

Table 55. Pharmacokinetic Data for Patients

Parameter	Range	Mean±SD	Median
AUC _{0-24(hrs)} (µg*hr/mL)	344.5 – 750.7	546.0±128.4	542.6
C _{max(ss)} (µg/mL)	16.3 – 35.4	25.9±5.8	26.6
C _{min(ss)} (µg/mL)	10.4 – 28.9	19.6±5.3	18.4
C _{av(ss)} (µg/mL)	14.4 – 31.3	22.8±5.3	22.6
% Peak-to-Trough Fluctuation	18.0% – 41.1%	28.5±7.2%	27.8%

17. Co-administration of Diazoxide Choline and Fenofibrate Choline in Patients with Very High Triglycerides

[00834] A group of 4 patients from the study described in Example 15, all males ranging in age from 28 to 62 years old, with very high triglycerides and low HDL, were treated with 290 mg DCCR for 12 weeks and with both 290 mg DCCR and 135 mg fenofibrate for an additional 2 weeks. All subjects at baseline had triglycerides above 500 mg/dL (very high triglycerides) and HDL-C below 40 mg/dL (low HDL-C). Additionally, all four patients had elevated non-HDL-C. The patients were at elevated risk of cardiovascular events due to marked elevations of non-HDL-C and low HDL-C.

[00835] Combined treatment with DCCR and fenofibrate in these patients normalized triglycerides (TG < 150 mg/dL), reduced non-HDL-C by 50%, and normalized HDL-C (increased by 58.5%). The risk of cardiovascular events in these patients was reduced significantly by treatment with DCCR and fenofibrate. Table 56 below summarizes the data averages for the lipid characteristics of each patient at baseline and end of treatment.

Table 56. Average Baseline and End-of-Treatment Lipid Parameters

	Baseline	End of Treatment	Change	% Change
Triglycerides (mg/dL)	728.8	115.5	-613.3	-84.20%
Non-HDL-C (mg/dL)	301.7	151	-150.7	-49.90%
HDL-C (mg/dL)	29.5	46.8	17.3	58.50%

18. Characterizing Bioavailability of Diazoxide Choline in Mice

[00836] A study was conducted in male mice to characterize the absolute bioavailability of diazoxide choline polymorph form B and the relative bioavailability of four structurally related molecules, all of which agonize the K_{ATP} channel. The related molecules have the same ring structure as diazoxide, namely 4H-1,2,4-benzothiadiazine

1,1-dioxide, but differ in the constituent at positions 3, 6 and 7. Position 6 was occupied either by hydrogen, chlorine, bromine, or fluorine. Position 7 was occupied either by hydrogen, fluorine, or methoxy. The substitutions at the 3 position included 3-amino-isopropylene and 3-amino-cyclobutane.

[00837] The study used 4 mice dosed per treatment arm. Following a single intravenous or oral dose, administered by gavage, pharmacokinetic samples were collected at 4 time points: 0.5, 1, 3, and 6 hours post-dosing. Two mice were sampled at each timepoint, with each mouse contributing samples to two timepoints. Each test drug was administered as a 50 mg/kg dose, which yields nearly equal molar concentrations. Diazoxide choline was administered as a diazoxide equivalent dose of 50 mg/kg. Blood samples were collected into tubes containing dipotassium EDTA as the anticoagulant and placed on ice packs until centrifugation (at 3000 rpm for 10 minutes at 4°C). After centrifugation, samples were stored at -70°C until they were thawed for analysis. Circulating drug levels were measured using a precise and reproducible LC-MS/MS assay.

[00838] The following pharmacokinetic parameters were measured: AUC_{0-6} , the area under the plasma concentration versus time curve from time 0 to 6 hours post-dosing calculated by the linear trapezoidal method; and C_{max} , the maximum measured plasma concentration over the time from 0 to 6 hours post-dosing. Absolute oral bioavailability of diazoxide choline was calculated by comparing the AUC_{0-6} of the oral dose to that of the IV dose. Relative oral bioavailability of the remaining KATP channel agonists was calculated as the ratio of the AUC_{0-6} for the molecule to that of the IV dose of diazoxide choline. A summary of the data obtained from the mouse study are summarized in Table 57 as follows.

Table 57. Bioavailability of DCCR and Related Molecules in Male Mice

Molecule	Mode of admin.	AUC ₀₋₆ (ng*hr/ml)	C _{max} (ng/mL)	Absolute oral bioavailability	Relative oral bioavail.
Diazoxide choline	IV	137176 ± 3352	34310 ± 3671	---	---
Diazoxide choline	Oral gavage	141260 ± 24134	29292 ± 2685	100%	---
7H-6-methoxy- 3-amino- isopropylene- 4H-1,2,4- benzothiadiazine 1,1-dioxide	Oral gavage	3590 ± 1860	1560 ± 982	---	2.6%
7-chloro-6- fluoro-3- amino- isopropylene- 4H-1,2,4- benzothiadiazine 1,1-dioxide	Oral gavage	313±15	80±12	---	0.2%
7-bromo-6H-- 3-amino- cyclobutane- 4H-1,2,4- benzothiadiazine 1,1-dioxide	Oral gavage	800±126	181±16	---	0.6%
7-fluoro-6H-3- amino- cyclobutane- 4H-1,2,4- benzothiadiazine 1,1-dioxide	Oral gavage	89±16	24±10	---	0.06%

[00839] The use of the choline salt of diazoxide provides for complete oral bioavailability of diazoxide (100%) in this mouse study, while administration of the free base of a range of structurally related molecules results in very limited oral bioavailability, between 0.06% and 2.6%.

19. Intravenous Administration of DCCR For Patients with Acute Pancreatitis

[00840] A patient with acute pancreatitis is given a bolus dose of diazoxide choline (between about 0.5 to 5 mg/kg) combined with insulin (typically in the range of 50 – 200

mg) over the course of 5-10 minutes, followed by continuous administration of diazoxide choline at a rate of about 0.02 to 0.2 mg/kg/hr to a total daily dosage of between about 100-400 mg/day, up to 500 mg/day. Insulin is co-administered at a rate of that is sufficient to maintain fasting glucose between about 70 mg/dL and 125 mg/dL and ensure peak post prandial glucose is less than 200 mg/dL. This may be accomplished using a basal insulin, a fast-acting prandial insulin, or both in combination. Administration of the combination of diazoxide choline and insulin may be continued until the pancreatitis has subsided.

* * * * *

[00841] All patents and other references cited in the specification are indicative of the level of skill of those skilled in the art to which the invention pertains, and are incorporated by reference in their entireties, including any tables and figures, to the same extent as if each reference had been incorporated by reference in its entirety individually.

[00842] One skilled in the art would readily appreciate that the present invention is well adapted to obtain the ends and advantages mentioned, as well as those inherent therein. The methods, variances, and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

[00843] Definitions provided herein are not intended to be limiting from the meaning commonly understood by one of skill in the art unless indicated otherwise.

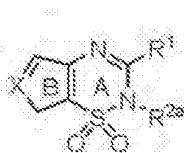
[00844] The inventions illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising", "including," "containing", etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be

understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the inventions embodied therein herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

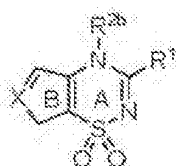
[00845] The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein. Other embodiments are within the following claims. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

THAT WHICH IS CLAIMED IS:

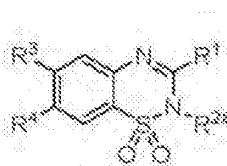
1. A method for treating dyslipidemia in a subject, the method comprising administering to the subject:
 - a. a formulation comprising one or more omega-3 fatty acids, and
 - b. a formulation comprising a therapeutically effective amount of a K_{ATP} channel opener, said K_{ATP} channel opener comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV,



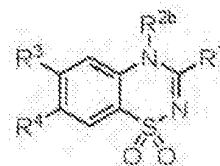
Formula I



Formula II



Formula III



Formula IV

wherein in Formulas I and II:

R^1 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, cycloalkyl, and substituted cycloalkyl provided however that when R^1 is a substituted C_1 - C_6 alkyl or a substituted cycloalkyl, then the substituent does not include an amino group;

R^{2a} is hydrogen;

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, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cycloalkyl, substituted cycloalkyl, or substituted C_1 - C_6 alkoxy, provided however that when an atom of the chain is substituted with substituted C_1 - C_6 alkyl, substituted C_1 - C_6 alkoxy or substituted cycloalkyl, then the

substituent does not include an amino group;

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

wherein in Formulas III and IV:

R^1 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, and cycloalkyl provided however that when R^1 is a substituted C_1 - C_6 alkyl, then the substituent does not include an amino group;

R^{2a} is hydrogen;

R^{2b} is hydrogen;

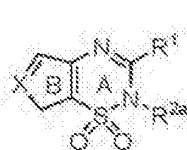
R^3 is selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, cycloalkyl and substituted cycloalkyl provided however that when R^3 is a substituted C_1 - C_6 alkyl, then the substituent does not include an amino group;

R^4 is selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, cycloalkyl and substituted cycloalkyl provided however that when R^4 is a substituted C_1 - C_6 alkyl, then the substituent does not include an amino group, and

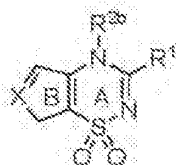
a cation selected from the group consisting of an alkali metal and a compound comprising an ammonium group comprising at least one tertiary amine group.

2. The method of claim 1, wherein said 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.

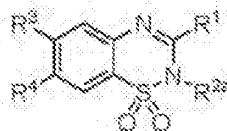
3. The method of any one of claims 1-2, wherein said dyslipidemia comprises abnormally high triglycerides.
4. The method of claim 3, wherein said abnormally high triglycerides comprises a triglyceride level of at least about 500 mg/dL.
5. The method of claim 3, wherein said abnormally high triglycerides comprises a triglyceride level of at least about 1000 mg/dL.
6. The method of any one of claims 1-5, wherein said K_{ATP} channel opener is formulated as a controlled release oral formulation.
7. The method of claim 6, wherein said controlled release oral formulation is formulated for once or twice daily administration.
8. The method of any one of claims 1-7, wherein said subject is administered about 145 to 435 mg per day of said K_{ATP} channel opener.
9. The method of any one of claims 1-8, wherein said K_{ATP} channel opener comprises a salt of diazoxide.
10. The method of any one of claims 1-9, wherein said K_{ATP} channel opener comprises diazoxide choline.
11. The method of any one of claims 1-10, wherein said omega-3 fatty acid formulation is substantially free of DHA.
12. A method for initiating treatment for a dyslipidemia in a subject, the method comprising administering a fibrate or a salt thereof and a K_{ATP} channel opener, said K_{ATP} channel opener comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV.



