents selected from the group consisting of, exenatide, nateglinide, mitglinide, repaglinide, and pharmaceutically acceptable salts or conjugates thereof.

[00115] Alternatively, the formulation may comprise 50 to 450 mg of diazoxide choline and is administered once per 24 hours as a controlled release oral formulation, and the anti-diabetic is a pharmaceutical composition comprising 5 to 10 μg exenatide and is administered twice per 24 hours, before meals. In such methods, the controlled release oral formulation may be a tablet and the exenatide may be administered by subcutaneous injection.

[00116] In some embodiments of methods of treating type II diabetes, the formulation comprises 50 to 500 mg of diazoxide choline and is administered once per 24 hours as a controlled release oral formulation, and the anti-diabetic is a pharmaceutical composition comprising the meglitinide and is administered three times per 24 hours, before meals.

[00117] Provided herein are methods of treating a dyslipidemia by (a) reducing an abnormally high total cholesterol level in a subject's blood, (b) reducing an abnormally high LDL cholesterol level in a subject's blood, (c) reducing an abnormally high VLDL cholesterol level in a subject's blood (d) reducing an abnormally high non-HDL cholesterol level in a subject's blood (e) reducing an abnormally high triglyceride level in a subject's blood and/or (b) raising an abnormally low HDL cholesterol level in a subject's blood level, comprising administering to said subject a therapeutically effective amount of a formulation selected from the group consisting of:

i) a formulation comprising a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, Formula V, Formula VI, Formula VII, and Formula VIII;

ii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group;

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iii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and

iv) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. As used herein, a reduction in the various specified cholesterol containing lipoproteins in the circulation amounts to a reduction , e.g., by about 1% to about 60%, by about 1% to about 30%, by about 2% to about 20%. In other embodiments the subject's HDL cholesterol level may be raised, e.g., by about 1% to about 60%, by about 1% to about 50%, by about 2% to about 40%. The subject's triglycerides level may also be reduced by the present methods by about 5% to about 95%, by about 5% to about 90%, by about 5% to about 85%, by about 10% to about 95%, by about 10% to about 90%, or by about 10% to about 85%. The subject may suffer from or may be at risk for pancreatitis and or may be obese. In some embodiments the formulation is administered once, twice or three times per 24 hours. In other embodiments, the formulation comprises diazoxide choline.

[00118] In some embodiments, multiple administrations of the formulation are given over a period of days. In such cases, the caloric intake of the subject during the period of days is substantially the same as before the formulation was administered. As used in this context, "substantially" means less than 15% change, more preferably less than 10% change, or even more preferably at least less than 5% change. In a most preferred embodiment, the caloric intake of the subject is the same before administration and during the period of days during administration.

[00119] Provided herein are methods of (a) reducing circulating androgen levels, or (b) reestablishing normal ovulation cycles, in a subject suffering from poly-cystic ovarian syndrome, comprising administering to said subject a therapeutically effective amount of a formulation of a KATP channel opener selected from the salts of the compounds of Formulae I – VIII. For example, the formulation may be selected from the group consisting of: i) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a

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compound comprising a tertiary amine or ammonium group; ii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and iii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline.

[00120] As noted above, methods described herein can be used to reduce the circulating androgen levels in a subject by, e.g., about 5% to about 95% of the level of circulating androgen compared to the subject prior to administration of the formulations of the present invention. In other instances, the level of circulating androgen is reduced by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 60%, 70% or 80% compared to the subject prior to administration of the formulations of the present invention, or prior to administration of a combination of the formulation as described herein and additional therapeutic agent(s). Circulating androgen can be measured in a subject using any suitable method known in the art.

[00121] The methods described herein can be used to reestablish normal ovulation cycles in a subject. Ovulation is the time in a female subject's menstrual cycle when the ovum, or egg, is released. It is when a woman is most fertile and likely to conceive. Ovulation occurs 12 or 14 days before menstruation. A menstruation period begins about every 28 days if the woman does not become pregnant in a given cycle. In one instance, a normal ovulation cycle of approximately 28 days is reestablished in a subject, where the subject experienced a cycle of greater than or fewer than 28 days prior to administration of the formulations of the present invention. Ovulation can be measured using any means available, including urinary kits, basal body temperature tests, a cervical mucus test and a blood test.

[00122] Still further provided are methods of treating a subject suffering from poly-cystic ovarian syndrome comprising co-administering to said subject a therapeutically effective amount of a formulation and an anti-androgen therapy, wherein the formulation is selected from the group consisting of: i) a formulation comprising a salt, said salt

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comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group; ii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and iii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. In the methods, the formulation and the anti-androgen therapy may be co-administered separately, sequentially or simultaneously. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline.

[00123] Also provided are methods of treating a subject suffering from poly-cystic ovarian syndrome comprising co-administering to said subject a therapeutically effective amount of a formulation and a selective estrogen receptor modulator (SERM) therapy, wherein the formulation is selected from the group consisting of: i) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group; ii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and iii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. In the methods, the formulation and the selective estrogen receptor modulator (SERM) therapy may be co-administered separately, sequentially or simultaneously. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline. In some embodiments of the methods the SERM includes clomiphene (or a salt thereof) or ormeloxifene.

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[00124] Further provided are methods of treating a subject suffering from poly-cystic ovarian syndrome comprising co-administering to said subject a therapeutically effective amount of a formulation and an ovulation inducing therapy, wherein the formulation is selected from the group consisting of: i) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group; ii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and iii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. In the methods, the formulation and the ovulation inducing therapy may be co-administered separately, sequentially or simultaneously. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline. In some embodiments of the methods the ovulation inducing therapy includes follicle stimulating hormone.

[00125] Still further provided are methods of treating a subject suffering from poly-cystic ovarian syndrome comprising co-administering to said subject a therapeutically effective amount of a formulation and an aromatase inhibitor therapy, wherein the formulation is selected from the group consisting of: i) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group; ii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and iii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. In the methods, the formulation and the aromatase inhibitor therapy may be co-administered separately, sequentially or simultaneously. In some

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embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline. In some embodiments of the methods the aromatase inhibitor therapy includes letrozole or anastrozole.

[00126] Provided herein are methods of treating a subject suffering from hypertension comprising administering to said subject a therapeutically effective amount of a single oral agent wherein the oral agent is a formulation of a KATP channel opener selected from the salts of the compounds of Formulae I – VIII. For example, the formulation may be selected from the group consisting of: i) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group; ii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and iii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline.

[00127] Also provided herein are methods of treating a subject suffering from hypertension comprising co-administering to said subject a therapeutically effective amount of a formulation and an oral anti-hypertensive agent, wherein the formulation of a KATP channel opener is selected from the salts of the compounds of Formulae I – VIII. For example, the formulation may be selected from the group consisting of: i) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group; ii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and iii) a formulation

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comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline.

[00128] Further provided are methods of treating a subject suffering from pulmonary hypertension comprising administering to said subject a therapeutically effective amount of a formulation selected from the group consisting of:

i) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group;

ii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and

iii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. The amount of the formulation is effective to lower pulmonary arteriolar resistance and pulmonary artery pressure and, in some embodiments, to bring pulmonary arteriolar resistance and pulmonary artery pressure within normal limits (systolic 15-30mm Hg, diastolic 6-12mm Hg). Treatment may be continued as long as the subject continues to suffer from pulmonary hypertension. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline, in the form of, e.g., controlled release tablets.

[00129] Also provided herein are methods of treatment to prevent late post-myocardial infarction arrhythmias comprising administering to a subject that has recently suffered a myocardial infarction a therapeutically effective amount of a pharmaceutical formulation wherein the formulation includes a K_{ATP} channel opener selected from the salts of the

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compounds of Formulae I – VIII. For example, the formulation may be selected from the group consisting of:

i) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group;

ii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and

iii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. By recently suffered a myocardial infarction is meant that the myocardial infarction has occurred within the last 48 hours. The subject is typically treated for a minimum of one year or until the period of late remodeling is complete. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline, in the form of, e.g., controlled release tablets.

[00130] Also provided herein are methods of treating a subject immediately following the detection of myocardial infarction to limit infarct size and prevent arrhythmias. The methods include administering to the subject a therapeutically effective amount of a pharmaceutical formulation selected from the group consisting of:

i) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group;

ii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and

iii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group.

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Treatment may be continued after the infarction for a minimum of one year or until the period of late remodeling is complete. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline, in the form of, e.g., controlled release tablets. As used herein, reference to beginning treatment "immediately" following the detection of myocardial infarction means that the treatment is begun within one hour after diagnosis of infarction, and less preferably between 1-2 hours, 2-3, 3-4 hours, 4-8 hours and 8-24 hours post diagnosis of infarction.

[00131] Provided herein are methods of treating a subject at risk for myocardial infarction to prevent infarction, limit infarct size, and/or to prevent arrhythmias. The methods include administering to the subject a therapeutically effective amount of a pharmaceutical formulation selected from the group consisting of:

i) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group;

ii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and

iii) a formulation comprising a salt, said salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. Treatment may be continued for as long as the subject is at risk for myocardial infarction. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. In certain embodiments, the formulation comprises diazoxide choline, in the form of, e.g., controlled release tablets.

[00132] In the above methods relating to treating heart disease such as myocardial infarction (or its prevention) or arrhythmias, the administration of the KATP channel opener (such as diazoxide) may be beneficial by acting as an anti-inflammatory agent. Diazoxide is known to have anti-inflammatory effects (see Xu et al., J. Hypertension. 2006 24: 915-922; Wang et al., Shock 2004, 22:23-28).

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[00133] Provided herein are methods of treating a subject suffering from hypoglycemia-associated autonomic failure comprising administering to said subject a therapeutically effective amount of a formulation of a KATP channel opener selected from the salts of the compounds of Formulae I – VIII. For example, the formulation may be selected from the group consisting of: i) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group; ii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; iii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group; and iv) a formulation comprising 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine. In the methods the subject may also be suffering from type I diabetes or type II diabetes. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24 hours. The formulation may also be an oral or an intranasal formulation. In certain embodiments, the formulation comprises diazoxide choline.

[00134] A method of inducing or increasing beta-cell rest in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of a formulation of a KATP channel opener selected from the salts of the compounds of Formulae I – VIII. For example, the formulation may be selected from the group consisting of: i) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group; ii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and iii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. In some embodiments of the methods, the formulation may be administered once, twice or three times per 24

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hours. In certain embodiments, the formulation comprises diazoxide choline. In the methods, the subject may also be obese or overweight or suffer from type II diabetes.

[00135] Also provided herein are polymorphic forms (i.e., "polymorphs") of the compounds of Formulae I – VIII, as exemplified by the X-ray Power Diffraction (XRPD) patterns shown in any of the figures.

[00136] Also provided are polymorphs of salts of diazoxide which include diazoxide and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or quaternary ammonium group.

[00137] Also provided herein are methods for producing a diazoxide choline salt, which includes suspending diazoxide in a solvent and mixing with a choline salt, adding a co-solvent to the suspension under conditions sufficient to cause formation and precipitation of the diazoxide choline salt, and harvesting the precipitate to provide the diazoxide choline salt.

[00138] Also provided herein are methods of treating obesity or obesity-related co-morbidity in an obese subject, wherein the method comprising administering to a subject in need thereof an effective amount of a compound of Formula V-VIII.

[00139] Also provided herein are methods for treatment of a subject suffering from or at risk for Alzheimer's disease (AD), which methods include administration to a subject a therapeutically effective amount of a pharmaceutical formulation comprising a compound of any of Formulae I-VIII as provided herein. In some embodiments, the compound is diazoxide. Also provided herein are methods for treatment of a subject suffering from or at risk for AD, which methods include administration to a subject a therapeutically effective amount of a salt of a compound according to any of Formulae I-VIII. In some embodiments, the compound is a salt of diazoxide.

[00140] In another embodiment, the invention provides a method for treating hypoglycemia by administration of an effective amount of a pharmaceutical formulation comprising a salt selected from the group consisting of a) a salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali

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metal and a compound comprising a tertiary amine or ammonium group; b) a salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and c) a salt comprising a cation of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group.

[00141] In further embodiments, the hypoglycemia is selected from the group consisting of a) nighttime hypoglycemia, b) hypoglycemia attributable to a defect in insulin secretion, c) attributable to an insulin secreting tumor, and d) drug-induced hypoglycemia.

[00142] Provided herein are methods of treating obesity or type 1 or type 2 diabetes in a companion animal. The methods include administering to said animal a therapeutically effective amount of a formulation selected from the group consisting of: i) a formulation comprising a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, Formula V, Formula VI, Formula VII, and Formula VIII; ii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising a tertiary amine or ammonium group; iii) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII; and iv) a formulation comprising a salt, said salt comprising an anion of a KATP channel opener selected from the group consisting of Formula V, Formula VI, Formula VII and Formula VIII, wherein at least one substituent comprises an amino group. Typically, the animal is a cat, a dog or a horse. The formulation can be suitable for oral administration, e.g., a controlled release tablet or capsule, or a chewable formulation. Alternatively, the formulation may be a granulated controlled release formulation which can be applied to food for the animal, e.g., a powder. In some embodiments, the formulation is administered once or twice per 24 hours. In certain embodiments, the formulation comprises diazoxide choline.

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[00143] Provided herein are methods of treating a dyslipidemia in a subject having a triglyceride level of at least about 500 mg/dL and an HDL-C level of about 40 mg/dL or less, the method comprising administering to the subject a therapeutically effective amount of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and salts thereof. In some embodiments, the K_{ATP} channel opener comprises an anion Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising an ammonium group comprising at least one tertiary amine group. In some embodiments, the said K_{ATP} channel opener comprises a salt of diazoxide; such as diazoxide choline. In some embodiments, the K_{ATP} channel opener is formulated as a controlled release formulation for oral administration; such as a formulation formulated for once or twice a day administration. In some embodiments, the subject is administered about 145 to 435 mg per day of said K_{ATP} channel opener. In some embodiments, the K_{ATP} channel opener is co-administered or co-formulated with a therapeutically effective amount of a second active compound for lowering triglycerides, raising HDL-C, lowering LDL-C, or any combination thereof. In some related embodiments, the second active compound comprises a statin or a fibrate. In some related embodiments, the second active compound comprises a fibrate or a salt thereof; such as fenofibrate or a salt thereof; such as fenofibrate choline. In some further related embodiments, the subject is administered about 45 to 200 mg per day of fenofibrate choline. In some embodiments, the subject is a human.