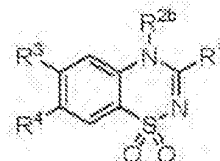
Formula I



Formula II



Formula III



Formula IV

wherein in Formulas I and II:

R^1 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, cycloalkyl, and substituted cycloalkyl provided however that when R^1 is a substituted C_1 - C_6 alkyl or a substituted cycloalkyl, then the substituent does not include an amino group;

R^{2a} is hydrogen;

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, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cycloalkyl, substituted cycloalkyl, or substituted C_1 - C_6 alkoxy, provided however that when an atom of the chain is substituted with substituted C_1 - C_6 alkyl, substituted C_1 - C_6 alkoxy or substituted cycloalkyl, then the substituent does not include an amino group;

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

wherein in Formulas III and IV:

R^1 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, and cycloalkyl provided however that when R^1 is a substituted C_1 - C_6 alkyl, then the substituent does not include an amino group;

R^{2a} is hydrogen;

R^{2b} is hydrogen;

R^3 is selected from the group consisting of hydrogen, halogen, C_1 - C_5 alkyl, substituted C_1 - C_6 alkyl, cycloalkyl and substituted cycloalkyl provided however that when R^3 is a substituted C_1 - C_5 alkyl, then the substituent does not include an amino group;

R^4 is selected from the group consisting of hydrogen, halogen, C_1 - C_5 alkyl, substituted C_1 - C_6 alkyl, cycloalkyl and substituted cycloalkyl provided however that when R^4 is a substituted C_1 - C_5 alkyl, then the substituent does not include an amino group, 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;

wherein said fibrate or a salt thereof and said 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.

13. The method of claim 12, wherein said dyslipidemia comprises a triglyceride level of at least about 500 mg/dL.

14. The method of any one of claims 12-13, wherein said dyslipidemia further comprises a HDL-C level of less than about 40 mg/dL.

15. The method of any one of claims 12-14, wherein said dyslipidemia comprises a triglyceride level of at least about 1000 mg/dL.

16. The method of any one of claims 12-15, wherein the titration doses of said fibrate and said K_{ATP} channel opener are about between about one third to about one half of the corresponding maintenance doses.

17. The method of any one of claims 12-16, wherein said K_{ATP} channel opener is formulated as a controlled release formulation for oral administration.

18. The method of claim 17, wherein said controlled release formulation is formulated for once or twice daily administration.

19. The method of any one of claims 12-18, wherein said K_{ATP} channel opener comprises a salt of diazoxide.

20. The method of any one of claims 12-19, wherein said K_{ATP} channel opener comprises diazoxide choline.

21. The method of any one of claims 12-20, wherein said K_{ATP} channel opener titration dose is about 70 mg to 220 mg.

22. The method of any one of claims 12-21, wherein said K_{ATP} channel opener maintenance dose is about 145 mg to 435 mg.

23. The method of any one of claims 12-22, wherein said fibrate is formulated as a controlled release formulation for oral administration.

24. The method of claim 23, wherein said controlled release formulation is formulated for once or twice daily administration.

25. The method of any one of claims 12-24, wherein said fibrate or a salt thereof comprises fenofibrate or a salt thereof.

26. The method of any one of claims 12-25, wherein said fibrate or a salt thereof comprises fenofibrate choline.

27. The method of any one of claims 12-26, wherein the titration dose of said

fibrate or a salt thereof is about 35 mg to 100 mg.

28. The method of any one of claims 12-27, wherein the maintenance dose of said fibrate or a salt thereof is about 100 mg to about 200 mg.

29. The method of any one of claims 12-28, wherein titration doses of said fibrate or a salt thereof and said K_{ATP} channel opener are co-formulated for single administration.

30. The method of claim 29, wherein said co-formulation is formulated as a controlled release formulation for oral administration.

31. The method of claim 30, wherein said controlled release formulation is formulated for once or twice daily administration.

32. The method of any one of claims 12-31, wherein maintenance doses of said fibrate or a salt thereof and said K_{ATP} channel opener are co-formulated for combined administration.

33. The method of claim 32, wherein said co-formulation is formulated as a controlled release formulation for oral administration.

34. The method of claim 33, wherein said controlled release formulation is formulated for once or twice daily administration.

35. A kit 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.

wherein the daily dosages of said K_{ATP} channel opener and said fibrate are sub-optimal titration dosages.

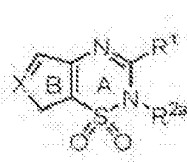
36. The kit of claim 35, wherein each of said plurality of blister cavities contains a pharmaceutical formulation comprising either a K_{ATP} channel opener or a fibrate or a salt thereof.

37. The kit of any one of claims 35-36, wherein each of said 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.

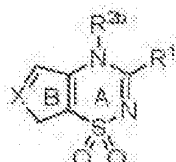
38. The kit of any one of claims 35-37, wherein said K_{ATP} channel opener and said fibrate are co-formulated in a single pharmaceutical formulation.

39. The kit of claim 38, wherein each of said plurality of blister cavities contains said co-formulated pharmaceutical formulation.

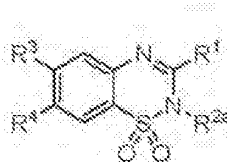
40. The kit of any one of claims 35-39, wherein said K_{ATP} channel opener comprises a salt comprising an anion of a K_{ATP} channel opener selected from the group consisting of Formula I, Formula II, Formula III and Formula IV,



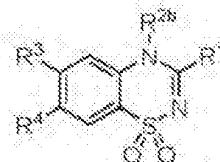
Formula I



Formula II



Formula III



Formula IV

wherein in Formulas I and II:

R^1 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, cycloalkyl, and substituted cycloalkyl provided

however that when R^1 is a substituted C_1 - C_6 alkyl or a substituted cycloalkyl, then the substituent does not include an amino group;

R^{2a} is hydrogen;

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, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, C_1 - C_6 alkoxy, cycloalkyl, substituted cycloalkyl, or substituted C_1 - C_6 alkoxy, provided however that when an atom of the chain is substituted with substituted C_1 - C_6 alkyl, substituted C_1 - C_6 alkoxy or substituted cycloalkyl, then the substituent does not include an amino group;

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

wherein in Formulas III and IV:

R^1 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, and cycloalkyl provided however that when R^1 is a substituted C_1 - C_6 alkyl, then the substituent does not include an amino group;

R^{2a} is hydrogen;

R^{2b} is hydrogen;

R^3 is selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, cycloalkyl and substituted cycloalkyl provided however that when R^3 is a substituted C_1 - C_6 alkyl, then the substituent does not include an amino group;

R^4 is selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, cycloalkyl and substituted cycloalkyl

provided however that when R^4 is a substituted C_1 - C_8 alkyl, then the substituent does not include an amino group, 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.

41. The kit of any one of claims 35-40, wherein said K_{ATP} channel opener comprises a salt of diazoxide.

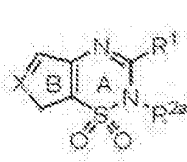
42. The kit of any one of claims 35-41, wherein said K_{ATP} channel opener comprises diazoxide choline.

43. The kit of any one of claims 35-42, wherein said fibrate or a salt thereof comprises fenofibrate or a salt thereof.

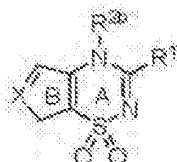
44. The kit of claim 36, wherein said fibrate or a salt thereof comprises fenofibrate choline.

45. A method 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:

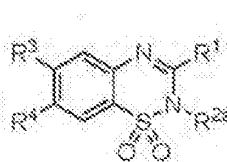
wherein said K_{ATP} channel opener is selected from the group consisting of Formula I, Formula II, Formula III and Formula IV.



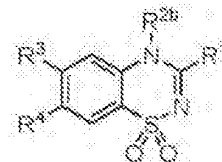
Formula I



Formula II



Formula III



Formula IV

wherein in Formulas I and II:

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, cycloalkyl, and substituted cycloalkyl provided however that when R^1 is a substituted C_1-C_6 alkyl or a substituted cycloalkyl, then the substituent does not include an amino group;

R^{2a} is hydrogen;

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, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_1-C_6 alkoxy, cycloalkyl, substituted cycloalkyl, or substituted C_1-C_6 alkoxy, provided however that when an atom of the chain is substituted with substituted C_1-C_6 alkyl, substituted C_1-C_6 alkoxy or substituted cycloalkyl, then the substituent does not include an amino group;

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

wherein in Formulas III and IV:

R^1 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, and cycloalkyl provided however that when R^1 is a substituted C_1-C_6 alkyl, then the substituent does not include an amino group;

R^{2a} is hydrogen;

R^{2b} is hydrogen;

R^3 is selected from the group consisting of hydrogen, halogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, cycloalkyl and substituted cycloalkyl provided however that when R^3 is a substituted C_1-C_6 alkyl, then the

substituent does not include an amino group;

R^4 is selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, cycloalkyl and substituted cycloalkyl provided however that when R^4 is a substituted C_1 - C_6 alkyl, then the substituent does not include an amino group, and

wherein said K_{ATP} channel opener is formulated for intravenous administration.

46. The method of claim 45, wherein the dose of K_{ATP} channel opener administered as a bolus is between about 50 to 200 mg.

47. The method of any one of claims 45-46, further comprising 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.

48. The method of claim 47, wherein said insulin comprises a basal insulin, a fast-acting prandial insulin, or a mixture thereof.

49. The method of any one of claims 45-48, wherein the K_{ATP} channel opener comprises diazoxide or an ion thereof.

50. The method of any one of claims 45-49, further comprising co-administration of nicorandil.

51. The method of any one of claims 45-50, further comprising treating the subject using plasmapheresis.

52. The method of any one of claims 45-51, wherein the subject is a human.

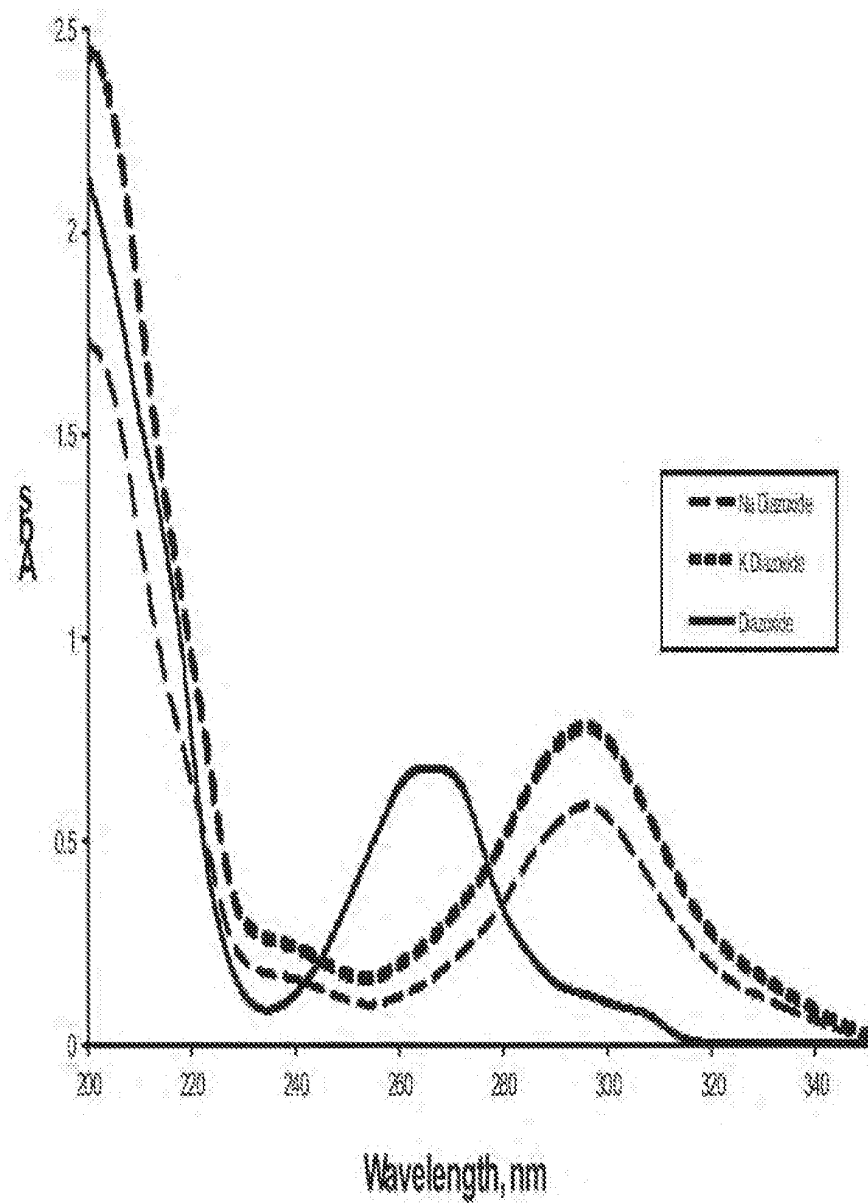
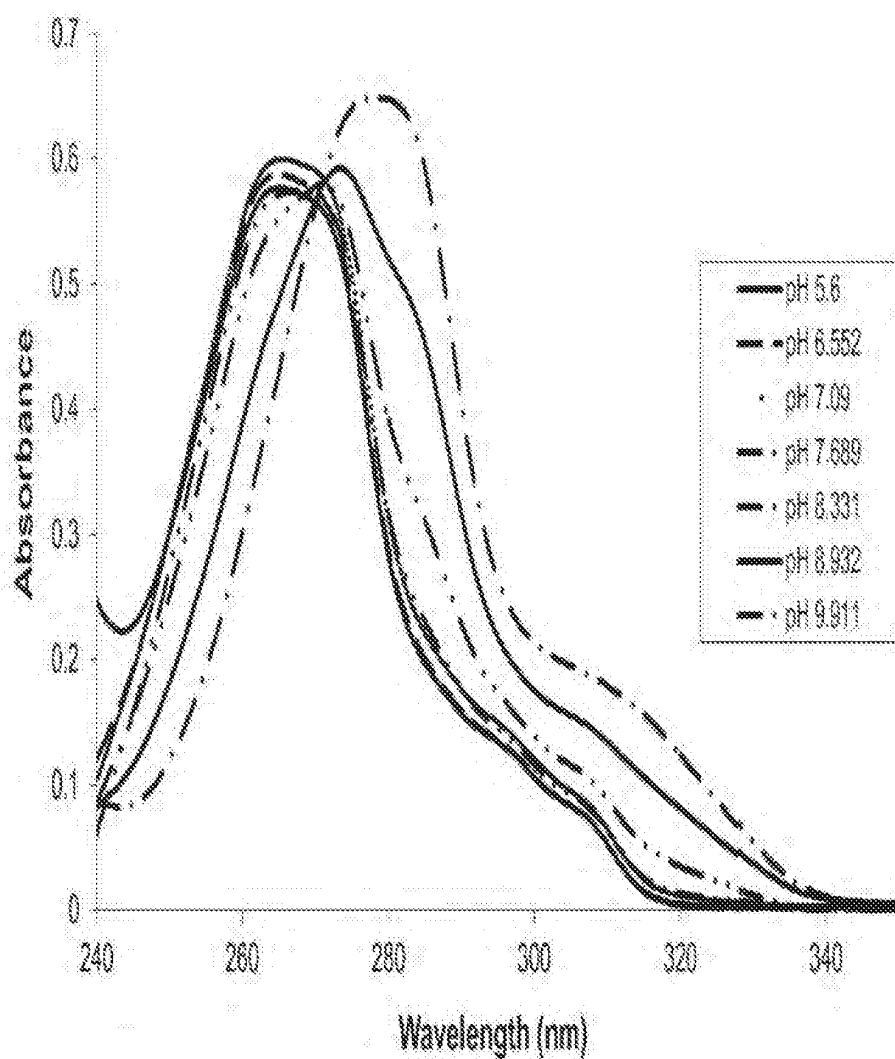
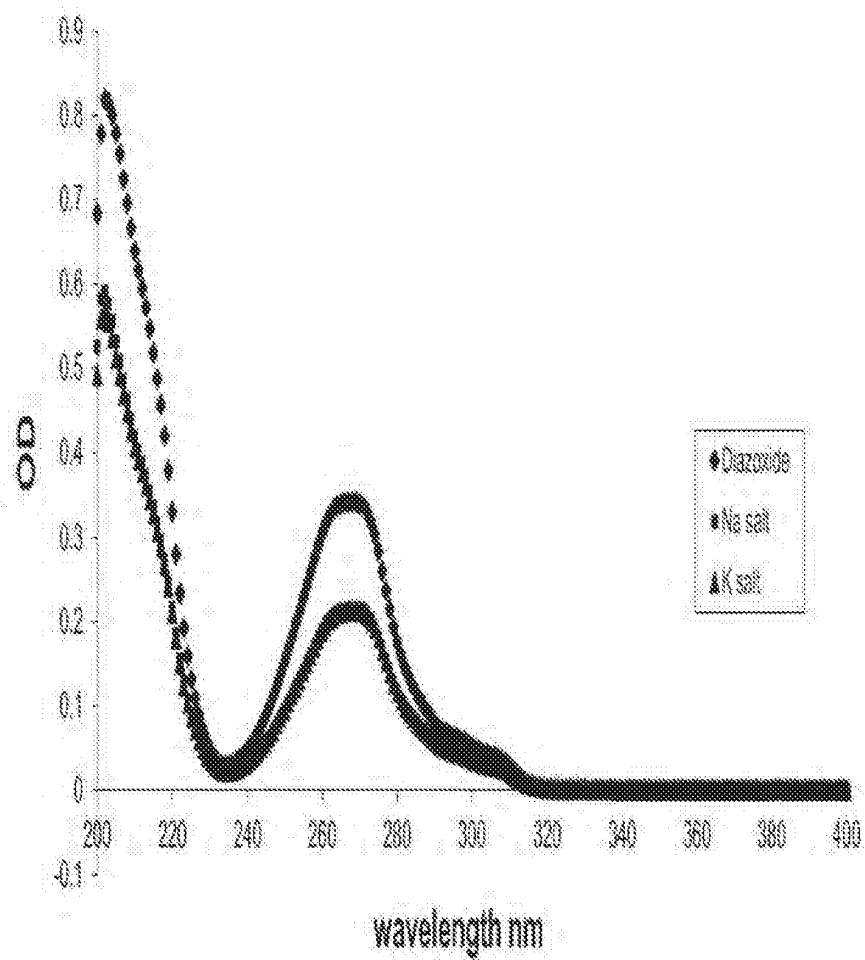