[00144] Provided herein are methods for treating dyslipidemia in a subject having a triglyceride level of at least about 1000 mg/dL, the methods comprising administering to the subject a therapeutically effective amount of a fibrate or a salt thereof and a therapeutically effective amount of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and salts thereof. In some embodiments, the K_{ATP} channel opener comprises an anion Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising an ammonium group comprising at least one tertiary amine group. In some embodiments, the said K_{ATP} channel opener comprises a salt of diazoxide; such as diazoxide choline. In some embodiments, the K_{ATP} channel opener is formulated as a controlled release formulation for oral administration; such as a

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formulation formulated for once or twice a day administration. In some embodiments, the subject is administered about 145 to 435 mg per day of said K_{ATP} channel opener. In some embodiments, the fibrate or a salt thereof; such as fenofibrate or a salt thereof; such as fenofibrate choline. In some related embodiments, the subject is administered about 45 to 200 mg per day of fenofibrate choline. In some embodiments, the fibrate or a salt thereof and the K_{ATP} channel opener are co-formulated, such as a controlled release formulation for oral administration, such as formulated for once or twice a day administration. In some embodiments, the subject is human.

[00145] Provided herein are methods for reducing elevated triglycerides in a subject undergoing statin therapy, the methods comprising administering to the subject a therapeutically effective amount of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and salts thereof. In some embodiments, the K_{ATP} channel opener comprises an anion Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising an ammonium group comprising at least one tertiary amine group. In some embodiments, the said K_{ATP} channel opener comprises a salt of diazoxide; such as diazoxide choline. In some embodiments, the K_{ATP} channel opener is formulated as a controlled release formulation for oral administration; such as a formulation formulated for once or twice a day administration. In some embodiments, the subject is administered about 145 to 435 mg per day of said K_{ATP} channel opener. In some embodiments, the K_{ATP} channel opener is co-administered or co-formulated with a therapeutically effective amount of a third active compound for lowering triglycerides. In some related embodiments, the third active compound comprises a fibrate or a salt thereof; such as fenofibrate or a salt thereof; such as fenofibrate choline. In some further related embodiments, the subject is administered about 45 to 200 mg per day of fenofibrate choline. In some related embodiments, the fibrate or a salt thereof and the K_{ATP} channel opener are co-formulated, such as a controlled release formulation for oral administration, such as for once or twice a day administration. In some related embodiments, the subject is human.

[00146] Provided herein are methods for treating a subject with nonalcoholic steatohepatitis (NASH), the methods comprising administering to the subject a

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therapeutically effective amount of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and salts thereof. In some embodiments, the K_{ATP} channel opener comprises an anion Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising an ammonium group comprising at least one tertiary amine group. In some embodiments, the said K_{ATP} channel opener comprises a salt of diazoxide; such as diazoxide choline. In some embodiments, the K_{ATP} channel opener is formulated as a controlled release formulation for oral administration; such as a formulation formulated for once or twice a day administration. In some embodiments, the subject is administered about 145 to 435 mg per day of said K_{ATP} channel opener. In some embodiments, the K_{ATP} channel opener is co-administered or co-formulated with a therapeutically effective amount of a second active compound. In some related embodiments, the second active compound comprises a fibrate or a salt thereof; such as fenofibrate or a salt thereof; such as fenofibrate choline. In some further related embodiments, the subject is administered about 45 to 200 mg per day of fenofibrate choline. In some related embodiments, the second active compound comprises a statin. In some related embodiments, the second active compound and the K_{ATP} channel opener are co-formulated, such as a controlled release formulation for oral administration, such as for once or twice a day administration. In some related embodiments, the subject is human.

[00147] Also provided herein are pharmaceutical formulations comprising diazoxide choline, wherein oral administration of a 290 mg dose of diazoxide choline in the formultations once daily to a subject results in steady state $AUC_{0-24} > 500$ µg*hr/mL. In some embodiments, oral administration of a 290 mg dose of diazoxide choline in the formulations once daily to a subject further results in steady state % Peak-to-Trough Fluctuation of less than 30%. In some embodiments, oral administration of a 290 mg dose of diazoxide choline in the formulations once daily to a subject results in steady state average circulating drug level ($C_{av(ss)}$) between 14 and 31 µg/mL. In some embodiments, the pharmaceutical formulations are compressed tablet formulations.

[00148] Also provided herein are parmaceutical formulations comprising a salt of diazoxide formulated for oral administration, wherein bioavailability of diazoxide is at

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least about 50%; such as at least about 75%; such as at least about 90%. In some related embodiments, the salt of diazoxide is diazoxide choline. In some further related embodiments, diazoxide choline is of polymorph form B. In some embodiments, the pharmaceutical formulations are compressed tablet formulations.

[00149] Also provided herein are methods for treating a dyslipidemia in a subject, the method comprising administering to the subject: a) a formulation comprising one or more omega-3 fatty acids, and b) a formulation comprising a therapeutically effective amount of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and salts thereof. In some embodiments, the K_{ATP} channel opener comprises an anion Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising an ammonium group comprising at least one tertiary amine group. In some embodiments, the dyslipidemia is selected from the group consisting of abnormally high total cholesterol level in a subject's blood, abnormally high LDL cholesterol, abnormally high VLDL cholesterol, abnormally high non-HDL cholesterol, abnormally high triglycerides, abnormally low HDL cholesterol, or any combination thereof. In some embodiments, the dyslipidemia comprises abnormally high triglycerides; such as a triglyceride level of at least about 500 mg/dL; such as a triglyceride level of at least about 1000 mg/dL. In some embodiments, the said K_{ATP} channel opener comprises a salt of diazoxide; such as diazoxide choline. In some embodiments, the K_{ATP} channel opener is formulated as a controlled release formulation for oral administration; such as a formulation formulated for once or twice a day administration. In some embodiments, the subject is administered about 145 to 435 mg per day of said K_{ATP} channel opener. In some embodiments, the omega-3 fatty acid formulation is substantially free of DHA.

[00150] Also provided herein are methods for initiating treatment for a dyslipidemia in a subject, the methods comprising administering a fibrate or a salt thereof and a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and salts thereof; wherein the fibrate or a salt thereof and the K_{ATP} channel opener are both initially administered at sub-optimal titration doses, and the doses of both are increased to maintenance doses over 7 to 28 days. In some embodiments, the K_{ATP} channel opener comprises an anion Formula I, Formula II,

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Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising an ammonium group comprising at least one tertiary amine group. In some embodiments, the dyslipidemia comprises a triglyceride level of at least about 500 mg/dL. In some related embodiments, the dyslipidemia further comprises a HDL-C level of less than about 40 mg/dL. In some embodiments, the dyslipidemia comprises a triglyceride level of at least about 1000 mg/dL. In some embodiments, the titration doses of the fibrate or a salt thereof and the K_{ATP} channel opener are about between about one third to about one half of the corresponding maintenance doses. In some embodiments, the K_{ATP} channel opener is formulated as a controlled release formulation for oral administration for oral administration; such as for once or twice daily administration. In some embodiments, the K_{ATP} channel opener comprises a salt of diazoxide; such as diazoxide choline. In some embodiments, the K_{ATP} channel opener titration dose is about 70 mg to 220 mg. In some embodiments, the K_{ATP} channel opener maintenance dose is about 145 mg to 435 mg. In some embodiments, the fibrate or a salt thereof is formulated as a controlled release formulation for oral administration; such as for once or twice daily administration. In some embodiments, the fibrate fibrate or a salt thereof comprises fenofibrate or a salt thereof; such as fenofibrate choline. In some embodiments, the titration dose of the fibrate or a salt thereof is about 35 mg to 100 mg. In some embodiments, the the maintenance dose of the fibrate or a salt thereof is about 100 mg to about 200 mg. In some embodiments, the titration doses of the fibrate or a salt thereof and the K_{ATP} channel opener are co-formulated; such as co-formulated as a controlled release formulation for oral administration; such as for once or twice daily administration. In some embodiments, the maintenance doses of the fibrate or a salt thereof and the K_{ATP} channel opener are co-formulated; such as co-formulated as a controlled release formulation for oral administration; such as for once or twice daily administration.

[00151] Also provided herein are kits comprising: a pharmaceutical treatment blister card with a plurality of blister cavities; seven to twenty eight daily dosages of a K_{ATP} channel opener; and seven to twenty eight daily dosages of a fibrate or a salt thereof. In these kits, the daily dosages of the K_{ATP} channel opener and the fibrate or a salt thereof are sub-optimal titration dosages. In some embodiments, each of the plurality of blister cavities contain a pharmaceutical formulation comprising either a K_{ATP} channel opener or

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a fibrate or a salt thereof. In some embodiments, each of the plurality of blister cavities contains two or more pharmaceutical formulations, wherein at least one of said pharmaceutical formulations comprises a K_{ATP} channel opener, and at least one other of said pharmaceutical formulations comprises a fibrate or a salt thereof. In some embodiments, the K_{ATP} channel opener and said fibrate are co-formulated in a single pharmaceutical formulation. In some related embodiments, each of the plurality of blister cavities contains the co-formulated pharmaceutical formulation. In some embodiments, the K_{ATP} channel opener is selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and salts thereof. In some embodiments, the K_{ATP} channel opener comprises an anion Formula I, Formula II, Formula III and Formula IV, and a cation selected from the group consisting of an alkali metal and a compound comprising an ammonium group comprising at least one tertiary amine group. In some embodiments, the K_{ATP} channel opener comprises a salt of diazoxide; such as diazoxide choline. In some embodiments, the fibrate or a salt thereof comprises fenofibrate or a salt thereof; such as fenofibrate choline.

[00152] Also provided herein are methods for treating a subject with acute pancreatitis, the method comprising intravenously administering a bolus dose of a K_{ATP} channel opener of between about 0.5 to 5 mg/kg over 5 to 10 minutes; wherein the K_{ATP} channel opener is selected from the group consisting of Formula I, Formula II, Formula III and Formula IV, and wherein the the K_{ATP} channel opener is formulated for intravenous administration. In some embodiments, the dose of K_{ATP} channel opener administered as a bolus is between about 50 to 200 mg. In some embodiments, the methods further comprise additional administration of the K_{ATP} channel opener after completion of the bolus at between about 0.02 to 0.2 mg/kg/hr, along with administration of insulin 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. In some related embodiments, the insulin comprises a basal insulin, a fast-acting prandial insulin, or a mixture thereof. In some embodiments, the K_{ATP} channel opener comprises diazoxide or an ion thereof. In some embodiments, the methods further comprise co-administration of nicorandil. In some embodiments, the methods further comprise treating the subject using plasmapheresis. In some embodiments, the subject is a human.

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[00153] In the present context, the term "therapeutically effective" or "effective amount" indicates that the materials or amount of material is effective to prevent, alleviate, or ameliorate one or more symptoms of a disease or medical condition, and/or to prolong the survival of the subject being treated.

[00154] The term "pharmaceutically acceptable" indicates that the identified material does not have properties that would cause a reasonably prudent medical practitioner to avoid administration of the material to a patient, taking into consideration the disease or conditions to be treated and the respective route of administration. For example, it is commonly required that such a material be essentially sterile, e.g., for injectibles.

[00155] As used herein, the term "composition" refers to a formulation suitable for administration to an intended animal subject for therapeutic purposes that contains at least one pharmaceutically active compound and at least one pharmaceutically acceptable carrier or excipient. Other terms as used herein are defined below.

[00156] As used herein, the term "co-administer" or "co-administration" refers to administration of two or more pharmaceutically active materials to a subject at the same time. For example, two compositions, each in tablet form, can be co-administered by oral ingestion at the same time or within minutes of each other. Co-administration also encompasses administration of two active materials co-formulated in a single delivery form. That is, two compositions can be combined in a single formulation (co-formulated) for administration to a subject so that the compositions are co-administered, e.g. in a single tablet, capsule, oral suspension, injectible liquid, etc.

[00157] Adipocyte: An animal connective tissue cell specialized for the synthesis and storage of fat.

[00158] Agonist: A chemical compound that has affinity for and stimulates physiological activity at cell receptors normally stimulated by naturally occurring substances, triggering a biochemical response. An agonist of a receptor can also be considered an activator of the receptor.

[00159] About: is used herein to mean in quantitative terms plus or minus 10%.

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[00160] Adipose tissue: Tissue comprised principally of adipocytes.

[00161] Adolescent: A person between 10 and 19 years of age.

[00162] Adiponectin: A protein hormone produced and secreted exclusively by adipocytes that regulates the metabolism of lipids and glucose. Adiponectin influences the body's response to insulin. Adiponectin also has anti-inflammatory effects on the cells lining the walls of blood vessels.

[00163] Alkali metal: refers to elements included in Group I of the periodic table, such as, lithium, sodium, potassium, rubidium, cesium and francium.

[00164] Amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition: refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

[00165] Analog: a compound that resembles another in structure but differs by at least one atom.

[00166] Antagonist: A substance that tends to nullify the action of another, as a drug that binds to a cell receptor without eliciting a biological response when confronted with an agonist for the receptor.

[00167] Anti-androgen therapy: a therapy using medications to block production of or interfere with the action of male sex hormones, e.g. testosterone. Anti-androgen therapies suitable for use in the methods described herein include but are not limited to Progestin, cyproterone, ethinylestradiol, cyproterone, and androgen receptor protein inhibitors.

[00168] Atherosclerotic Plaque: A buildup of cholesterol and fatty material within a blood vessel due to the effects of atherosclerosis

[00169] Bariatric Surgery: A range of surgical procedures which are designed to aid in the management or treatment of obesity and allied diseases.

[00170] Beta cell rest: Temporarily placing beta cells in a condition in which there is reduced metabolic stress due to suppressed secretion of insulin.

Ex. 2002-1006

[00171] Bilaminate: A component of a pharmaceutical dosage form that consists of the lamination of two distinct materials.

[00172] Bioavailability: Refers to the amount or extent of therapeutically active substance that is released from the drug product and becomes available in the body at the intended site of drug action. The amount or extent of drug released can be established by the pharmacokinetic-parameters, such as the area under the blood or plasma drug concentration-time curve (AUC) and the peak blood or plasma concentration (C max) of the drug.