FIG. 1



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FIG. 2



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FIG. 3

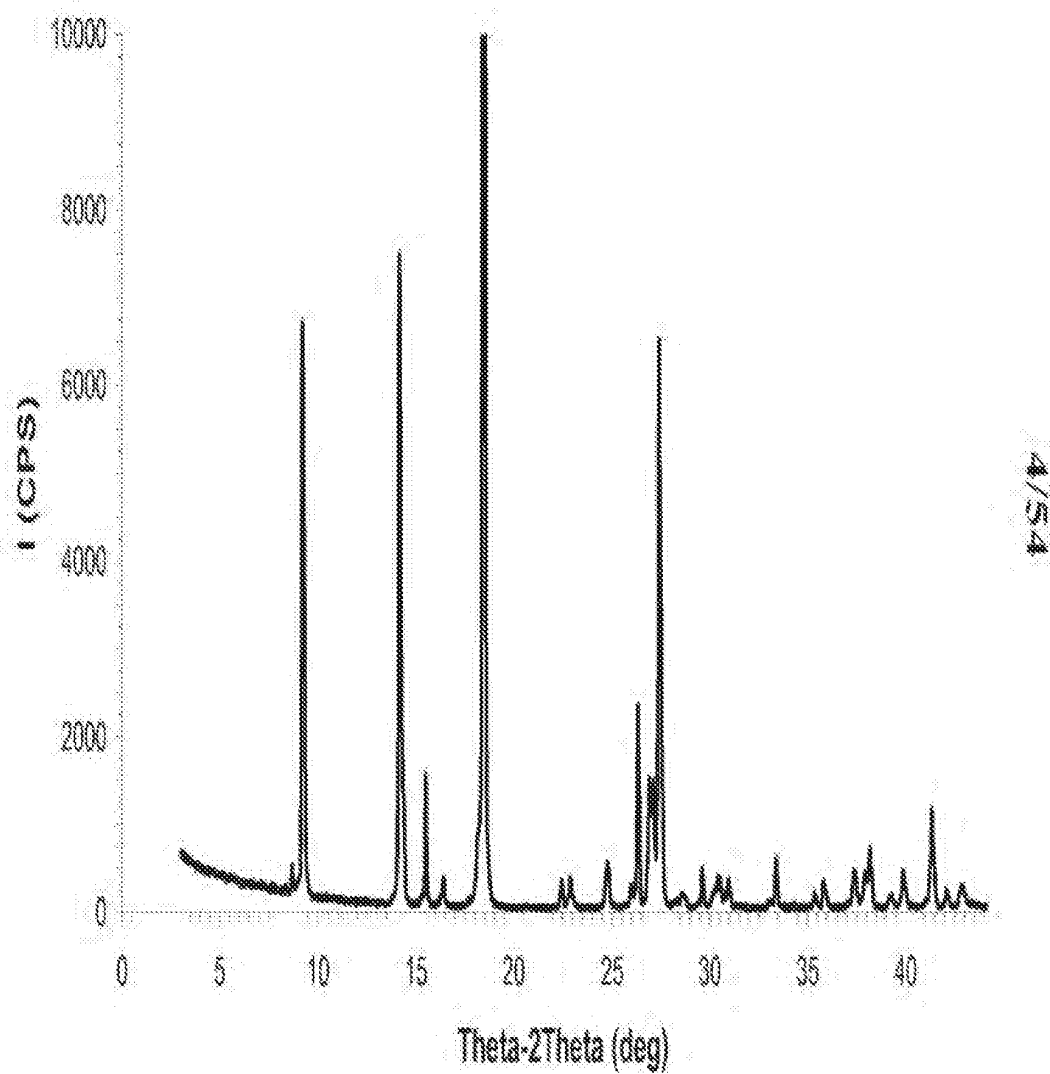


FIG. 4A

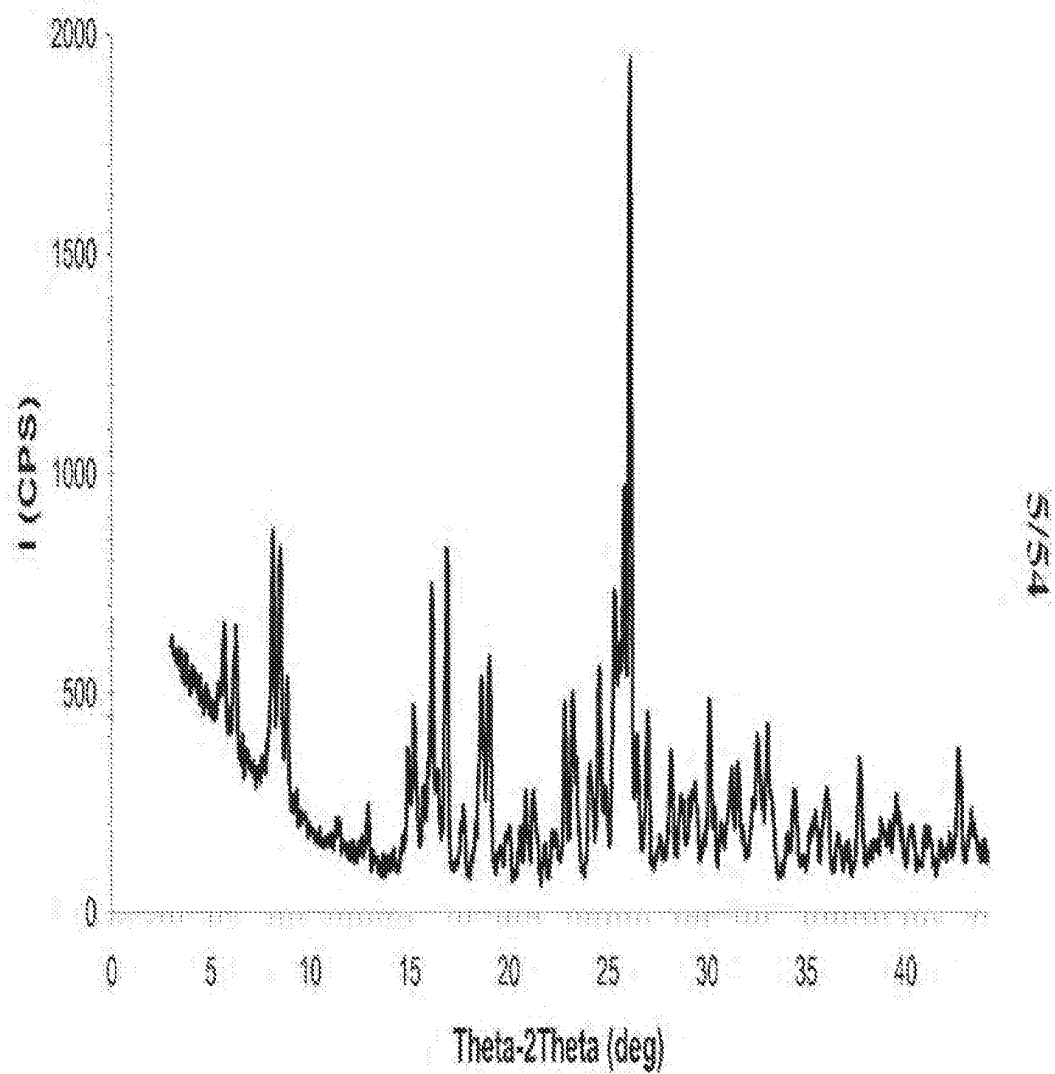
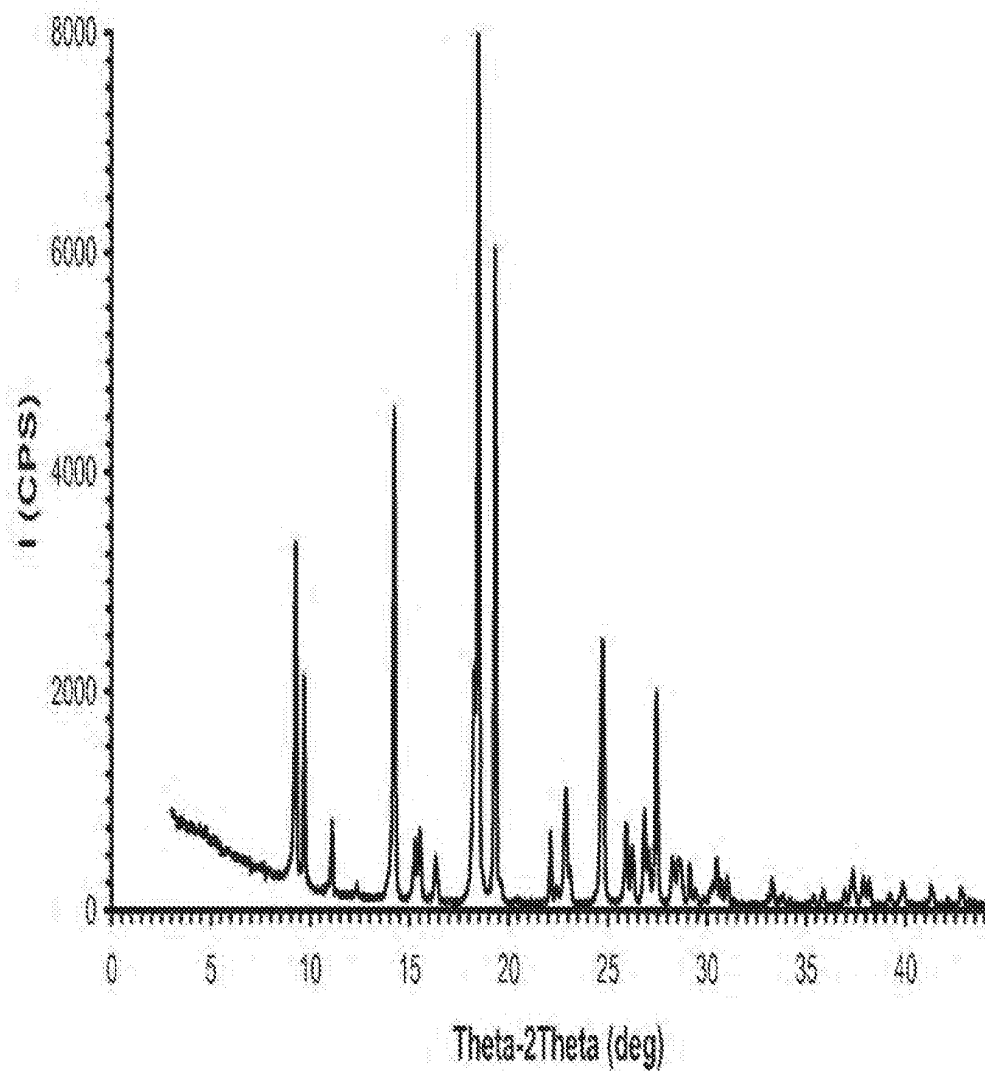


FIG. 4B



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FIG. 4C

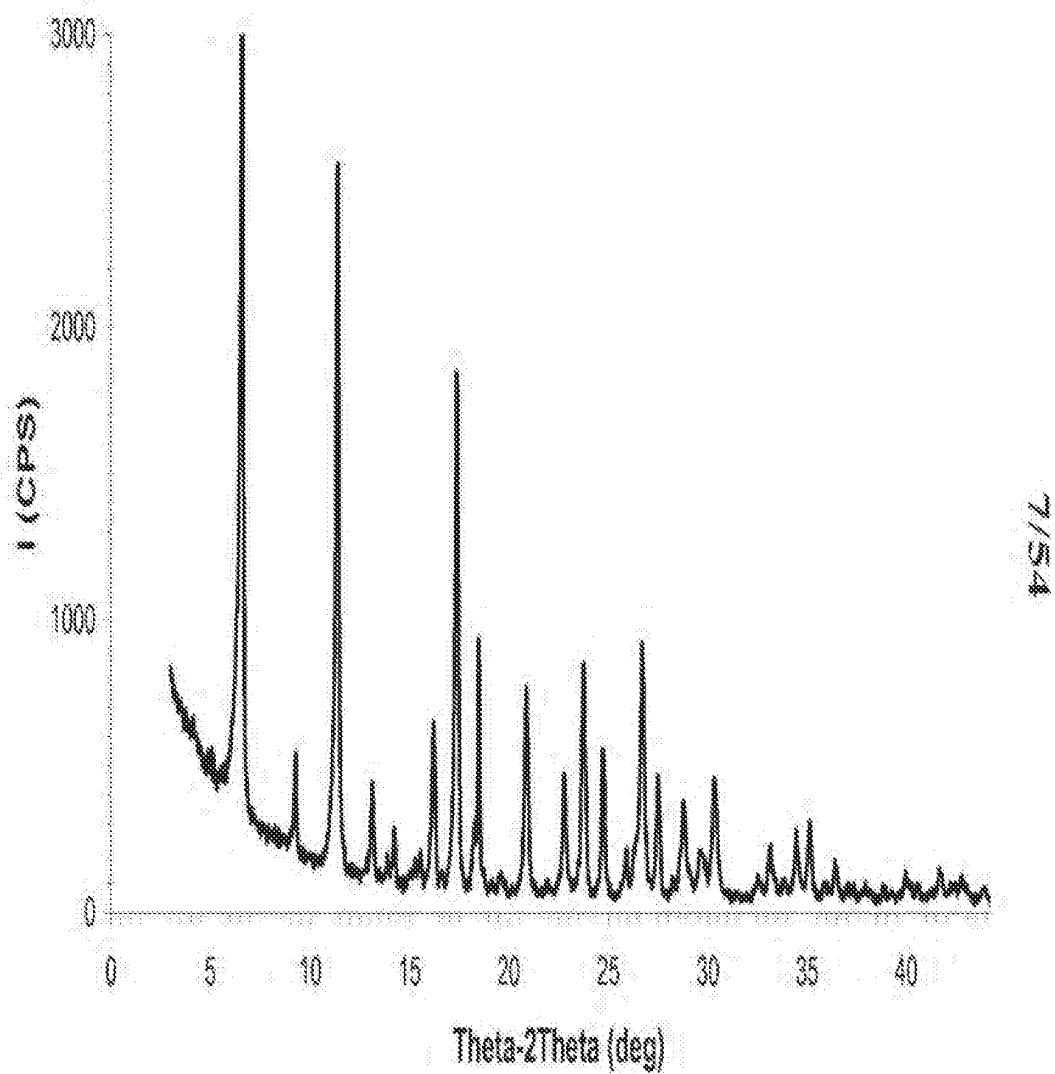


FIG. 5A

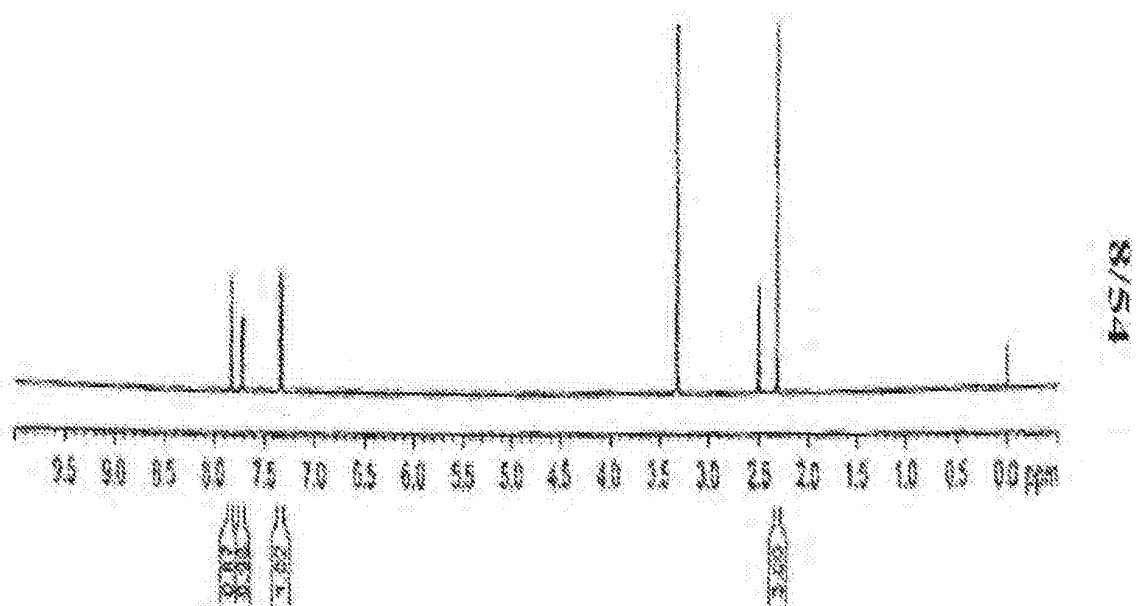