[00173] Bioequivalent: Two formulations of the same active substance are bioequivalent when there is no significant difference in the rate and extent to which the active substance becomes available at the site of drug action when administered at the same molar dose under similar conditions. "Formulation" in this definition may include the free base of the active substance or different salts of the active substance. Bioequivalence may be demonstrated through several in vivo and in vitro methods. These methods, in descending order of preference, include pharmacokinetic, pharmacodynamic, clinical and in vitro studies. In particular, bioequivalence is demonstrated using pharmacokinetic measures such as the area under the blood or plasma drug concentration-time curve (AUC) and the peak blood or plasma concentration (Cmax) of the drug, using statistical criteria.

[00174] Cannabinoid Receptor: Receptors in the endocannabinoid (EC) system associated with the intake of food and tobacco dependency. Blocking the cannabinoid receptor may reduce dependence on tobacco and the craving for food.

[00175] Capsule: refers to a softgel, caplet, or any other encapsulated dosage form known to practitioners in the art, or a portion thereof. Softgel refers a soft gelatin capsule, in agreement with the accepted nomenclature adopted by the SoftGel Association. A softgel is a one-piece, sealed, soft gelatin (or other film-forming material) shell that contains a solution, a suspension, or a semi-solid paste.

[00176] Combination: Refers to any association between or among two or more items. The combination can be two or more separate items, such as two compositions or two

Ex. 2002-1007

collections. It can be a mixture thereof, such as a single mixture of the two or more items, or any variation thereof.

[00177] Combined hyperlipidemia: Refers to a commonly occurring form of hypercholesterolemia (elevated cholesterol level) characterized by increased LDL cholesterol and triglyceride concentrations, often accompanied by decreased HDL cholesterol.

[00178] Companion animal: Animals kept for the purpose of providing companionship to humans, e.g., house pets, including cats and dogs and horses.

[00179] Compression tablet: Tablet formed by the exertion of pressure to a volume of tablet matrix in a die.

[00180] Compression coated tablet: A tablet formed by the addition of a coating by compression to a compressed core containing the pharmaceutical active. As used herein the term "tablet" is intended to mean the same as a compression tablet unless indicated otherwise.

[00181] Derivative: A chemical substance derived from another substance by modification or substitution.

[00182] Daily dosage: The total amount of a drug taken in a 24 hour period whether taken as a single dose or taken in multiple doses.

[00183] DPP-IV inhibitor: A class of anti-diabetic drugs which inhibit the enzyme dipeptidylpeptidase-IV, also known as DPP-IV. The DPP-IV enzyme cleaves the N-terminal dipeptide from GLP-1, inactivating it. DPP-IV inhibitors thus increase the potency of GLP-1 biological effects.

[00184] Disaccharidase inhibitor: A class of anti-diabetic drugs which act by inhibiting disaccharidase enzymes. Disaccharidases break down disaccharides into monosaccharides and include, e.g., lactase, sucrase, trehalase, and maltase. Inhibition of disaccharidases delays and decreases absorption of monosaccharides by the body, decreasing post-meal glucose peaks.

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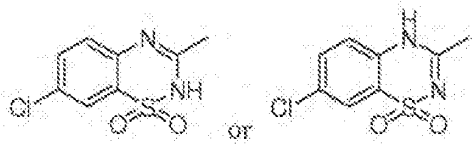
[00185] Diazoxide: 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1 dioxide (shown below with its tautomer) with the empirical formula C8H7ClN2O2S and a molecular weight of 230.7.



[00186] Dyslipidemia: A disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Dyslipidemias may be manifested by elevation of the total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride, and a decrease in high-density lipoprotein (HDL) cholesterol concentration in the blood. Optimal LDL cholesterol level for adults is less than 100 mg/dL (2.60 mmol/L), optimal HDL cholesterol level is equal to or greater than 40 mg/dL (1.02 mmol/L), and optimal triglyceride level is less than 150 mg/dL (1.7 mmol/L). As used herein, a dyslipidemia is defined as an abnormal level which is at least 5% greater (or lower) than the normal level, more preferably at least 10% greater (or lower) than the normal level, more preferably at least 20% greater or lower than the normal level. Dyslipidemia is a risk factor for cardiovascular disease, predisposing affected individuals to atherosclerosis. Obese and obese diabetic patients experience higher rates of dyslipidemia. Although diazoxide administration has been reported to reduce circulating triglyceride levels in treated obese patients (Alemzadeh et al. 1998, J Clin Endocrinol Metab 83: 1911–1915) no statistically significant reduction in cholesterol has been shown. In animal models of obesity and obese diabetes, reductions in both total cholesterol and circulating triglycerides have been reported (Alemzadeh et al. European Journal of Endocrinology (2002) 146 871–879; Alemzadeh and Tushaus Med Sci Monit, 2005; 11(12): BR439-444). In these models, diazoxide was administered when the treated animals transitioned from a normal phenotype to either obese or obese diabetic disease states.

[00187] Encapsulation system: A structural feature that contains drug within such as a pharmaceutical capsule. A gel into which drug is incorporated also is considered an encapsulation system.

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[00188] Endogenous hyperlipidemia: characterized primarily by elevated VLDL (both triglycerides and cholesterol associated with VLDL may also be elevated). Endogenous hyperlipidemia results from an endogenous metabolic source of the increased lipids rather than from a dietary source of the increased lipids.

[00189] Equivalent amount: An amount of a derivative of a drug that in assays or upon administration to a subject produces an equal effect to a defined amount of the non-derivatized drug.

[00190] Fatty acid synthase: The central enzyme of a multienzyme complex that catalyses the formation of palmitate from acetylcoenzyme A, malonylcoenzyme A, and NADPH.

[00191] Fibrates: A class of amphipathic carboxylic acids primarily used for decreasing serum triglycerides, while increasing high density lipoprotein (HDL).

[00192] Fructose-1, 6-bisphosphatase inhibitor: A class of anti-diabetic drugs which act by inhibiting fructose-1,6-bisphosphatase, a key enzyme in the gluconeogenesis pathway. Inhibition of this enzyme lowers elevated glucose levels typical of type II diabetes.

[00193] Gastric Lipase: An enzyme secreted into the gastrointestinal tract that catalyzes the hydrolysis of dietary triglycerides.

[00194] Glidant: An inactive component of a pharmaceutical formulation that prevents caking of the matrix during processing steps.

[00195] GLP-1: Glucagon like peptide 1 is a peptide produced by intestinal endocrine cells in two principle forms, GLP-1(7-36 amide) and GLP-1(7-37), upon the ingestion of food. It is involved in stimulation of glucose-dependent insulin secretion and insulin biosynthesis, inhibition of glucagon secretion and gastric emptying, and inhibition of food intake.

[00196] HDL cholesterol: The cholesterol found in high density lipoprotein particles. HDL particles are believed to transport cholesterol from tissues in the body to the liver.

Ex. 2002-1010

[00197] HMG-CoA reductase inhibitors (or statins) form a class of hypolipidemic agents, used as pharmaceutical agents to lower cholesterol levels in people with or at risk of cardiovascular disease. They lower cholesterol by inhibiting the enzyme HMG-CoA reductase, which is the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis.

[00198] Hypercholesterolemia: A condition characterized by elevated cholesterol.

[00199] Hyperinsulinemia: Excessively high blood insulin levels, which is differentiated from hyperinsulinism, excessive secretion of insulin by the pancreatic islets. Hyperinsulinemia may be the result of a variety of conditions, such as obesity and pregnancy.

[00200] Hyperinsulinism: Excessive secretion of insulin by the pancreatic islets.

[00201] Hyperlipidemia: A general term for elevated concentrations of any or all of the lipids in the plasma, such as cholesterol, triglycerides and lipoproteins.

[00202] Hyperphagia: Ingestion of a greater than optimal quantity of food.

[00203] Hypertension: Chronic high blood pressure, typically above 140 (systolic) over 90 (diastolic) mm Hg. Chronically elevated blood pressure can cause blood vessel changes in the back of the eye, thickening of the heart muscle, kidney failure, and brain damage.

[00204] Hypertriglyceridemia (or hypertriglyceridaemia) denotes high (hyper-) blood levels (-emia) of triglycerides without elevated cholesterol, the most abundant fatty molecule in most organisms. It has been associated with atherosclerosis, even in the absence of hypercholesterolemia (high cholesterol levels). It can also lead to pancreatitis in excessive concentrations.

[00205] Hypoglycemia-associated autonomic failure: A condition where hypoglycemic patients, e.g., patients with type I diabetes or advanced type II diabetes, become unable to recognize the symptoms of hypoglycemia, and/or lose counter-regulatory hormonal responses, primarily glucagon and epiepherine extending periods of hypoglycemia with their associated sequelae.

Ex. 2002-1011

[00206] Ingredient of a pharmaceutical composition: Refers to one or more materials used in the manufacture of a pharmaceutical composition. Ingredient can refer to an active ingredient (an agent) or to other materials in the compositions. Ingredients can include water and other solvents, salts, buffers, surfactants, non-aqueous solvents, and flavorings.

[00207] Insulin dosing: The administration of exogenous insulin to a subject.

[00208] Insulin resistance: A condition in which the tissues of the body are diminished in their ability to respond to insulin.

[00209] Ischemic injury: Injury to tissue that results from a low oxygen state usually due to obstruction of the arterial blood supply or inadequate blood flow leading to hypoxia in the tissue.

[00210] Ketoacidosis: Acidosis accompanied by the accumulation of ketone bodies (ketosis) in the body tissue and fluids, as in diabetic acidosis.

[00211] Kit: Refers to a packaged combination. A packaged combination can optionally include a label or labels, instructions and/or reagents for use with the combination.

[00212] Kir: Pore forming subunit of the KATP channel. Also known as the inwardly rectifying subunit of the KATP channel. Typically existing as Kir6.x and infrequently as Kir2.x subspecies.

[00213] KATP channel: An ATP sensitive potassium ion channel across the cell membrane formed by the association of 4 copies of a sulfonylurea receptor and 4 copies of a pore forming subunit Kir. Agonizing the channel can lead to membrane hyperpolarization.

[00214] KATP channel opener: As used herein refers to a compound of any of Formulae I – VIII, or a derivative, salt or prodrug thereof, having one or more or preferably all of the following three properties: (1) opening SURx/Kir6.y potassium channels, where x = 1, 2A or 2B and y = 1 or 2; (2) binding to the SURx subunit of

Ex. 2002-1012

KATP channels; and (3) inhibiting glucose induced release of insulin following administration of the compound in vivo.

[00215] Late myocardial remodeling: myocardial infarction induced alterations of left ventricular (LV) architecture with scar formation, ventricular dilatation, and hypertrophy of the noninfarcted (remote) myocardium.

[00216] Leptin: Product (16 kD) of the ob (obesity) locus. It is found in plasma of mammals and exerts a hormonal action, which reduces food uptake and increases energy expenditure.

[00217] Lipogenesis: The generation of new lipids, primarily triacylglycerides. It is dependent on the action of multiple distinct enzymes and transport molecules.

[00218] Lipolysis: The breakdown of fat by the coordinated action of multiple enzymes.

[00219] Lipoprotein lipase: An enzyme of the hydrolase class that catalyses the reaction of triacyglycerol and water to yield diacylglycerol and a fatty acid anion. The enzyme hydrolyses triacylglycerols in chylomicrons, very-low-density lipoproteins, low-density lipoproteins, and diacylglycerols.

[00220] Lubricant: An inactive component of a pharmaceutical formulation that provides for the flow of materials in various processing steps, particularly tableting.

[00221] Meglitinide: A class of anti-diabetic drugs which block potassium channels by antagonism of sulfonylurea receptor component of the channel in beta cells, resulting in increased insulin secretion.

[00222] Microparticle: A small particulate formed in the process of developing pharmaceutical formulations that may be coated prior to producing the final dosage from.

[00223] MTP (microsomal triglyceride transfer protein) inhibitors: A class of pharmaceutical compounds that inhibit MTP activity to lower cholesterol and triglycerides.

Ex. 2002-1013

[00224] Nonalcoholic steatohepatitis (NASH): Nonalcoholic steatohepatitis or NASH is a common, silent liver disease. It resembles alcoholic liver disease, but occurs in people who drink little or no alcohol. The major features in NASH are fat in the liver, inflammation and liver damage. The disease may progress to cirrhosis.

[00225] Obesity: An increase in body weight beyond the limitation of skeletal and physical requirement, as the result of an excessive accumulation of fat in the body. Formally defined as having a body mass index greater than 30 kg/m2.

[00226] Obesity Prone: Subjects who because of genetic predisposition or prior history of obesity are at above average risk of becoming obese.

[00227] Obesity related co-morbidities: Any disease or condition of animals or humans that are increased incidence in obese or overweight subjects. Examples of such conditions include hypertension, prediabetes, type 2 diabetes, osteoarthritis and cardiovascular conditions.

[00228] Oral anti-hypertensive agent: An orally administered therapeutic agent which is used to treat high blood pressure. Oral anti-hypertensive agents suitable for use in methods described herein include but are not limited to diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, rennin inhibitors, angiotensin II antagonists, and alpha-1 blockers.

[00229] Osmotically controlled release: A pharmaceutical dosage form in which the release of the active drug is principally achieved by the hydration of a swellable component of the formulation.

[00230] Overweight: An subject whose weight is above that which is ideal for their height but who fails to meet the criteria for classification as obese. In humans using Body Mass Index (kg/m2) an overweight subjects has a BMI between 25 and 30.

[00231] Oxidation of Fat: A series of reactions involving acyl-coenzyme A compounds, whereby these undergo beta oxidation and thioclastic cleavage, with the formation of acetyl-coenzyme A; the major pathway of fatty acid catabolism in living tissue.

Ex. 2002-1014

[00232] Pharmaceutical composition: Refers to a composition that contains an agent and one or more other ingredients that is formulated for administration to a subject. An agent refers to an active ingredient of a pharmaceutical composition. Typically active ingredients are active for treatment of a disease or condition. For example, agents that can be included in pharmaceutical compositions include agents for treating obesity or diabetes. The pharmaceutically active agent can be referred to as "a pharmaceutical active."

[00233] Pharmaceutical effect: Refers to an effect observed upon administration of an agent intended for treatment of a disease or disorder or for amelioration of the symptoms thereof.

[00234] Pharmacodynamic: An effect mediated by drug action.

[00235] Pharmacokinetic: Relating to the absorption, distribution, metabolism and elimination of the drug in the body.

[00236] Poly-cystic ovarian syndrome: A disorder where the ovary secretes abnormally high levels of testosterone and estrogens, which results in irregular or no menses, excess body hair growth, occasionally baldness, and often obesity, diabetes and hypertension.

[00237] PEO: An abbreviation for polyoxyethylene. As used herein, and except as otherwise indicated, polyoxyethylene is a polyether polymer of ethylene glycol having an average molecular weight of greater than 20,000 g/mol. In some embodiments, the average molecular weight of PEO is from greater than 20,000 up to 300,000 g/mol. PEO may be used in the form of copolymers with other polymers or as a mixture of a combination of grades. Preferred concentrations of PEO include 3% to 40% either as a single grade or as a mixture of grades (molecular weights).

[00238] Polymorph: A crystalline form of a compound that exists in at least two crystalline forms. Polymorphic forms of any given compound are defined by the same chemical formula and/or composition and are as distinct in chemical structure as crystalline structures of two different chemical compounds. Such compounds may differ in packing or geometrical arrangement of respective crystalline lattices. The chemical

Ex. 2002-1015

and/or physical properties or characteristics of the various polymorphs may vary with each distinct polymorphic form, and may include, but are not limited to, variations in solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapor pressure, and stability.

[00239] Preadipocyte: A progenitor cell to adipocytes.

[00240] PPAR agonist: Peroxisome proliferator-activated receptor agonists include compounds that activate, e.g. the PPARγ receptor, leading to, e.g., a decrease in insulin resistance, modification of adipocyte differentiation, and a decrease in leptin levels. Thiazolidinediones target PPARγ.

[00241] PPAR partial agonist: Peroxisome proliferator-activated receptor partial agonists are PPAR agonists that can only incompletely agonize the receptor.

[00242] Prediabetic: A condition that precedes diagnosis of type II diabetes. Type II diabetes is a form of diabetes mellitus which is characterized by insulin insensitivity or resistance.

[00243] Prodrug: Refers to a compound which, when metabolized, yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties. For example, some prodrugs are esters of the active compound; during metabolysis, the ester group is cleaved to yield the active drug. Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound.

[00244] Prolonged Administration (prolonged basis): Administration of a pharmaceutically acceptable formulation of a drug for 7 or more days. Typically, prolonged administration is for at least two weeks, preferably at least one month, and even more preferably at least two months (i.e. at least 8 weeks).

[00245] Quick dissolving formulation: A pharmaceutical formulation which upon oral administration may release substantially all of the drug active from the formulation within 10 minutes.

Ex. 2002-1016

[00246] QD, BID and TID: QD (quaque die) means once per day administration of a pharmaceutical substance or formulation ; BID (bis in die) means twice per day; and TID (Ter In Die) means three time per day.

[00247] Release formulation (sustained), (or "sustained release formulation"): A formulation of pharmaceutical product that, upon administration to animals, provides for release of the active pharmaceutical over an extended period of time than provided by formulations of the same pharmaceutical active that result in rapid uptake. Similar terms are extended-release, prolonged-release, and slow-release. In all cases, the preparation, by definition, has a reduced rate of release of active substance.

[00248] Release formulation (delayed), (or "delayed release formulation"): Delayed-release products are modified-release, but are not extended-release. They involve the release of discrete amount(s) of drug some time after drug administration, e.g. enteric-coated products, and exhibit a lag time during which little or no absorption occurs.

[00249] Release formulation (controlled), (or "controlled release formulation"): A formulation of pharmaceutical product that may include both delay of release of pharmaceutical active upon administration and control of release in the manner described for sustained release.

[00250] Salt: The neutral, basic or acid compound formed by the union of an acid or an acid radical and a base or basic radical. Used generally to describe any ionic compound not containing an oxide or hydroxide ion.

[00251] A "short-acting anti-diabetic drug" refers to an agent that helps the pancreas produce insulin. Typically, a short-acting anti-diabetic drug is taken with meals to boost the insulin response to each meal. Short acting anti-diabetic drugs typically have rapid onset of effects with maximal effects typically realized between 30 minutes and 3 hours after administration and with circulating half-lives less than 5 hours.

[00252] Solid oral dosage form: Pharmaceutical formulations designed for oral administration including capsules and tablets.

Ex. 2002-1017

[00253] Squalene synthase: squalene synthase is an enzyme at a branch point in the isoprenoid biosynthetic pathway capable of diverting carbon flow to the biosynthesis of sterols.

[00254] Squalene Synthase inhibitor: an inhibitor of squalene synthase.

[00255] Subject: Refers to animals, including mammals, such as human beings, domesticated animals, and animals of commercial value.

[00256] Sulfonylurea receptor: A component of the KATP channel responsible for interaction with sulfonylurea, other KATP channel antagonists, diazoxide and other KATP channel agonists.

[00257] Sulfonylurea receptor antagonist: a molecule which upon interaction with the sulfonylurea receptor acts to block the KATP channel.

[00258] Tablet: Pharmaceutical dosage form that is produced by forming a volume of a matrix containing pharmaceutical active and excipients into a size and shape suitable for oral administration.

[00259] Thermogenesis: The physiological process of heat production in the body.

[00260] Thiazolidinedione: A class of anti-diabetic drugs comprising a thiazolidine ring having 2 oxo groups attached. Thiazolidinediones bind to and activate the PPARγ receptor.

[00261] Threshold Concentration: The minimum circulating concentration of a drug required to exert a specific metabolic, physiological or compositional change in the body of a treated human or animal.

[00262] Thyroid receptor: The thyroid (hormone) receptor regulates a diverse set of genes that control processes from embryonic development to adult homeostasis. Receptors for thyroid hormones are members of a large family of nuclear receptors that include those of the steroid hormones. Upon binding of thyroid hormone, the thyroid receptor releases corepressor proteins and undergoes a conformational change that allows for the interaction of coactivating proteins necessary for gene transcription.

Ex. 2002-1018

[00263] Thyroid receptor activator: A molecule which upon interaction with the thyroid hormone receptor acts to increase activity of the thyroid hormone receptor.

[00264] Treatment: Any manner in which the symptoms of a condition, disorder or disease or other indication, are ameliorated or otherwise beneficially altered.

[00265] Triglyceride: Storage fats of animal and human adipose tissue principally consisting of glycerol esters of saturated fatty acids.

[00266] Type I diabetes: A chronic condition in which the pancreas makes little or no insulin because the beta cells have been destroyed.

[00267] Type II diabetes: A chronic condition that is primarily characterized by insulin resistance, relative insulin deficiency, and hyperglycemia.

[00268] Uncoupling protein: A family of proteins that allow oxidation in mitochondria to proceed without the usual concomitant phosphorylation to produce ATP.

[00269] Visceral fat: Human adipose tissues principally found below the subcutaneous fat and muscle layer in the body.

BRIEF DESCRIPTION OF THE FIGURES

[00270] FIG. 1 shows UV spectra of the free form diazoxide and the sodium and potassium salts of diazoxide in acetonitrile.

[00271] FIG. 2 shows UV spectra of the free form diazoxide at varying pH.

[00272] FIG. 3 shows UV spectra of the free form diazoxide and sodium and potassium salts of diazoxide in methanol.

[00273] FIG. 4A, FIG. 4B, FIG. 4C and FIG. 4D show X-Ray Powder Diffraction patterns for (a) free form diazoxide, (b) potassium salt of diazoxide from THF, (c) lysine salt of diazoxide from MEK, and (d) sodium salt of diazoxide from acetonitrile, respectively.

[00274] FIG. 5A, FIG. 5B and FIG. 5C show NMR spectra (DMSO-d6 solvent) for (a) free form diazoxide, (b) potassium salt, and (c) sodium salt, respectively.

Ex. 2002-1019

[00275] FIG. 6A, FIG. 6B and FIG. 6C show X-Ray Powder Diffraction patterns for (a) sodium salt of diazoxide, (b) sodium salt of diazoxide after slurrying in water, and (c) free form diazoxide, respectively.

[00276] FIG. 7 shows DSC spectra for the free form diazoxide (top) and potassium salt of diazoxide (bottom). Description: "a" (Integral = -317.56 mJ; normalized = -84.82 Jg 1; Onset = 120.81 °C; Peak = 121.29 °C); "b" (Integral = -1170.43 mJ; normalized = 154.64 Jg-1; Onset = 329.54 °C; Peak = 329.21 °C); "c" (Extrap. Peak = 355.01 °C; Peak Value = -4.58 mW; normalized = -1.22 Wg-1; Peak = 353.53 °C).

[00277] FIG. 8 shows TGA spectra for the free form diazoxide (top) and potassium salt of diazoxide (bottom).

[00278] FIG. 9A, FIG. 9B and FIG. 9C show X-Ray Powder Diffraction patterns for (a) potassium salt of diazoxide, (b) potassium salt of diazoxide after slurrying in toluene, and (c) potassium salt of diazoxide after slurrying in toluene for 14 days, respectively.

[00279] FIG. 10A, FIG. 10B and FIG. 10C show X-Ray Powder Diffraction patterns for (a) free form diazoxide, (b) choline salt of diazoxide, and (c) hexamethyl hexamethylene diammonium hydroxide salt of diazoxide, respectively.

[00280] FIG. 11 shows DSC spectra for the free form diazoxide (top) and choline salt of diazoxide (bottom). Description: "a" (Integral = -41.24 mJ; normalized = -8.05 Jg 1; Onset = 101.23 °C; Peak = 119.29 °C); "b" (Integral = -497.37 mJ; normalized = 97.10 Jg-1; Onset = 166.03 °C; Peak = 167.27 °C); "c" (Integral = -1167.83 mJ; normalized = 154.29 Jg-1; Onset = 329.54 °C; Peak = 329.21 °C).

[00281] FIG. 12 shows TGA spectra for the free form diazoxide (top) and choline salt of diazoxide (bottom).

[00282] FIG. 13A, FIG. 13B and FIG. 13C show X-Ray Powder Diffraction patterns for (a) choline salt of diazoxide, (b) choline salt of diazoxide after slurrying in dichloromethane for 7 days, and (c) choline salt of diazoxide after moisture sorption analysis, respectively.

Ex. 2002-1020

[00283] FIG. 14A, FIG. 14B and FIG. 14C show NMR spectra (DMSO-d6 solvent) for (a) free form diazoxide, (b) choline salt, and (c) hexamethyl hexamethylene diammonium hydroxide salt of diazoxide, respectively.

[00284] FIG. 15A shows overlay XRPD patterns of free form diazoxide, the product of potassium methoxide in methanol, and the product of sodium methoxide in methanol. FIG. 15B, FIG. 15C and FIG. 15D show the XRPD patterns for product of potassium methoxide reaction with diazoxide in methanol, product of sodium methoxide reaction with diazoxide in methanol, and freeform diazoxide, respectively.

[00285] FIG. 16A and FIG. 16B show XRPD patterns of (a) polymorphic Form A of the choline salt of diazoxide, and (b) a mixture of polymorphic forms A and B of the choline salt of diazoxide, respectively.

[00286] FIG. 17A and FIG. 17B show the NMR spectra (DMSO-d6 solvent) for (a) polymorphic Form A of the choline salt of diazoxide, and (b) polymorphic Form B of the choline salt of diazoxide, respectively.

[00287] FIG. 18A, FIG. 18B and FIG. 18C show XRPD patterns of (a) polymorphic Form A of the potassium salt of diazoxide, (b) polymorphic Form B of the potassium salt of diazoxide, and (c) polymorphic Form C of the potassium salt of diazoxide, respectively.

[00288] FIG. 19A, FIG. 19B, FIG. 19C and FIG. 19D show XRPD patterns of (a) polymorphic Form D of the potassium salt of diazoxide, (b) polymorphic Form E of the potassium salt of diazoxide, (c) polymorphic Form F of the potassium salt of diazoxide, and (d) polymorphic Form G of the potassium salt of diazoxide, respectively.

[00289] FIG. 20 shows the DSC spectra of diazoxide choline salt Form A. Description: "a" (Extrap. Peak = 120.44 °C; Peak Value = -1.02 mW; normalized = -0.20 Wg-1; Peak = 118.63 °C); "b" (Extrap. Peak = 167.94 °C; Peak Value = -19.39 mW; normalized = -3.79 Wg-1; Peak = 167.27 °C).

Ex. 2002-1021

[00290] FIG. 21 shows the DSC spectra of diazoxide choline salt Form B. Description: "a" (Extrap. Peak = 165.05 °C; Peak Value = -3.85 mW; normalized = -0.86 Wg-1; Peak = 162.66 °C).

[00291] FIG. 22 provides systolic blood pressure (SBP) and diastolic blood pressure (DBP) for Proglycem Oral Suspension (Proglycem) and Diazoxide Choline Controlled-Release Tablets (DCCRT) at various times following dose administration (mean±SEM).

[00292] FIG. 23 provides pulse rate for Proglycem Oral Suspension (Proglycem) and Diazoxide Choline Controlled-Release Tablets (DCCRT) at various times following dose administration (mean±SEM).

[00293] Fig. 24 provides mean plasma diazoxide (±SD) concentrations after a 200 mg dose of diazoxide (linear coordinates).

[00294] Fig. 25 provides mean plasma diazoxide (±SD) concentrations after a 200 mg dose of diazoxide (semilog coordinates).

[00295] Fig. 26 provides simulations to steady-state of once daily dosing with 200 mg diazoxide.

[00296] Fig. 27 provides a bar graph comparing the median percentage change in levels of different lipid measurements for patients that were treated with DCCR for 12 weeks followed by co-administation of DCCR with fenofibrate choline for 6 weeks, and patients that received placebo for 12 weeks followed by co-administation of placebo with fenofibrate choline for 6 weeks. Lipids measured for these studies were triglycerides (TG), total cholesterol (TC), non-HDL-C, VLDL-C, LDL-C, and HDL-C. Details are described in Example sections 15.1 and 15.2.

[00297] Fig. 28 provides a bar graph comparing the median percentage change in levels of different lipid measurements for patients that were treated with DCCR for 12 weeks followed by co-administation of DCCR with fenofibrate choline for 6 weeks, and patients that only received fenofibrate choline for 6 weeks. Lipids measured for these studies were triglycerides (TG), total cholesterol (TC), non-HDL-C, VLDL-C, LDL-C, and HDL-C. Details are described in Example section 15.1 and 15.3.