FIG. 5B

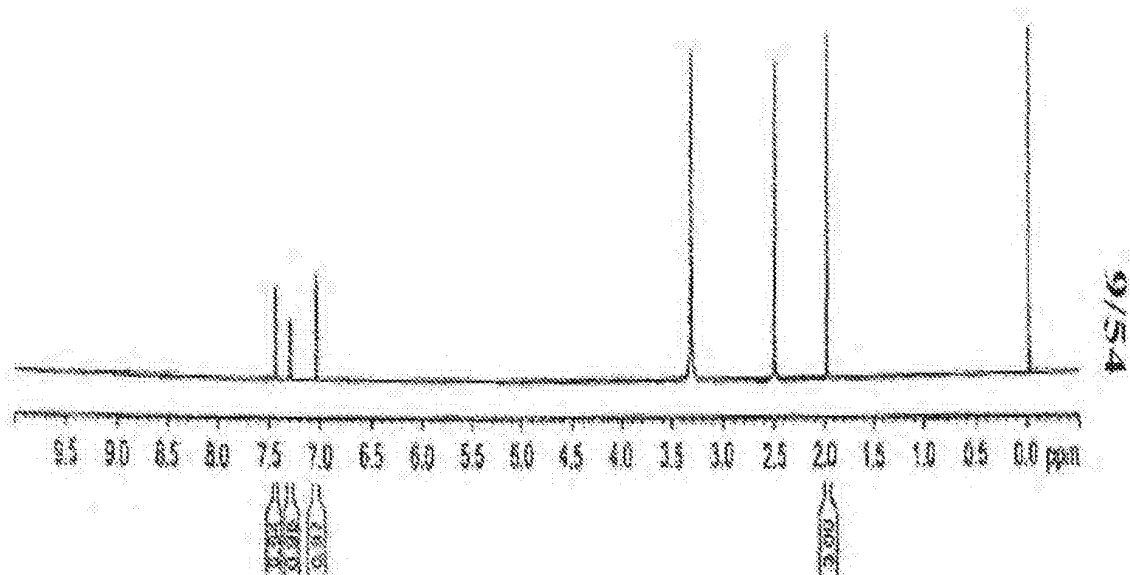
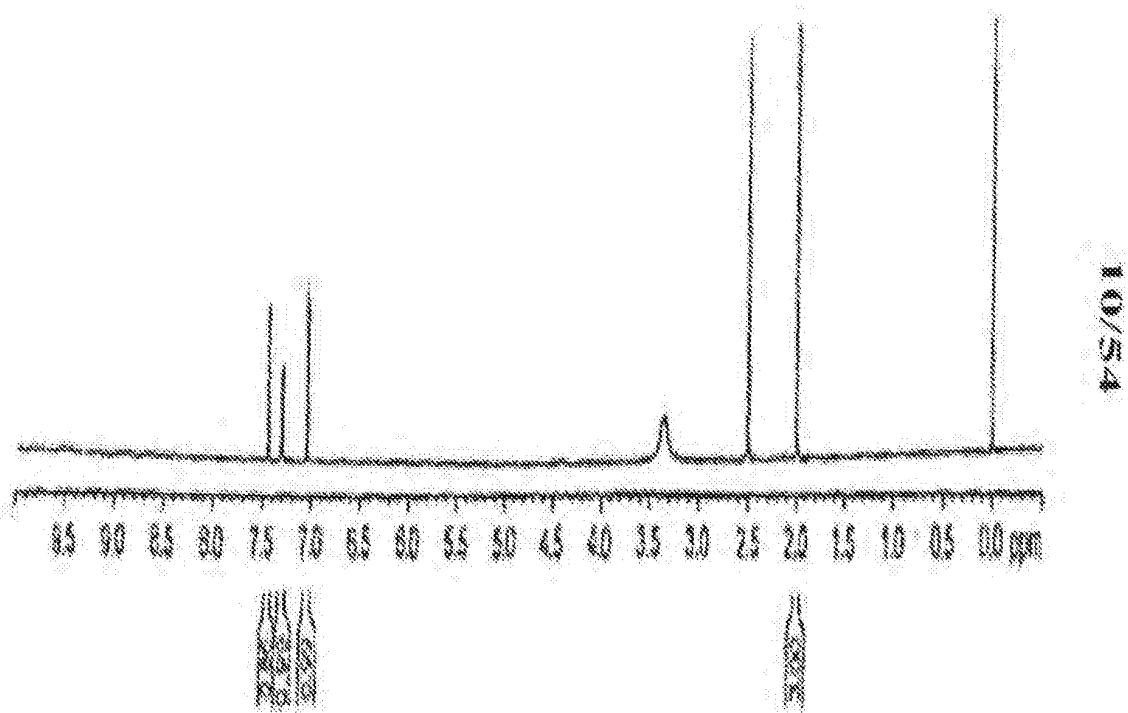
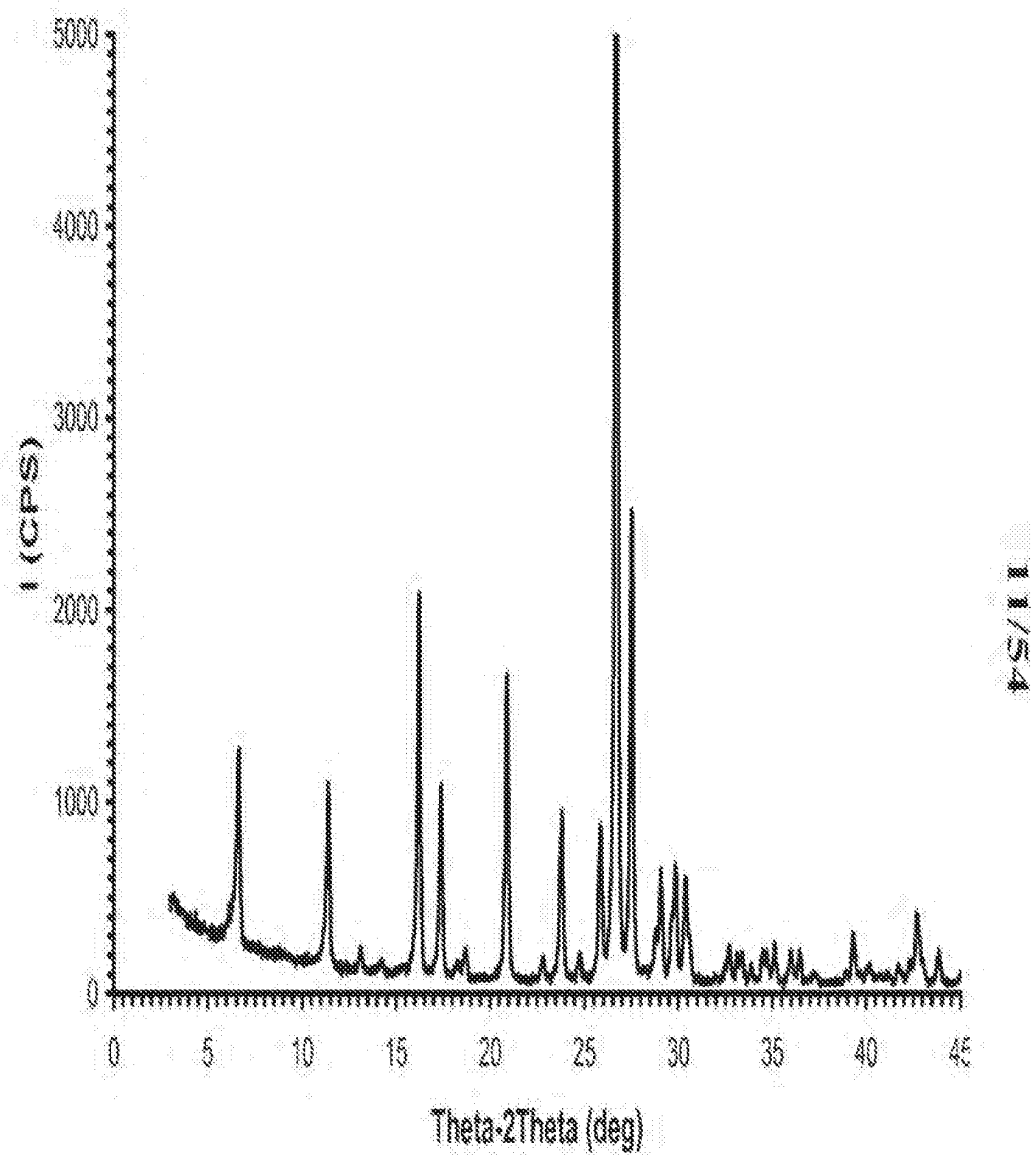
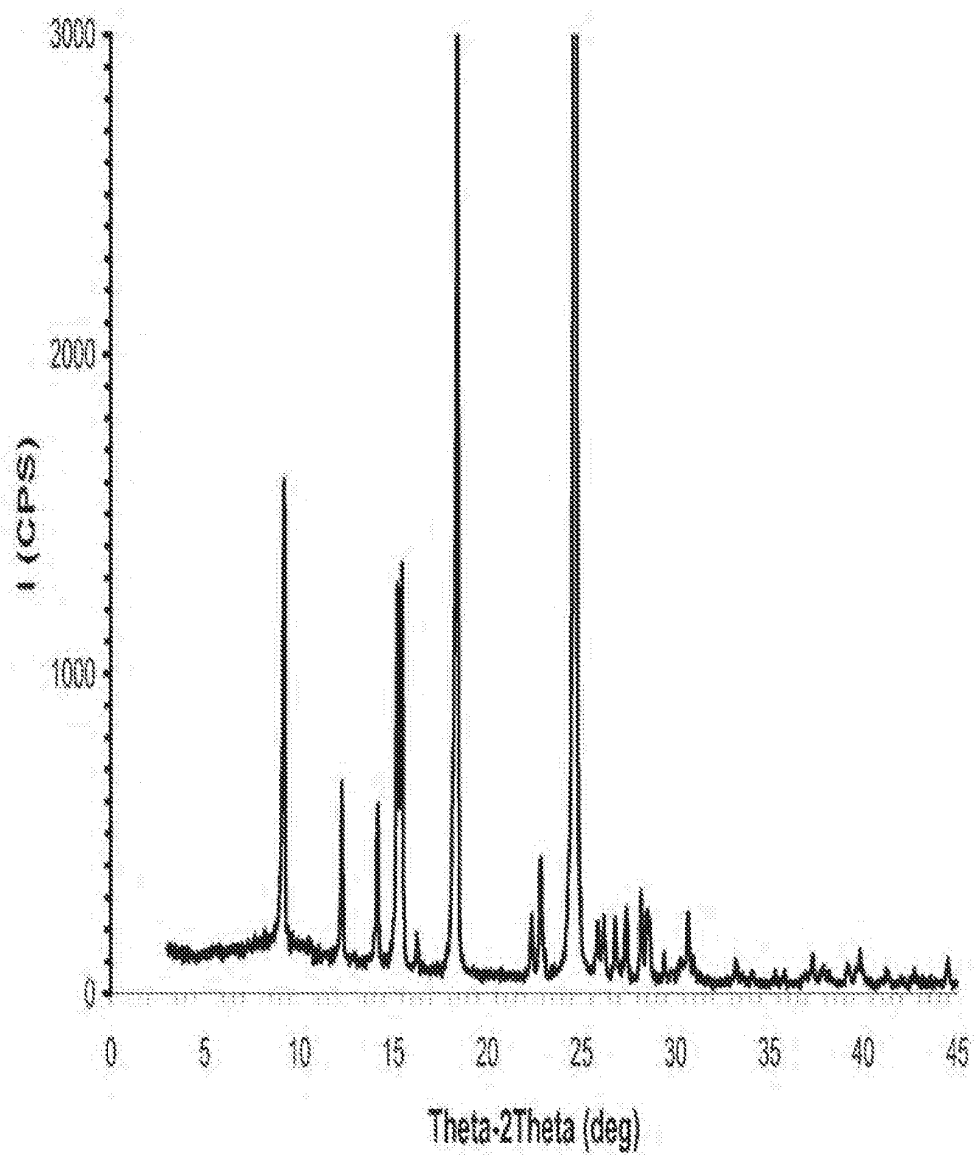