Ex. 2002-1022

[00298] Fig. 29 provides a bar graph comparing the median percentage change in levels of different lipid measurements for patients that were treated with DCCR for 12 weeks followed by co-administation of DCCR with fenofibrate choline for 6 weeks, patients that received omega-3 fatty acids and fenofibrate for 8 weeks (Figure 2 of Roth et al. J Cardiovasc Pharmacol. 2009 Sep;54(3):196-203), and their respective controls. Lipids measured in these studies were triglycerides (TG), total cholesterol (TC), non-HDL-C, VLDL-C, LDL-C, and HDL-C. JCP = Data from Roth et al. (J Cardiovasc Pharmacol. 2009 Sep;54(3):196-203). Details are described in section 15.1 and 15.4.

DETAILED DESCRIPTION OF THE INVENTION

[00299] The present invention provides salts of compounds of Formulae I – VIII and methods for their preparation. Salts of compounds of Formulae I – IV may be prepared using monovalent alkali metal cations and compounds which include one or more of a tertiary amine or quaternary ammonium moiety. In such salts, the compounds of Formulae I – IV exist in their anionic form. Furthermore, it has been discovered that the selection of a solvent for the preparation of these salts plays an important role in salt formation. Also described herein is the failure to obtain a salt of diazoxide from an alkali metal alkoxide using the method described in U.S. Pat. No. 2,986,573.

[00300] Compounds of Formulae V – VIII can form both anions and cations, and thus salts can be prepared using a variety of counter ions, including both anions and cations. Cations of the compounds of Formulae V – VIII can be formed at an amino group, and anions of the compounds of Formulae V – VIII can be formed at either an amino group or at the sulfonyl group. The formation of salts based on compounds of Formulae V – VIII can be done in a variety of solvents, preferably organic solvents.

[00301] As discussed herein, two polymorphic forms (i.e., Forms A and B) of the choline salt of diazoxide have been identified. In summary, both Forms A and B are anhydrous crystals of diazoxide choline salt. Diazoxide choline salt Form A can be formed using fast cooling procedures as provided herein, whereas slow cooling procedures generally favor formation of Form B. Slurry studies shows that Form A readily converts to Form B. Without wishing to be bound by theory, the slurry studies indicate that Form B of diazoxide choline salt is the thermodynamically more stable form.

Ex. 2002-1023

[00302] Regarding the potassium salt of diazoxide, seven polymorphic forms have been identified (i.e., Forms A-G). Diazoxide potassium salt Forms C, D, and F were observed be an acetone solvent, a hemihydrate, and a dioxane solvent, respectively. Forms A, B, E, and G were not commonly observed during screening, and elemental analysis suggests that Forms A, B, E and G may be mixtures, have residual solvent present, and/or not be a potassium salt, at least in part. Without wishing to be bound by theory, slurry studies suggest that Form D is the thermodynamically most stable polymorph of the diazoxide potassium salt polymorphs.

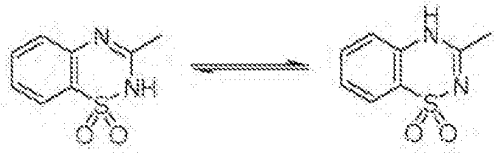
[00303] Further provided are pharmaceutical formulations of particular KATP channel openers of salts of compounds of Formulae I – VIII that when administered to subjects achieve novel pharmacodynamic, pharmacokinetic, therapeutic, physiological, and metabolic outcomes. Yet further provided are pharmaceutical formulations, methods of administration and dosing of particular KATP channel openers selected from salts of the compounds defined by Formulae I – VIII that achieve therapeutic outcomes while reducing the incidence of adverse effects.

[00304] Still further provided are pharmaceutical formulations of particular KATP channel openers of salts of compounds of Formulae I – VIII that may be administered to subjects once per day (QD), twice per day (BID) or three time per day (TID). The skilled artisan would realize each dosage per day per time may comprise one or more tablets administered to a subject. In preferred embodiments, the total effective dose per day can be 100, 200, 300, 400, 500 or 600 mg of KATP channel openers as active agent (administered as control release formulations). Such doses can be effective in achieving weight loss or reduction in total cholesterol, reduction in LDL cholesterol, reduction in non-HDL cholesterol, reduction in VLDL cholesterol, increase in HDL cholesterol, and reduction in triglyceride without substantial caloric reduction, more preferably with no caloric reduction. Such control release formulations comprise particular KATP channel openers of salts of compounds of formulae I – VIII formulation that require once per day dosing with or without caloric restricted diet. In addition, with control release formulations, the dosing required per day to reach clinical efficacy is much less compared to immediate release formulations.

Ex. 2002-1024

[00305] In particular, pharmaceutical formulations selected from salts of compounds defined by Formulae I – VIII and formulated for oral administration exhibit advantageous properties including: facilitating consistency of absorption, pharmacokinetic and pharmacodynamic responses across treated patients, contributing to patient compliance and improving the safety profile of the product, such as by reducing the frequency of serious adverse effects. Method of treatment of metabolic and other diseases of humans and animals by administering the formulations are also provided.

[00306] As shown below, diazoxide and derivatives thereof can exist as proton tautomers. Proton tautomers are isomers that differ from each other only in the location of a hydrogen atom and a double bond. The hydrogen atom and double bond switch locations between a carbon atom and a heteroatom, such as for example N. Thus, when the substituent on the nitrogen is hydrogen, the two isomeric chemical structures may be used interchangeably.



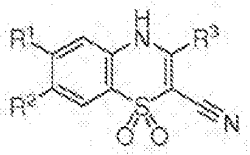
[00307] The particular KATP channel openers that can be used in the invention formulations include salts of any of the compounds within Formulae I to VIII. Exemplary compounds which have been previously reported include diazoxide, BPDZ 62, BPDZ 73, NN414 and BPDZ 154 (see, for example, Schou et al., Bioorg. Med. Chem., 13, 141-155 (2005)). Compound BPDZ 154 also is an effective KATP channel activator in patients with hyperinsulinism and in patients with pancreatic insulinoma. The synthesis of BPDZ compound is provided in Cosgrove et al., J. Clin. Endocrinol. Metab., 87, 4860-4868 (2002).

[00308] Channel openers demonstrating decreased activity in the inhibition of insulin release and increased activity in vascular smooth muscle tissue have been previously reported and include analogs of diazoxide such as, for example, 3-isopropylamino-7-methoxy-4H-1,2,4,-benzothiadiazine 1,1-dioxide, (a selective Kir6.2/SUR1 channel opener; see Dabrowski et al., Diabetes, 51, 1896-1906 (2002), and 2-alkyl substituted diazoxides (see, for example, Ouedraogo et al., Biol. Chem., 383, 1759-1768 (2002)).

Ex. 2002-1025

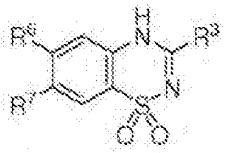
The 2-alkyl substituted diazoxides generally do not function as traditional potassium channel activators, but instead show potential as Ca2+ blockers.

[00309] Other diazoxide analogs which have been previously reported include described in Schou et al., Bioorg. Med. Chem., 13, 141-155 (2005), are shown below.



R^1, R^2 and R^3 are:
a) H, Cl, $NHCH(CH_3)_2$
b) CF_3, H, $NHCH(CH_3)_2$
c) H, Cl, $NHCH_2CH_2CH(CH_3)_2$
d) H, Cl, NH-cyclobutyl

[00310] Diazoxide analogs having different alkyl substituents at the 3 position of the molecule (identified as R3 shown below) are described in Bertolino et al., Receptors and Channels, 1, 267-278 (1993).



R^3, R^6 and R^7 are:
a) H, H, CH_3
b) H, H, Cl
c) CH_3, Cl, H
d) CH_2Cl, H, Cl
e) NH_2, H, H
f) CH_2CH_2Cl, H, Cl
g) nC_4H_9, H, Cl
h) nC_5H_{11}, H, Cl
i) nC_7H_{15}, H, Cl
j) nC_3H_7, Cl, H
k) nC_4H_9, Cl, H
l) nC_5H_{11}, Cl, H
m) nC_7H_{15}, Cl, H
n) nC_3H_7, Cl, Cl
o) nC_4H_9, Cl, Cl
p) nC_5H_{11}, Cl, Cl
q) nC_7H_{15}, Cl, Cl
r) H, Cl, H

[00311] KATP channel activity of salts of the compounds of Formulae I – VIII and related compounds can be measured by membrane potential studies as described in Schou et al., Bioorg. Med. Chem., 13, 141-155 (2005) and Dabrowski, et al., Diabetes, 51, 1896-1906 (2002).

Ex. 2002-1026

[00312] Measurement of the inhibition of glucose-stimulated insulin release from βTC6 cells is described in Schou et al., Bioorg. Med. Chem., 13, 141-155 (2005). The ability of particular KATP channel openers to inhibit release of insulin from incubated rat pancreatic islets can be performed as described by Ouedraogo et al., Biol. Chem., 383, 1759-1768 (2002).

[00313] Activation of recombinant KATP channels by KATP channel openers can be examined by monitoring macroscopic currents of inside-out membrane patches from Xenopus oocytes co-expressing Kir6.2 and either SUR1, SUR2A or SUR2B. SUR expressing membranes can be prepared by known methods. See, for example, Dabrowski et al., Diabetes, 51, 1896-1906 (2002).

[00314] Binding experiments can be used to determine the ability of KATP channel openers to bind SUR1, SUR2A and SUR2B. See, for example, Schwanstecher et al., EMBO J., 17, 5529-5535 (1998).

[00315] Preparation of SUR1 and SUR2A chimeras, as described by Babenko et al., allows for comparison of pharmacologic profiles (i.e. sulfonyl sensitivity and responsiveness to diazoxide or other potassium channel openers) of the SUR1/Kir6.2 and SUR2A/Kir6.2 potassium channels. See Babenko et al., J. Biol. Chem., 275(2), 717-720 (2000). The cloning of a sulfonylurea receptor and an inwardly rectifying K+ channel is described by Isomoto et al., J. Biol. Chem., 271 (40), 24321-24324 (1996); D'hahan et al., PNAS, 96(21), 12162-12167 (1999).

[00316] Differences between the human SUR1 and human SUR2 genes are described and shown in Aguilar-Bryan et al., Physiological Review, 78(1):227-245 (1998).

[00317] "Halo" and "halogen" refer to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[00318] "Hydroxyl" and "hydroxy" refer to the group -OH.

[00319] "Substituted oxy" refers to the group -ORaa, where Raa can be alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, heteroaryl, substituted

Ex. 2002-1027

heteroaryl, aralkyl, substituted aralkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

[00320] "Substituted thiol" refers to the group –SRbb, where Rbb can be alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aralkyl, substituted aralkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

[00321] "Alkyl" refers to an alkane-derived radical containing from 1 to 10, preferably 1 to 6, more preferably 1-4, yet more preferably 1-2, carbon atoms. Alkyl includes straight chain alkyl, branched alkyl and cycloalkyl, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. The alkyl group can be attached at any available point to produce a stable compound. An "alkylene" is a divalent alkyl.

[00322] A "substituted alkyl" is an alkyl group independently substituted with 1 or more, e.g., 1, 2, or 3, groups or substituents such as halo, hydroxy, optionally substituted alkoxy, optionally substituted alkylthio, alkylsulfinyl, alkylsulfonyl, optionally substituted amino, optionally substituted amido, amidino, urea optionally substituted with alkyl, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, alkylsulfonylamino, carboxyl, heterocycle, substituted heterocycle, nitro, cyano, thiol, sulfonylamino or the like attached at any available point to produce a stable compound. In particular, "fluoro substituted" refers to substitution by 1 or more, e.g., 1, 2, or 3 fluorine atoms. "Optionally fluoro substituted" means that substitution, if present, is fluoro. The term "optionally substituted" as used herein means that substitution may, but need not, be present.

[00323] "Lower alkyl" refers to an alkyl group having 1-6 carbon atoms.

[00324] A "substituted lower alkyl" is a lower alkyl which is substituted with 1 or more, e.g., 1, 2, or 3, groups or substituents, as defined above, attached at any available point to produce a stable compound.

[00325] "Cycloalkyl" refers to saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic carbon ring systems of 3-8, more preferably 3-6, ring members per

Ex. 2002-1028

ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl, and the like. "Cycloalkylene" is a divalent cycloalkyl.

[00326] "Substituted cycloalkyl" refers to saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic carbon ring systems of 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl, and the like independently substituted with 1 or more, e.g., 1, 2, or 3, groups or substituents such as halo, hydroxy, optionally substituted alkoxy, optionally substituted alkylthio, alkylsulfinyl, alkylsulfonyl, optionally substituted amino, optionally substituted amido, amidino, urea optionally substituted with alkyl, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, alkylsulfonylamino, carboxyl, heterocycle, substituted heterocycle, nitro, cyano, thiol, sulfonylamino or the like attached at any available point to produce a stable compound.

[00327] "Aryl" alone or in combination means phenyl or naphthyl optionally carbocyclic fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members.

[00328] "Substituted aryl" refers to an aryl group as defined above independently substituted with 1 or more, e.g., 1, 2, or 3, groups or substituents such as halo, hydroxy, optionally substituted alkoxy, optionally substituted alkylthio, alkylsulfinyl, alkylsulfonyl, optionally substituted amino, optionally substituted amido, amidino, urea optionally substituted with alkyl, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, alkylsulfonylamino, carboxyl, heterocycle, substituted heterocycle, nitro, cyano, thiol, sulfonylamino or the like attached at any available point to produce a stable compound.

[00329] "Alkoxy" denotes the group -ORee, where Ree is alkyl. "Lower alkoxy" denotes the group -ORece, where Rece is lower alkyl

[00330] "Substituted alkoxy" denotes the group -ORdd, where Rdd is substituted alkyl. "Substituted lower alkoxy" denotes the group -ORddd, where Rddd is substituted lower alkyl.

[00331] "Alkylthio" or "thioalkoxy" refers to the group -S-Ree, where Ree is alkyl.

Ex. 2002-1029

[00332] "Substituted alkylthio" or "substituted thioalkoxy" refers to the group -S-R, where R is substituted alkyl.