FIG. 5C







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FIG. 6B

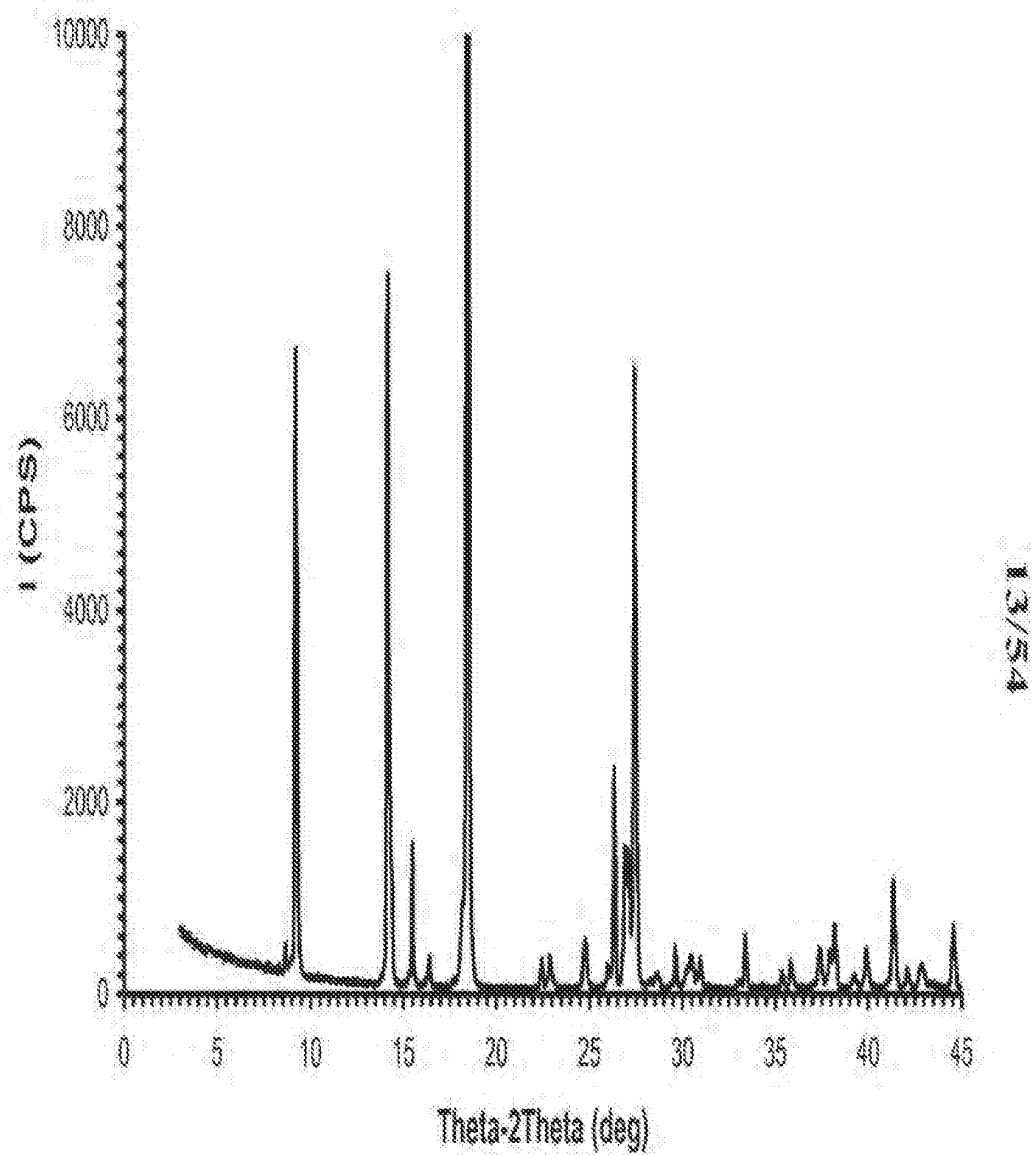
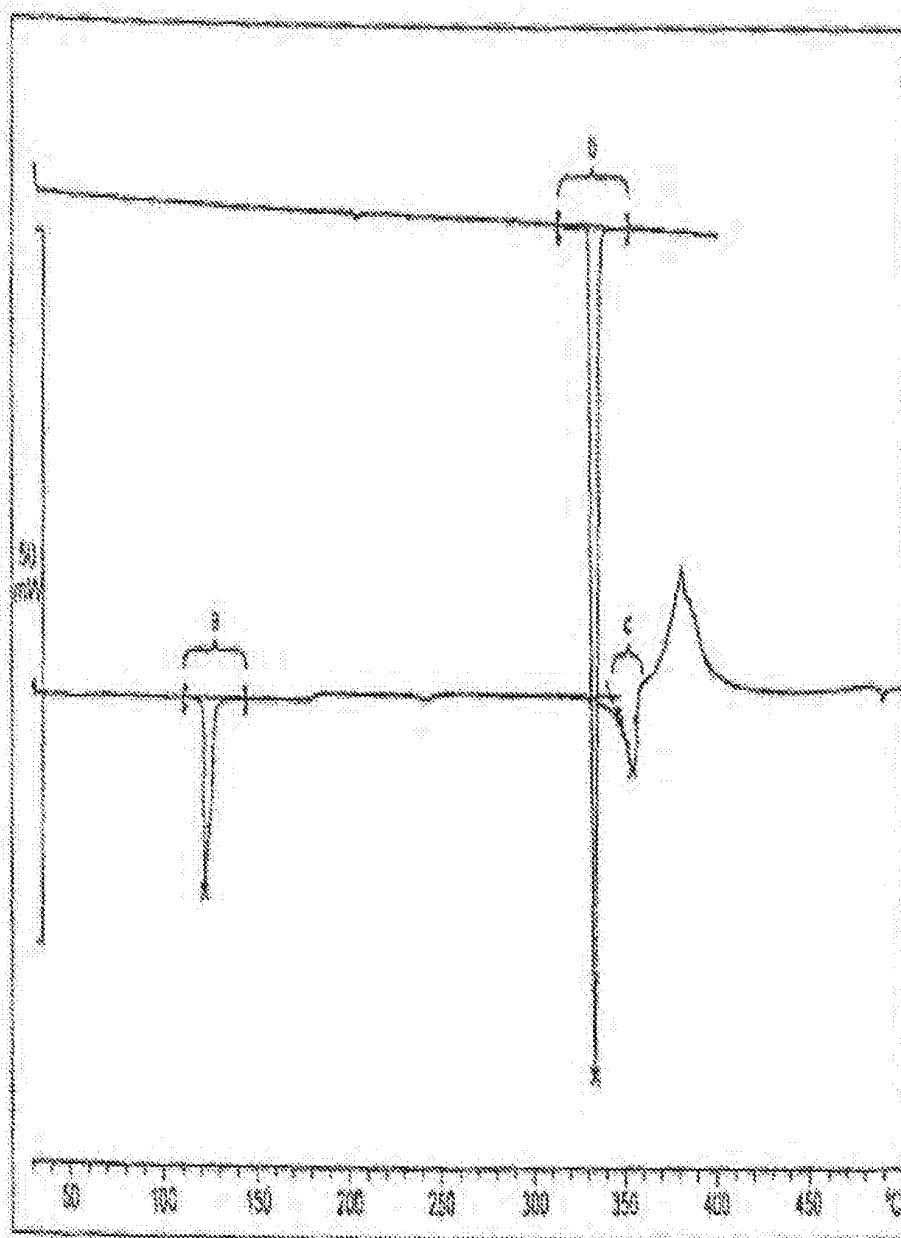
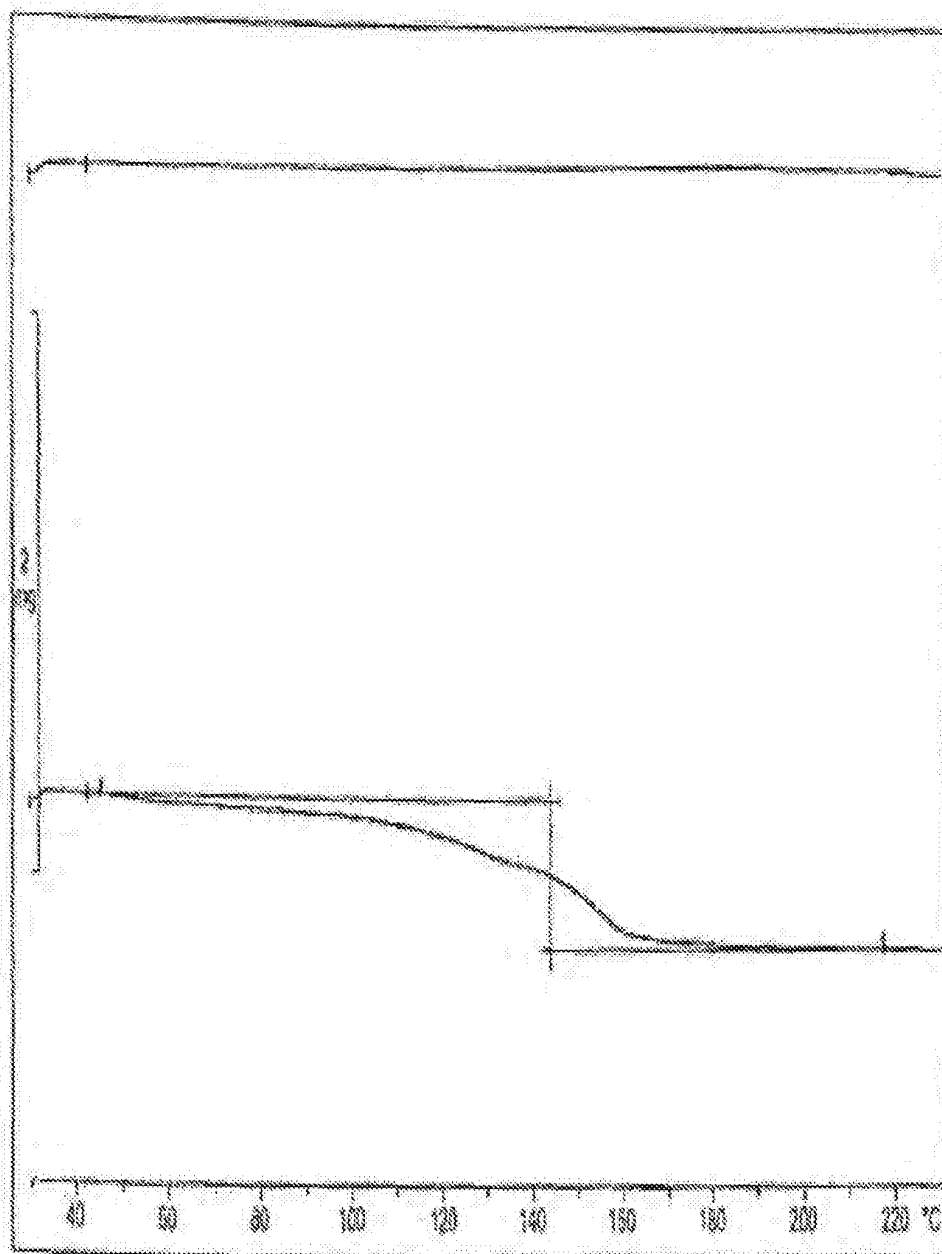