[00333] "Sulfinyl" denotes the group -S(O)-.

[00334] "Sulfonyl" denotes the group -S(O)2-.

[00335] "Substituted sulfinyl" denotes the group -S(O) -Rff, where Rff is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted hetereocyclylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

[00336] "Substituted sulfonyl" denotes the group -S(O)2Rgg, where Rgg is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted hetereocyclylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

[00337] "Sulfonylamino" denotes the group – S(O)2NRhh- where Rhh is hydrogen or alkyl.

[00338] "Substituted sulfonylamino" denotes the group -S(O)2NRii-Rjj, where Rii is hydrogen or optionally substituted alkyl, and Rjj is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

[00339] "Amino" or "amine" denotes the group –NH2. A "divalent amine" denotes the group –NH-. A "substituted divalent amine" denotes the group –NRkk- wherein Rkk is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, sulfonyl or substituted sulfonyl.

[00340] "Substituted amino" or "substituted amine" denotes the group -NRmmRnn, wherein Rmm and Rnn are independently hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, sulfonyl,

Ex. 2002-1030

substituted sulfonyl, or cycloalkyl provided, however, that at least one of Rmm and Rnn is not hydrogen. RmmRnn in combination with the nitrogen may form an optionally substituted heterocyclic or heteroaryl ring.

[00341] "Alkylsulfinyl" denotes the group -S(O)Roo, wherein Roo is optionally substituted alkyl.

[00342] "Alkylsulfonyl" denotes the group -S(O)2Rpp, wherein Rpp is optionally substituted alkyl.

[00343] "Alkylsulfonylamino" denotes the group -NRqqS(O)2Rrr, wherein Rrr is optionally substituted alkyl, and Rqq is hydrogen or alkyl.

[00344] A "primary amino substituent" denotes the group –NH2.

[00345] A "secondary amino substituent" denotes the group -NHRss, wherein Rss is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, sulfonyl, substituted sulfonyl, or cycloalkyl.

[00346] A "tertiary amino substituent" denotes the group –NRssRtt, wherein Rss and Rtt are independently alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, sulfonyl, substituted sulfonyl, or cycloalkyl.

[00347] "Quaternary ammonium substituent" denotes the group –N+RssRttRuu, wherein Rss, Rtt and Ruu are independently alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, sulfonyl, substituted sulfonyl, or cycloalkyl.

[00348] "Heteroaryl" means a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group consisting of O, S, and N. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable aromatic ring is retained. Examples of heteroaryl groups are pyridinyl, pyridazinyl, pyrazinyl, quinaoxalyl, indolizinyl, benzo[b]thienyl, quinazolinyl,

Ex. 2002-1031

purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazinyl, furanyl, benzofuryl, indolyl, and the like. "Heteroarylene" means a divalent heteroaryl.

[00349] "Heterocycle" or "heterocyclyl" means a saturated or unsaturated, non-aromatic carbocyclic group having a single ring or multiple condensed rings, e.g. a cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in a ring are replaced by heteroatoms, such as O, S, N, and are optionally fused with benzo or heteroaryl of 5-6 ring members and/or are optionally substituted. Heterocyclyl is intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. Examples of heterocycle or heterocyclyl groups are morpholino, tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, piperazinyl, dihydrobenzofuryl, dihydroindolyl, and the like.

[00350] "Heterocyclylalkyl" refers to the group -R-Het where Het is a heterocycle group and R is an alkylene group.

[00351] A "substituted heteroaryl," "substituted heterocyclyl," or "substituted heterocyclylalkyl" is a heteroaryl, heterocyclyl, or heterocyclylalkyl, respectively, independently substituted with 1 or more, e.g., 1, 2, or 3, groups or substituents such as halogen, hydroxy, optionally substituted alkoxy, optionally substituted alkylthio, alkylsulfinyl, alkylsulfonyl, acyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heteroaryloxy, optionally substituted amino, optionally substituted amido, amidino, urea optionally substituted with alkyl, aryl, heteroaryl or heterocyclyl groups, aminosulfonyl optionally N-mono- or N,N-di-substituted with alkyl, aryl or heteroaryl groups, alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, carboxyl, heterocycle, substituted heterocycle, heteroaryl, substituted heteroaryl, nitro, cyano, thiol, sulfonylamino, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl, attached at any available point to produce a stable compound.

[00352] "Amido" denotes the group -C(O)NH2. "Substituted amido" denotes the group -C(O)NRkRl, wherein Rk and Rl are independently hydrogen, lower alkyl,

Ex. 2002-1032

substituted lower alkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl, provided, however, that at least one of Rk and Rl is not hydrogen. RkRl in combination with the nitrogen may form an optionally substituted heterocyclic or heteroaryl ring.

[00353] "Amidino" denotes the group -C(=NRm)NRnRo, wherein Rm, Rn, and Ro are independently hydrogen or optionally substituted lower alkyl.

[00354] "Acyloxy" denotes the group -OC(O)Rh, where Rh is hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl and the like.

[00355] "Aryloxy" denotes the group -OAr, where Ar is an aryl, or substituted aryl, group. "Heteroaryloxy" denotes groups -OHet, wherein Het is an optionally substituted heteroaryl group.

[00356] "Arylsulfonylamino" denotes the group -NRqS(O)2Rs, wherein Rs is optionally substituted aryl, and Rq is hydrogen or lower alkyl.
"Heteroarylsulfonylamino" denotes the group -NRqS(O)2Rt, wherein Rt is optionally substituted heteroaryl, and Rq is hydrogen or lower alkyl.

[00357] "Alkylcarbonylamino" denotes the group -NRqC(O)Rp, wherein Rp is optionally substituted alkyl, and Rq is hydrogen or lower alkyl.

[00358] "Arylcarbonylamino" denotes the group -NRqC(O)Rs, wherein Rs is optionally substituted aryl, and Rq is hydrogen or lower alkyl.

[00359] "Heteroarylcarbonylamino" denotes the group -NRqC(O)Rt, wherein Rt is optionally substituted aryl, and Rq is hydrogen or lower alkyl.

[00360] Pharmaceutical formulations containing KATP channel openers can include the free base of a compound defined by any of Formulae I – VIII, or a salt thereof. Salts of the compounds of Formulae I – VIII as provided herein may have one or more of the following characteristics: (1) stability in solution during synthesis and formulation, (2) stability in a solid state, (3) compatibility with excipients used in the manufacture of tablet formulations, (4) quantitatively yield the KATP channel opener upon exposure to simulated or actual gastric and duodenal conditions, (5) release KATP channel opener

Ex. 2002-1033

from sufficiently small particles that are readily dissolved and absorbed, (6) provide, when incorporated into a pharmaceutical formulation, for absorption of greater than 80% of the administered dose, (7) present no elevated toxicological risk as compared to the free base of the KATP channel opener, (8) can be formulated into acceptable pharmaceutical formulations to treat obesity and other diseases of humans, (9) are acceptable to the FDA as the basis of a drug product, (10) can be recrystallized to improve purity, (11) can be used to form co-crystals of two or more salts of the KATP channel opener, (12) have limited hygroscopicity to improve stability, (13) synthetic and crystallization conditions under which the salt is formed can be varied resulting in different crystal structures (polymorphs) can be controlled in the synthesis of the salt, or (14) have improved solubility as compared to the free base in aqueous systems at physiological pH values.

[00361] The KATP channel openers provided in Formulae I – VIII are preferably formulated as pharmaceutically acceptable salts. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of a compound without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering lower effective doses of the drug.

[00362] Salts of the compounds of Formulae I – IV can include metal cations, preferably alkali metal cations, such as for example, sodium or potassium. Cations can be selected from any group I alkali metal. Divalent metals cations, such as alkaline earth metals (e.g., magnesium, calcium and the like), have not been found to be useful for salt formation with the compounds of Formulae I - IV.

[00363] Salts of the compounds of Formulae I – IV which include alkali metal cations can be prepared by reacting the compounds of Formulae I – IV with an alkali metal hydroxide or alkali metal alkoxide, such as for example, NaOH, KOH or NaOCH3, in a variety of solvents which may be selected from low molecular weight ketones (e.g., acetone, methyl ethyl ketone), tetrahydrofuran (THF), dimethylformamide (DMF), and n-methyl pyrrolidinone, and the like. Surprisingly, salt formation with an alkali metal

Ex. 2002-1034

hydroxide or alkoxide is not observed when an alcohol, particularly a lower alcohol such as for example methanol or ethanol, is used as the solvent. This result was confirmed by both X-Ray Powder Diffraction and NMR, and is contrary to the disclosure of U.S. Pat. No. 2,986,573, which purports to describe formation of diazoxide salts in alcohol.

[00364] The compounds of Formulae I – IV can also form salts with organic cations that include at least one tertiary amine or ammonium cation. Organic cation compounds can be monovalent, divalent, trivalent and tetravalent by inclusion of one, two, three or four tertiary amine or ammonium ions within the compound, respectively. When a multivalent compound is used, the tertiary amine or quaternary ammonium moieties are preferably separated by a chain of at least 4 atoms, more preferably by a chain of at least 6 atoms, such as for example, hexamethyl hexamethylene diammonium dihydroxide, wherein the quaternary ammonium moieties are separated by –(CH2)6–. Primary and secondary amines do not to effectively form salts with the compounds of Formulae I – IV.

[00365] Salts of the compounds of Formulae I – IV can be prepared by reacting the compounds of Formulae I – IV with compounds that include at least one tertiary amine or quaternary ammonium ion (e.g., choline hydroxide, hexamethylhexamethylene diammonium dihydroxide) in a solvent selected from low molecular weight ketones (e.g., acetone, methyl ethyl ketone), tetrahydrofuran, dimethylformamide, and n-methyl pyrrolidinone. As with the preparation of salts from alkali metal hydroxides, amine and ammonium containing compounds do not form salts when the solvent is an alcohol.

[00366] Pharmaceutically acceptable salts of the compounds of Formulae I - IV can also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethylamino-ethanol, hydroxyethyl pyrrolidine, ammonium, tetrapropylammonium, tetrabutylphosphonium, hexamethyl diammonium, methyldiethanamine, triethylamine, meglumine, and procaine, and can be prepared using the appropriate corresponding bases.

[00367] Preferred basic addition salts of the compounds of Formulae I – IV can include those containing hexamethyl hexamethylene diammonium, choline, sodium, potassium, methyldiethyl amine, triethylamine, diethylamino-ethanol, hydroxyethyl pyrrolidine, tetrapropylammonium and tetrabutylphosphonium ions.

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[00368] Preferred basic addition salts of the compounds of Formulae I – IV can be prepared using hexamethyl hexamethylene diammonium dihydroxide, choline hydroxide, sodium hydroxide, sodium methoxide, potassium hydroxide, potassium methoxide, ammonium hydroxide, tetrapropylammonium hydroxide, and tetrabutylphosphonium hydroxide. The basic addition salts can be separated into inorganic salts (e.g., sodium, potassium and the like) and organic salts (e.g., choline, hexamethyl hexamethylene diammonium hydroxide, and the like).

[00369] The compounds of Formulae V – VIII have the unique property of being able to form both anions and cations. In basic media, the compounds of Formulae V – VIII typically form anions. Anions can be formed at either an amino or substituted amino substituent, or at the sulfonyl group. In acidic media, the compounds of Formulae V – VIII generally form cations by protonation of an amino group, thereby forming an ammonium moiety.

[00370] Salts of the anions of compounds of Formulae V – VIII can include metal cations, including monovalent metal cations of any group I alkali metal (e.g., sodium, potassium, and the like), divalent metal cations of any group II alkaline earth metal (e.g., calcium, magnesium, and the like), and aluminum cations.

[00371] Salts of the compounds of Formulae V – VIII which include metal cations can be prepared by reacting the compounds of Formulae V – VIII with a alkali or alkaline earth metal hydroxides or alkoxides, such as for example, sodium hydroxide or sodium methoxide, in an organic solvent, such as for example lower alcohols, low molecular weight ketones (e.g., acetone, methyl ethyl ketone, and the like), tetrahydrofuran, dimethylformamide, and n-methyl pyrrolidinone, and the like.

[00372] Salts of the compounds of Formulae V - VIII, may include organic or inorganic counter ions, including but not limited to, acetate, acetonide, acetyl, adipate, aspartate, besylate, biacetate, bitartrate, bromide, butoxide, butyrate, calcium, camsylate, caproate, carbonate, citrate, cypionate, decanoate, diacetate, dimegulumine, dinitrate, dipotassium, dipropionate, disodium, disulfide, edisylate, enanthate, estolate, etabonate, ethylsuccinate, fumarate, furoate, gluceptate, gluconate, hexacetonide, hippurate, hyclate, hydrobromide, hydrochloride, isethionate, lactobionate, malate, maleate, meglumine,

Ex. 2002-1036

methylbromide, methylsulfate, metrizoate, nafate, napsylate, nitrate, oleate, palmitate, pamoate, phenpropionate, phosphate, pivalate, polistirex, polygalacturonate, probutate, propionate, saccharate, sodium glycinate, sodium phosphate, sodium succinate, stearate, succinate, sulfate, sulfonate, sulfosalicylate, tartrate, tebutate, terephalate, terephthalate, tosylate, triflutate, trihydrate, trisilicate, tromethamine, valerate, or xinafoate. Preferred organic cations include compounds having tertiary amines or quaternary ammonium groups.

[00373] Other, pharmaceutically acceptable salts of the compounds of Formulae V – VIII include acid addition salts such as those containing sulfate, chloride, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluene sulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts of the compounds of Formulae V - VIII can be obtained from acids such as 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, and quinic acid.

[00374] Pharmaceutically acceptable salts of the compounds of Formulae V – VIII also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present. For example, see Remington's Pharmaceutical Sciences, 19th ed., Mack Publishing Co., Easton, PA, Vol. 2, p. 1457, 1995. Such salts of the compounds of Formulae V – VIII can be prepared using the appropriate corresponding bases.

[00375] Salts of the compounds of Formulae V – VIII can be prepared, for example, by dissolving the free-base form of a compound in a suitable solvent, such as an aqueous or aqueous-alcohol in solution containing the appropriate acid and then isolated by evaporating the solution. In another example, a salt is prepared by reacting the free base and acid in an organic solvent.

Ex. 2002-1037

[00376] The salts of the compounds of Formulae V – VIII may be present as a complex. Examples of complexes include 8-chlorotheophylline complex (analogous to, e.g., dimenhydrinate: diphenhydramine 8-chlorotheophylline (1:1) complex; Dramamine) and various cyclodextrin inclusion complexes.

[00377] Solvents useful in the preparation of pharmaceutically acceptable salts of the compounds of Formulae V – VIII include organic solvents, such as for example, acetonitrile, acetone, alcohols (e.g., methanol, ethanol and isopropanol), tetrahydrofuran, methyl ethyl ketone (MEK), ethers (e.g., diethyl ether), benzene, toluene, xylenes, dimethylformamide (DMF), and N-methyl pyrrolidinone (NMP), and the like. Preferably, the solvents are selected from acetonitrile and MEK.

[00378] The salts of compounds of Formulae V - VIII may be present as a complex. Examples of complexes include 8-chlorotheophylline complex (analogous to, e.g., dimenhydrinate: diphenhydramine 8-chlorotheophylline (1:1) complex; Dramamine) and various cyclodextrin inclusion complexes.

[00379] Formulations of salts of the compounds of Formulae I – VIII provided herein exhibit at least one, or preferably some or even more preferably, all the following characteristics: (1) they are stable at ambient temperatures for a minimum of one year; (2) they provide for ease of oral administration; (3) they facilitate patient compliance with dosing; (4) upon administration, they consistently facilitate high levels of absorption of the pharmaceutical active; (5) upon once or twice daily oral administration they allow release of the KATP channel opener over a sustained time frame such that the circulating concentration of the KATP channel opener or its metabolically active metabolites does not fall below a therapeutically effective concentration; (6) they achieve these results independent of the pH of the gastrointestinal tract of treated subjects, and (7) they delay release until gastric transit is complete or nearly complete.

[00380] Formulations designed for oral administration of the salts of the compounds of Formulae I – VIII can be provided, for example, as capsules, tablets, or as quick dissolve tablets or films. Capsule or tablet formulations include a number of distinguishing components. One is a component to improve absorption of the KATP channel opener.

Ex. 2002-1038

Another sustains release of the drug over more than 2 hours. A third delays substantial release of the drug until gastric transit is completed.

[00381] Oral administration formulations of the salts of the compounds of Formulae I – VIII can also be provided, for example, as oral suspensions, oral solutions, encapsulated oral suspensions, and encapsulated oral solutions. Formulations can be designed for immediate release or controlled release. Preferably, such oral formulations are not produced from a liquid form of the sodium salt of diazoxide.

[00382] Formulations of the salts of the compounds of Formulae I – VIII can also be prepared for transdermal, intranasal and intravenous (I.V.) administration, provided that when the anion is diazoxide and the cation is sodium, the formulation is not for intravenous use.

[00383] In another embodiment, formulations of the salts of the compounds of Formulae I – VIII are prepared for transdermal or intranasal ,administration, provided that when the anion is diazoxide and the cation is sodium, the formulation is not produced using a liquid form of the salt of the compounds of Formulae I – VIII.

[00384] In another embodiment, formulations of the salts of the compounds of Formulae I – VIII are prepared for transdermal, intranasal and intravenous (I.V.) administration excluding the sodium salt of diazoxide.

[00385] Formulations of KATP channel openers prepared using salts of the compounds selected from Formulae I – VIII exhibit improved solubility and absorption compared to previous formulations of these drugs. These advantageous properties are achieved by any one or more of the following approaches: (1) reducing particle size of the formulation by comminution, spray drying, or other micronising techniques, (2) using an ion exchange resin in the formulation, (3) using inclusion complexes, for example using a cyclodextrin, (4) compaction of the salt of KATP channel opener with a solubilizing agent including low viscosity hypromellose, low viscosity methylcellulose or similarly functioning excipient and combinations thereof, (5) associating the salt of the KATP channel opener with a distinct salt prior to formulation, (6) using a solid dispersion of the salt of the KATP channel opener, (7) using a self emulsifying system, (8) adding one or more

Ex. 2002-1039

surfactants to the formulation, (9) using nanoparticles in the formulation, or (10) combinations of these approaches.

[00386] Release of KATP channel opener selected from salts of the compounds of Formulae I – VIII over a sustained period of time (e.g., 2-30 hours) can be achieved by the use of one or more approaches including, but not limited to: (1) the use of pH sensitive polymeric coatings, (2) the use of a hydrogel, (3) the use of a film coating that controls the rate of diffusion of the drug from a coated matrix, (4) the use of an erodable matrix that controls rate of drug release, (5) the use of polymer coated pellets, granules, or microparticles which can be further encapsulated or compressed into a tablet, (6) the use of an osmotic pump system, (7) the use of a compression coated tablet, or (8) combinations of these approaches.

[00387] Delay of release of KATP channel openers selected from the salts of the compounds of Formulae I – VIII from the formulation until gastric transit is complete can be achieved in the formulations provided herein by any of several mechanisms. For example, pH sensitive polymer or co-polymer can be used which when applied around the drug matrix functions as an effective barrier to release of active at pH 3.0 or lower and is unstable at pH 5.5 and above. This provides for control of release of the active compound in the stomach but rapidly allows release once the dosage form has passed into the small intestine. An alternative to a pH sensitive polymer or co-polymer is a polymer or co-polymer that is non-aqueous-soluble. The extent of resistance to release in the gastric environment can be controlled by coating with a blend of the non-aqueous-soluble and a aqueous soluble polymer. In this approach neither of the blended polymers or co-polymers are pH sensitive. One example of a pH sensitive co-polymer is the Eudragit® methacrylic co-polymers, including Eudragit® L 100, S 100 or L 100-55 solids, L 30 D-55 or FS 30D dispersions, or the L 12,5 or S 12,5 organic solutions.

[00388] Polymers that delay release can be applied to a tablet either by spray coating (as a thin film) or by compression coating. If a capsule is used, then the polymer(s) may be applied over the surface of the capsule or applied to microparticles of the drug, which may then be encapsulated such as in a capsule or gel. If the capsule is coated, then it will resist disintegration until after gastric transit. If microparticles are coated, then the capsule may disintegrate in the stomach but little to no drug will be released until after the

Ex. 2002-1040

free microparticles complete gastric transit. Finally, an osmotic pump system that uses e.g., a swellable hydrogel can be used to delay drug release in the stomach. The swellable hydrogel takes up moisture after administration. Swelling of the gel results in displacement of the drug from the system for absorption. The timing and rate of release of the drug depend on the gel used, and the rate at which moisture reaches the gel, which can be controlled by the size of the opening in the system through which fluid enters. See Drug Delivery Technologies online article Dong et al., "L-OROS® SOFTCAP™ for Controlled Release of Non-Aqueous Liquid Formulations."

[00389] Accordingly, delay of release of formulations of KATP channel openers prepared as salts of the compounds of Formulae I - VIII until after gastric transit is complete can be achieved by any of several mechanisms, including, but not limited to: (a) a pH sensitive polymer or co-polymer applied as a compression coating on a tablet; (b) a pH sensitive polymer or co-polymer applied as a thin film on a tablet; (c) a pH sensitive polymer or co-polymer applied as a thin film to an encapsulation system; (d) a pH sensitive polymer or co-polymer applied to encapsulated microparticles, (e) a non-aqueous-soluble polymer or copolymer applied as a compression coating on a tablet; (f) a non-aqueous-soluble polymer or co-polymer applied as a thin film on a tablet; (g) a non-aqueous soluble polymer applied as a thin film to an encapsulation system; (h) a non-aqueous soluble polymer applied to microparticles; (i) incorporation of the formulation in an osmotic pump system, or (j) use of systems controlled by ion exchange resins, or (k) combinations of these approaches, wherein the pH sensitive polymer or co-polymer is resistant to degradation under acid conditions.

[00390] Formulations are provided that are designed for administration once daily (i.e., once per 24 hours). These formulations can contain between 25 and 500 mg of KATP channel openers selected from salts of the compounds of Formulae I – VIII. Formulations intended for administration twice daily (per 24 hours) may also be provided. These can contain between 25 and 250 mg of KATP channel openers.

[00391] The formulations provided herein exhibit improved safety of the administered drug product. This improvement in safety occurs by at least two mechanisms. First, delay of release of active drug until gastric transit is complete can reduce the incidence of a range of gastrointestinal adverse side effects including nausea, vomiting, dyspepsia,

Ex. 2002-1041

abdominal pain, diarrhea and ileus. Second, by sustaining release of the active drug over 2 or more hours up to as long as 24 hours, peak drug levels are reduced relative to the peak drug levels observed for the same administered dose using any oral formulation that does not have sustained or controlled release. This reduction in peak drug levels can contribute to reductions in adverse effects that are partially or completely determined by peak drug levels. These adverse effects include: fluid retention with the associated reduced rates of excretion of sodium, chloride and uric acid, edema, hyperglycemia and the associated potential for progression to ketoacidosis, cataracts and non-ketotic hyperosmolar coma, headaches, tachycardia and palpitations.

[00392] Also provided herein are controlled release formulations of KATP channel openers prepared from salts of compounds of Formulae I – VIII, which have one feature from each of A-D as shown in Table 1.

Table 1: Controlled Release Formulation Characteristics and Properties

A. Unit Form:	Tablet or Capsule
B. Dosage/unit:	10-100 mg
	100-200 mg
	200-300 mg
	300-500 mg
	500-2000 mg
C. Dosing	Once daily (24 hours)
	Twice daily (24 hours)
D. Release time:	2-4 hrs
	4-8 hrs
	8-24 hours

[00393] For example, a controlled release composition can be a tablet containing 25-100 mg of a salt of a compound of Formulae I – VIII, wherein such tablet administered

Ex. 2002-1042

once daily to achieve a controlled release time of 2-4 hours. All of these formulations can further include the feature of substantially delaying pharmaceutical active release until after gastric transit is complete.

[00394] In addition, any of the above formulations from Table 1 can include at least one feature that improves the solubility or absorption of the KATP channel opener.

[00395] Exemplary controlled release formulations provided herein include the active compound (i.e., a KATP channel opener selected from a salt of a compound of any of Formulae I – VIII) and a matrix which includes a gelling agent that swells upon contact with aqueous fluid. The active compound entrapped within the gel is slowly released into the body upon dissolution of the gel. The active compound can be evenly dispersed within the matrix or can be present as pockets of drug in the matrix. For example, the drug can be formulated into small granules which are dispersed within the matrix. In addition, the granules of drug also can include a matrix, thus, providing a primary and a secondary matrix as described in U.S. Pat. No. 4,880,830 to Rhodes.

[00396] The gelling agent preferably is a polymeric material, which can include, for example, any pharmaceutically acceptable water soluble or water insoluble slow releasing polymer such as xantham gum, gelatin, cellulose ethers, gum arabic, locust bean gum, guar gum, carboxyvinyl polymer, agar, acacia gum, tragacanth, veegum, sodium alginate or alginic acid, polyvinylpyrrolidone, polyvinyl alcohol, or film forming polymers such as methyl cellulose (MC), carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose, hyroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), ethylcellulose (EC), acrylic resins or mixtures of the above (see e.g., U.S. Pat. No. 5,415,871).

[00397] The gelling agent of the matrix also can be a heterodisperse gum comprising a heteropolysaccharide component and a homopolysaccharide component which produces a fast-forming and rigid gel as described in U.S. Pat. No. 5,399,359. The matrix also can include a cross-linking agent such as a monovalent or multivalent metal cations to further add rigidity and decrease dissolution of the matrix, thus further slowing release of drug. The amount of crosslinking agent to add can be determined using methods routine to the ordinary skilled artisan.

Ex. 2002-1043

[00398] The matrix of the controlled release composition also can include one or more pharmaceutically acceptable excipients recognized by those skilled in the art, i.e. formulation excipients. Such excipients include, for example, binders: polyvinylpyrrolidone, gelatin, starch paste, microcrystalline cellulose; diluents (or fillers): starch, sucrose, dextrose, lactose, fructose, xylitol, sorbitol, sodium chloride, dextrins, calcium phosphate, calcium sulphate; and lubricants: stearic acid, magnesium stearate, calcium stearate, Precirol ® and flow aids for example talc or colloidal silicon dioxide.

[00399] The matrix of the controlled release composition can further include a hydrophobic material which slows the hydration of the gelling agent without disrupting the hydrophilic nature of the matrix, as described in U.S. Pat. No. 5,399,359. The hydrophobic polymer can include, for example, alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or copolymers derived from acrylic or methacrylic acid esters, copolymers of acrylic and methacrylic acid esters, zein, waxes, shellac, hydrogenated vegetable oils, waxes and waxy substances such as carnauba wax, spermaceti wax, candellila wax, cocoa butter, cetosteryl alcohol, beeswax, ceresin, paraffin, myristyl alcohol, stearyl alcohol, cetylalcohol and stearic acid, and any other pharmaceutically acceptable hydrophobic material known to those skilled in the art.

[00400] The amount of hydrophobic material incorporated into the controlled release composition is that which is effective to slow the hydration of the gelling agent without disrupting the hydrophilic matrix formed upon exposure to an environmental fluid. In certain preferred embodiments, the hydrophobic material is included in the matrix in an amount from about 1 to about 20 percent by weight and replaces a corresponding amount of the formulation excipient. A solvent for the hydrophobic material may be an aqueous or organic solvent, or mixtures thereof.

[00401] Examples of commercially available alkylcelluloses are Aquacoat ® (aqueous dispersion of ethylcellulose available from FMC) and Surelease ® (aqueous dispersion of ethylcellulose available from Colorcon). Examples of commercially available acrylic polymers suitable for use as the hydrophobic material include Eudragit ® RS and RL (copolymers of acrylic and methacrylic acid esters having a low content (e.g., 1:20 or 1:40) of quaternary ammonium compounds).

Ex. 2002-1044

[00402] The controlled release composition also can be coated to retard access of liquids to the active compound and/or retard release of the active compound through the film-coating. The film-coating can provide characteristics of gastroresistance and enterosolubility by resisting rapid dissolution of the composition in the digestive tract. The film-coating generally represents about 5-15% by weight of the controlled release composition. Preferably, the core by weight represents about 90% of the composition with the remaining 10% provided by the coating. Such coating can be a film-coating as is well known in the art and include gels, waxes, fats, emulsifiers, combination of fats and emulsifiers, polymers, starch, and the like.

[00403] Polymers and co-polymers are useful as thin film coatings. Solution coatings and dispersion coatings can be used to coat the active compound, either alone or combined with a matrix. The coating is preferably applied to the drug or drug and matrix combination as a solid core of material as is well known in the art.

[00404] A solution for coating can include polymers in both organic solvent and aqueous solvent systems, and typically further including one or more compounds that act as a plasticizer. Polymers useful for coating compositions include, for example, methylcellulose (Methocel ® A; Dow Chemical Co.), hydroxypropylmethylcellulose with a molecular weight between 1,000 and 4,000,000 (Methocel ® E; Dow Chemical Co. or Pharmacoat ®; Shin Etsu), hydroxypropyl cellulose with a molecular weight between 2,000 and 2,000,000, ethyl cellulose, cellulose acetate, cellulose triacetate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose acetate trimellitate (Eastman Kodak), carboxymethylethyl cellulose (Duodcel ®), hydroxypropyl methylcellulose phthalate, ethylcellulose, methylcellulose and, in general, cellulosic derivatives, polymethacrylic acid-methacrylic acid copolymer (Type A 1:1 Eudragit L100; Type B 1:2 Eudragit S100; and Type C 1:1 Eudragit L100-55, aqueous dispersion 30% solids, Eudragit L30D), poly(meth)acryl ester: poly(ethyl acrylate, methyl methacrylate 2:1), Eudragit NE30D aqueous dispersion 30% solids, polyaminomethacrylate Eudragit E100, poly(trimethylammonioethyl methacrylate chloride) ammoniomethacrylate copolymer, Eudragit RL30D and Eudragit RS30D, carboxyvinyl polymers, polyvinylalcohols, glucans scleroglucans, mannans, and xanthans.

Ex. 2002-1045

[00405] Aqueous polymeric dispersions include Eudragit L30D and RS/RL30D, and NE30D, Aquacoat® brand ethyl cellulose, Surelease brand ethyl cellulose, EC brand N-10F ethyl cellulose, Aquateric brand cellulose acetate phthalate, Coateric brand Poly(vinyl acetate phthalate), and Aqacoat brand hydroxypropyl methylcellulose acetate succinate. Most of these dispersions are latex, pseudolatex powder or micronized powder mediums.

[00406] A plasticizing agent may be included in the coating to improve the elasticity and the stability of the polymer film and to prevent changes in the polymer permeability over prolonged storage. Such changes may affect the drug release rate. Suitable conventional plasticizing agents include, for example, diethyl phthalate, glycerol triacetate, acetylated monoglycerides, acetyltributylcitrate, acetyltriethyl citrate, castor oil, citric acid esters, dibutyl phthalate, dibutyl sebacate, diethyloxalate, diethyl malate, diethylfumarate, diethylphthalate, diethylsuccinate, diethylmalonate, diethyltartarate, dimethylphthalate, glycerin, glycerol, glyceryl triacetate, glyceryltributyrate, mineral oil and lanolin alcohols, petrolatum and lanolin alcohols, phthalic acid esters, polyethylene glycols, propylene glycol, rape oil, sesame oil, triacetin, tributyl citrate, triethyl citrate, and triethyl acetyl citrate, or a mixture of any two or more of the foregoing. Plasticizers which can be used for aqueous coatings include, for example, propylene glycol, polyethylene glycol (PEG 400), triacetin, polysorbate 80, triethyl citrate, and diethyl d-tartrate.

[00407] A coating solution comprising a mixture of hydroxypropylmethylcellulose and aqueous ethylcellulose (e.g. Aquacoat brand) as the polymer and dibutyl sebacate as plasticizer can be used for coating microparticles. (Aquacoat is an aqueous polymeric dispersion of ethylcellulose and contains sodium lauryl sulfate and cetyl alcohol). Preferably, the plasticizer represents about 1-2% of the composition.

[00408] In addition to the polymers, the coating layer can include an excipient to assist in formulation of the coating solution. Such excipients may include a lubricant or a wetting agent. Suitable lubricants as excipients for the film coating include, for example, talc, calcium stearate, colloidal silicon dioxide, glycerin, magnesium stearate, mineral oil, polyethylene glycol, and zinc stearate, aluminum stearate or a mixture of any two or more of the foregoing. Suitable wetting agents include, for example, sodium lauryl sulfate,

Ex. 2002-1046

acacia, benzalkonium chloride, cetomacrogol emulsifying wax, cetostearyl alcohol, cetyl alcohol, cholesterol, diethanolamine, docusate sodium, sodium stearate, emulsifying wax, glyceryl monostearate, hydroxypropyl cellulose, lanolin alcohols, lecithin, mineral oil, monoethanolamine, poloxamer, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, propylene glycol alginate, sorbitan esters, stearyl alcohol and triethanolamine, or a mixture of any two or more of the foregoing.

[00409] The specified tablet or capsule formulations of Table 1 may include co-formulation with an obesity treating drug (in addition to a KATP channel opener selected from a salt of a compound of Formulae I – VIII). Obesity treating drugs that may be used include, but are not limited to, sibutramine hydrochloride (5-30 mg/unit), orlistat (50-360 mg/unit), phentermine hydrochloride or resin complex (15 to 40 mg/unit), zonisamide (100 to 600 mg/unit), topiramate (64 to 400 mg/unit), naltrexone hydrochloride (50 to 600 mg/unit), rimonabant (5 to 20 mg/unit), ADP356 (5 to 25 mg/unit), ATL962 (20 to 400 mg/unit), or AOD9604 (1 to 10 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of KATP channel opener selected from a salt of a compound of Formulae I – VIII is one half the amount included in the once daily formulation and the co-formulated obesity treating drug is half of the amount specified. Alternative obesity treating drugs may include, but are not limited to: selective serotonin 2c receptor agonists, dopamine antagonists, cannabinoid-1 receptor antagonists, leptin analogues, leptin transport and/or leptin receptor promoters, neuropeptide Y and agouti-related peptide antagonists, proopiomelanocortin and cocaine and amphetamine regulated transcript promoters, melanocyte-stimulating hormone analogues, melanocortin-4 receptor agonists, and agents that affect insulin metabolism/activity, which can include protein-tyrosine phosphatase-1B inhibitors, peroxisome proliferator activated receptor antagonists, short-acting bromocriptine (ergoset), somatostatin agonists (octreotide), and adiponectin, gastrointestinal-neural pathway agents, including those that increase cholecystokinin activity, increase glucagon-like peptide-1 activity (e.g., exendin 4, liraglutide, dipeptidyl peptidase IV inhibitors), and increase protein YY3-36 activity and those that decrease ghrelin activity, as well as amylin analogues, agents that may increase resting metabolic rate ("selective" β-3 stimulators/agonist, uncoupling protein homologues, and thyroid receptor agonists), melanin concentrating hormone antagonists,

Ex. 2002-1047

phytostanol analogues, amylase inhibitors, growth hormone fragments, synthetic analogues of dehydroepiandrosterone sulfate, antagonists of adipocyte 11Bhydroxysteroid dehydrogenase type 1 activity, corticotropin releasing hormone agonists, inhibitors of fatty acid synthesis, carboxypeptidase inhibitors, indanones/indanols, aminosterols, and other gastrointestinal lipase inhibitors.

[00410] The specified tablet or capsule formulations of Table 1 may include co-formulation with a diabetes treating drug (in addition to a KATP channel opener selected from a salt of a compound of Formulae I – VIII). Diabetes treating drugs that may be used include, but are not limited to, acarbose (50 to 300 mg/unit), miglitol (25 to 300 mg/unit), metformin hydrochloride (300 to 2000 mg/unit), repaglinide (1-16 mg/unit), nateglinide (200 to 400 mg/unit), rosiglitazone (5 to 50 mg/unit), metaglidasen (100 to 400 mg/unit) or any drug that improves insulin sensitivity, or improves glucose utilization and uptake. These formulations are preferably used once daily. For a twice daily dosing, the amount of the KATP channel opener selected from a salt of a compound of Formulae I – VIII is half the amount included in the once daily formulation and the co-formulated diabetes treating drug is half of the amount specified.

[00411] The specified tablet or capsule formulations of Table 1 may include co-formulation with a cholesterol lowering drug. Cholesterol lowering drugs that may be used include, but are not limited to, pravastatin, simvastatin, atorvastatin, fluvastatin, rosuvastatin, or lovastatin (all at 10 to 80 mg/unit), fibrates (50 to 300 mg/unit), niacin (500 to 2000 mg/unit), thyroid receptor activators (0.5 to 100 mg/unit), MTP inhibitors (20 to 1000 mg/unit), PPAR delta agonists and modulators (5 to 400 mg/unit), and squalene synthase inhibitor (10 to 1000 mg/unit). These formulations are preferably used once daily. Each of these classes of active may also be used to raise HDL cholesterol. For a twice daily dosing, the amount of KATP channel opener selected from a salt of a compound of Formulae I – VIII is preferably 25 to 200 mg/unit and the co-formulated cholesterol lowering drug is half of the amount specified.

[00412] The specified tablet or capsule formulations of Table 1 may include co-formulation with a depression treating drug. Depression treating drugs that may be used include, but are not limited to, citalopram hydrobromide (10 to 80 mg/unit), escitalopram hydrobromide (5 to 40 mg/unit), fluvoxamine maleate (25 to 300 mg/unit), paroxetine

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hydrochloride (12.5 to 75 mg/unit), fluoxetine hydrochloride (30 to 100 mg/unit), setraline hydrochloride (25 to 200 mg/unit), amitriptyline hydrochloride (10 to 200 mg/unit), desipramine hydrochloride (10 to 300 mg/unit), nortriptyline hydrochloride (10 to 150 mg/unit), duloxetine hydrochloride (20 to 210 mg/unit), venlafaxine hydrochloride (37.5 to 150 mg/unit), phenelzine sulfate (10 to 30 mg/unit), bupropion hydrochloride (200 to 400 mg/unit), or mirtazapine (7.5 to 90 mg/unit). These formulations are preferably used once daily. 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 depression treating drug is half of the amount specified.

[00413] The specified tablet or capsule formulations of Table 1 may include co-formulation with a hypertension treating drug. Hypertension treating drugs that may be used include, but are not limited, to enalapril maleate (2.5 to 40 mg/unit), captopril (2.5 to 150 mg/unit), lisinopril (10 to 40 mg/unit), benzaepril hydrochloride (10 to 80 mg/unit), quinapril hydrochloride (10 to 80 mg/unit), peridopril erbumine (4 to 8 mg/unit), ramipril (1.25 to 20 mg/unit), trandolapril (1 to 8 mg/unit), fosinopril sodium (10 to 80 mg/unit), moexipril hydrochloride (5 to 20 mg/unit), losartan potassium (25 to 200 mg/unit), irbesartan (75 to 600 mg/unit), valsartan (40 to 600 mg/unit), candesartan cilexetil (4 to 64 mg/unit), olmesartan medoxamil (5 to 80 mg/unit), telmisartan (20 to 160 mg/unit), eprosartan mesylate (75 to 600 mg/unit), atenolol (25 to 200 mg/unit), propranolol hydrochloride (10 to 180 mg/unit), metoprolol tartrate, succinate or fumarate (each at 25 to 400 mg/unit), nadolol (20 to 160 mg/unit), betaxolol hydrochloride (10 to 40 mg/unit), acebutolol hydrochloride (200 to 800 mg/unit), pindolol (5 to 20 mg/unit), bisoprolol fumarate (5 to 20 mg/unit), nifedipine (15 to 100 mg/unit), felodipine (2.5 to 20 mg/unit), amlodipine besylate (2.5 to 20 mg/unit), nicardipine (10 to 40 mg/unit), nisoldipine (10 to 80 mg/unit), terazosin hydrochloride (1 to 20 mg/unit), doxazosin mesylate (4 to 16 mg/unit), prazosin hydrochloride (2.5 to 10 mg/unit), or alfuzosin hydrochloride (10 to 20 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of KATP channel opener is preferably half the amount included in the once daily formulation and the co-formulated hypertension treating drug is half of the amount specified.

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[00414] The specified tablet or capsule formulations of Table 1 may include co-formulation with a diuretic to treat edema. Diuretics that may be used include, but are not limited to amiloride hydrochloride (1 to 10 mg/unit), spironolactone (10 to 100 mg/unit), triamterene (25 to 200 mg/unit), bumetanide (0.5 to 4 mg/unit), furosemide (10 to 160 mg/unit), ethacrynic acid or ethacrynate sodium (each at 10 to 50 mg/unit), torsemide (5 to 100 mg/unit), chlorthalidone (10 to 200 mg/unit), indapamide (1 to 5 mg/unit), hydrochlorothiazide (10 to 100 mg/unit), chlorothiazide (50 to 500 mg/unit), bendroflumethiazide (5 to 25 mg/unit), hydroflumethiazide (10 to 50 mg/unit), mythyclothiazide (1 to 5 mg/unit), or polythiazide (1 to 10 mg/unit). These formulations are preferably used once daily. 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 diuretic is half of the amount specified.

[00415] The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat inflammation or pain. Drugs for treating inflammation or pain that may be used include, but are not limited to aspirin (100 to 1000 mg/unit), tramadol hydrochloride (25 to 150 mg/unit), gabapentin (100 to 800 mg/unit), acetaminophen (100 to 1000 mg/unit), carbamazepine (100 to 400 mg/unit), ibuprofen (100 to 1600 mg/unit), ketoprofen (12 to 200 mg/unit), fenprofen sodium (100 to 600 mg/unit), flurbiprofen sodium or flurbiprofen (both at 50 to 200 mg/unit), or combinations of any of these with a steroid or aspirin. These formulations are preferably used once daily. 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 diuretic is half of the amount specified.

[00416] The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat obesity associated co-morbidities include those specified above for treating diabetes, cholesterol, depression, hypertension and edema, or drugs to treat atherosclerosis, osteoarthritis, disc herniation, degeneration of knees and hips, breast, endometrial, cervical, colon, leukemia and prostate cancers, hyperlipidemia, asthma/reactive airway disease, gallstones, GERD, obstructive sleep apnea, obesity hypoventilation syndrome, recurrent ventral hernias, menstrual irregularity and infertility.

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