FIG. 6C



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FIG. 7



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FIG. 8

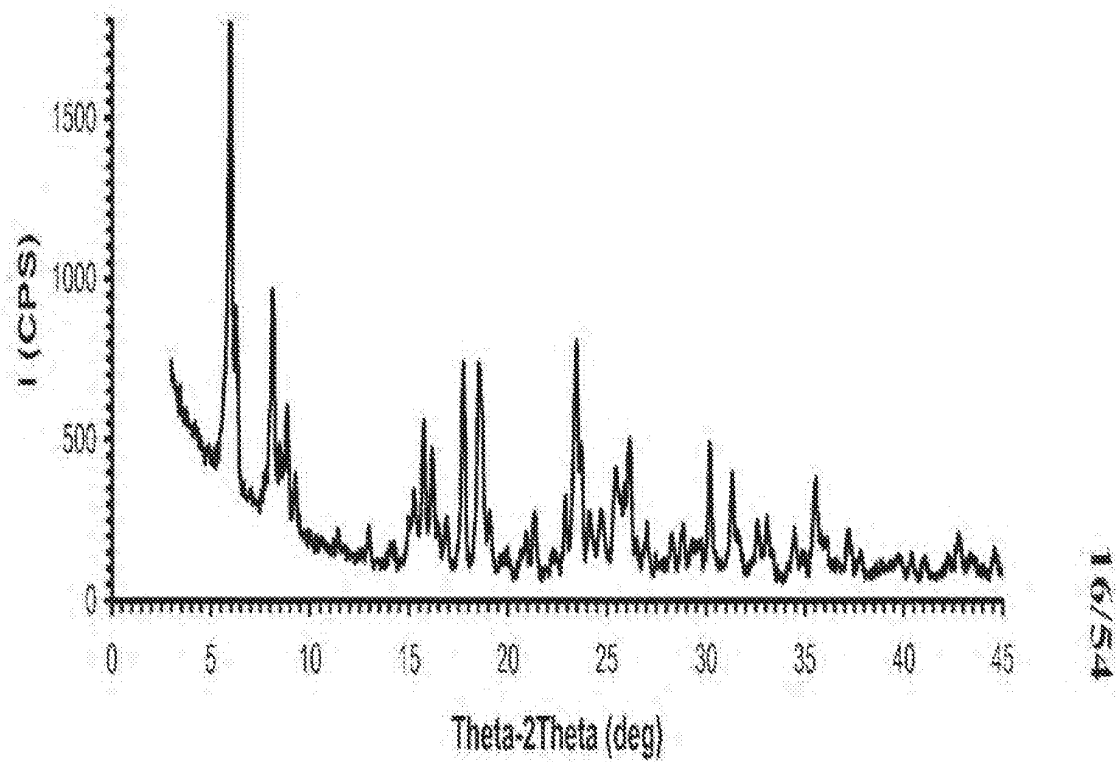


FIG. 9A

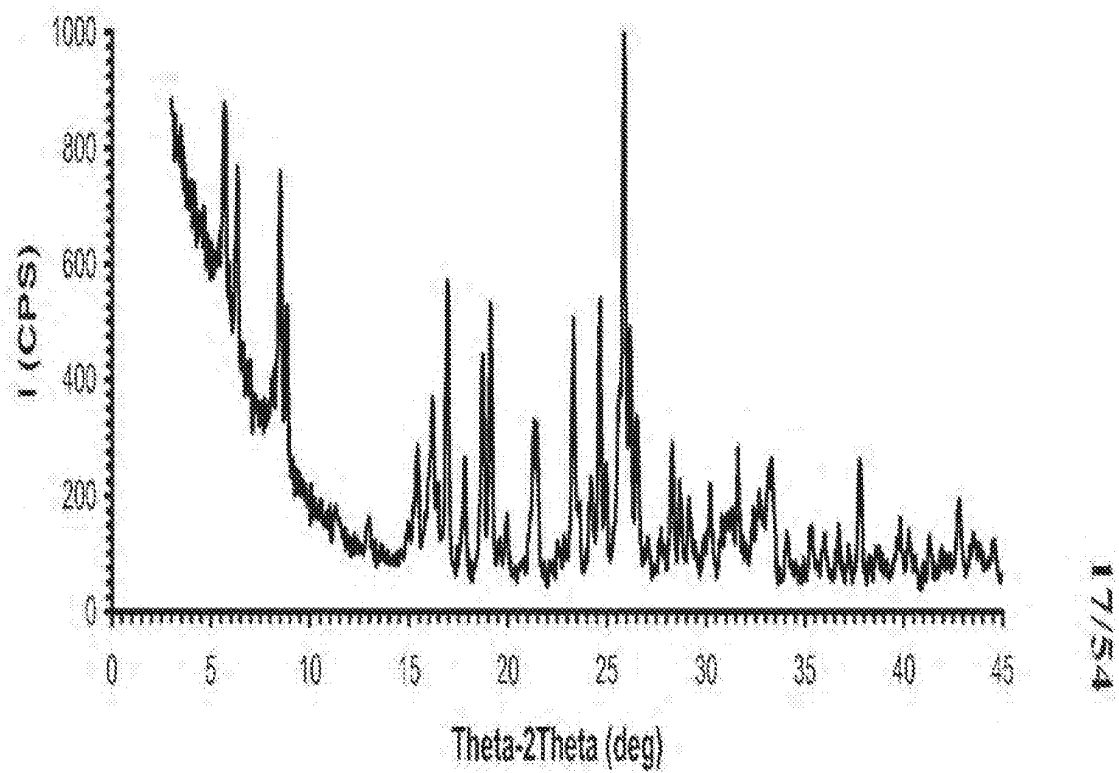


FIG. 9B

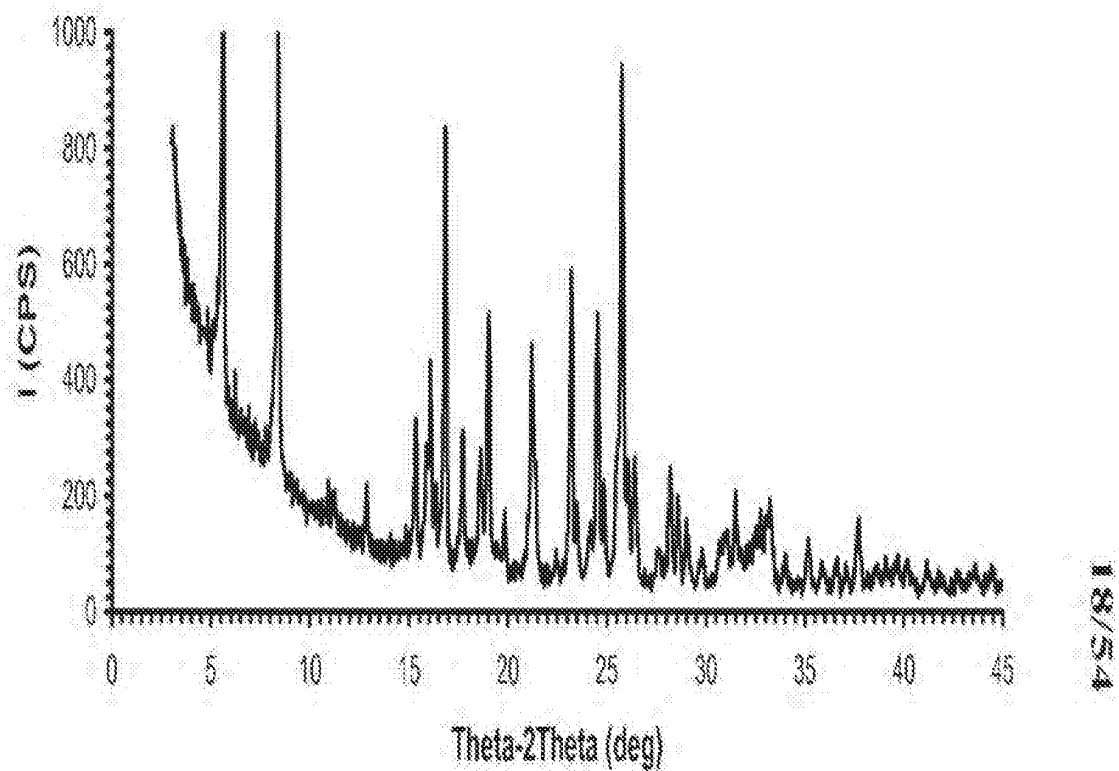


FIG. 9C

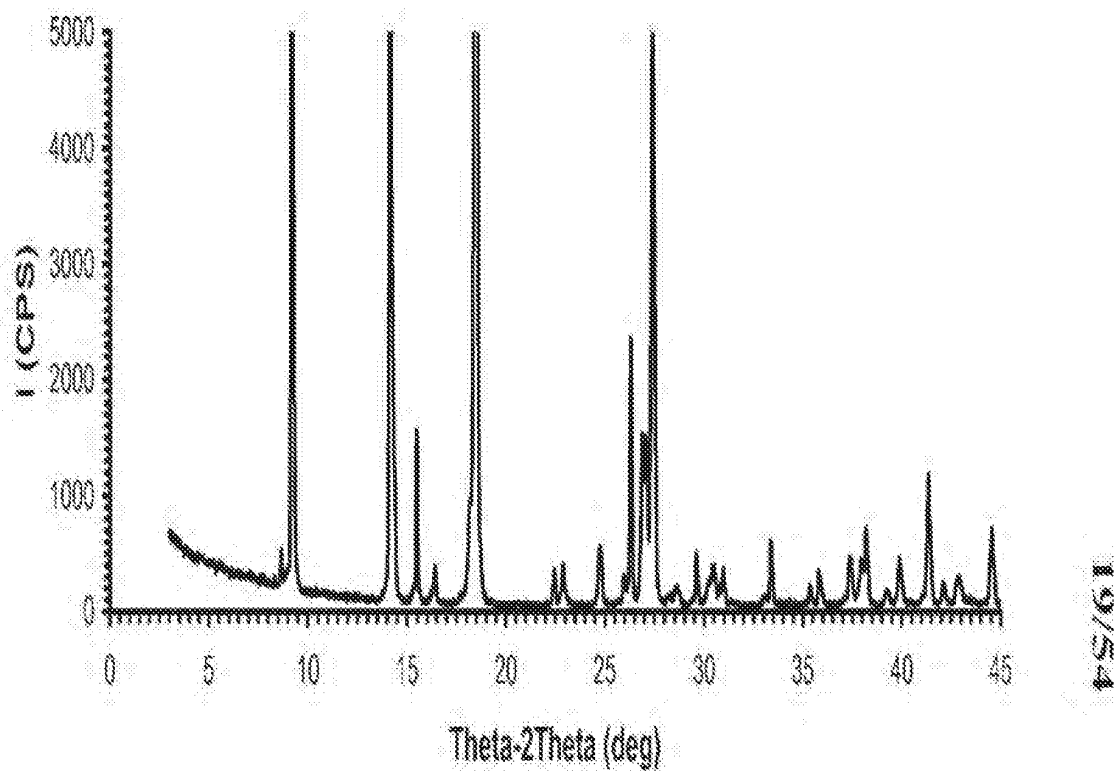


FIG. 10A

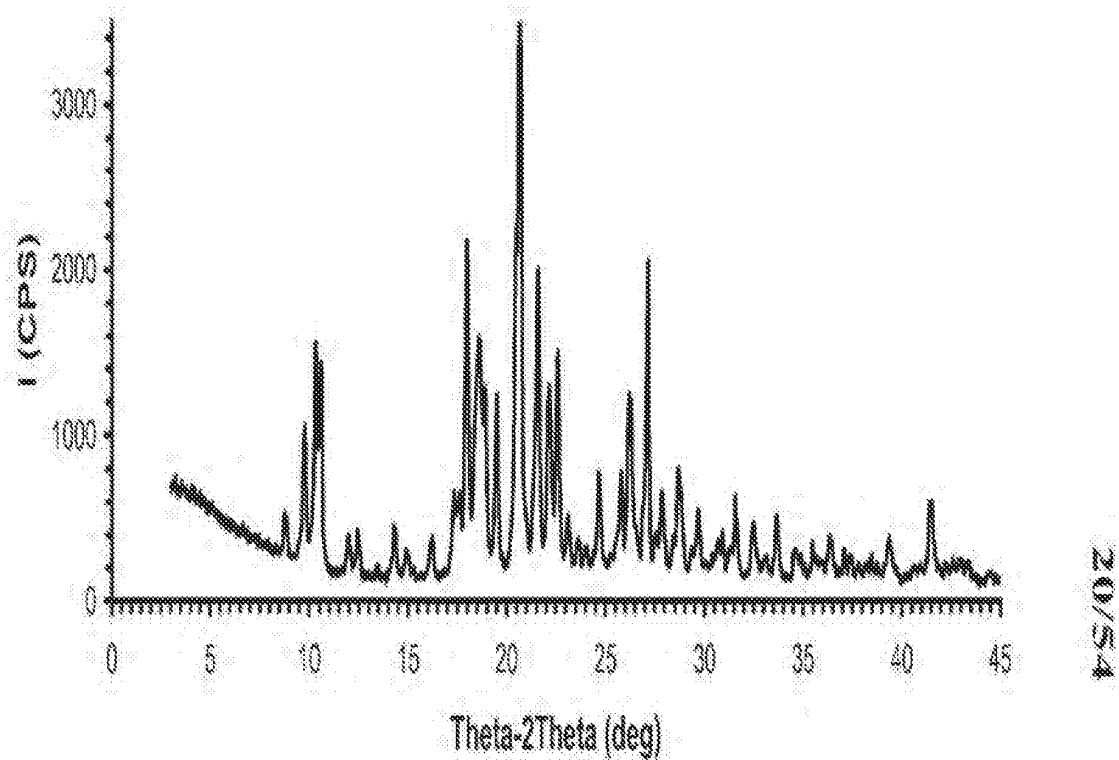


FIG. 10B

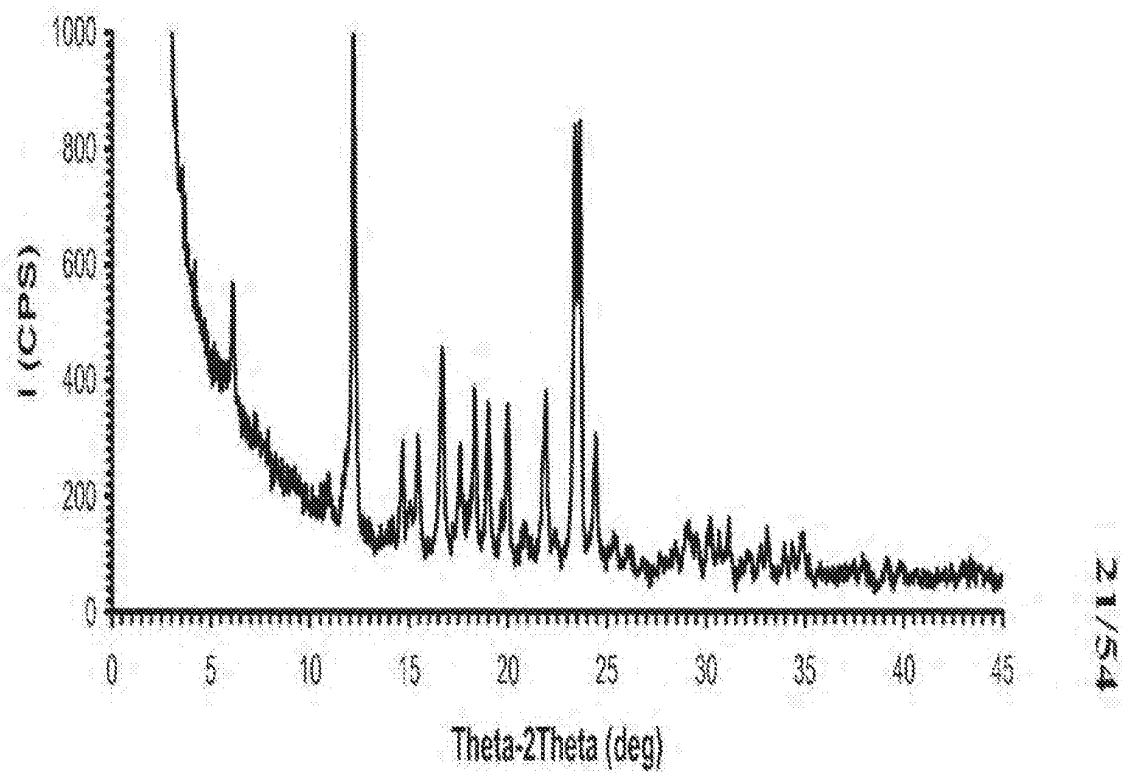


FIG. 10C

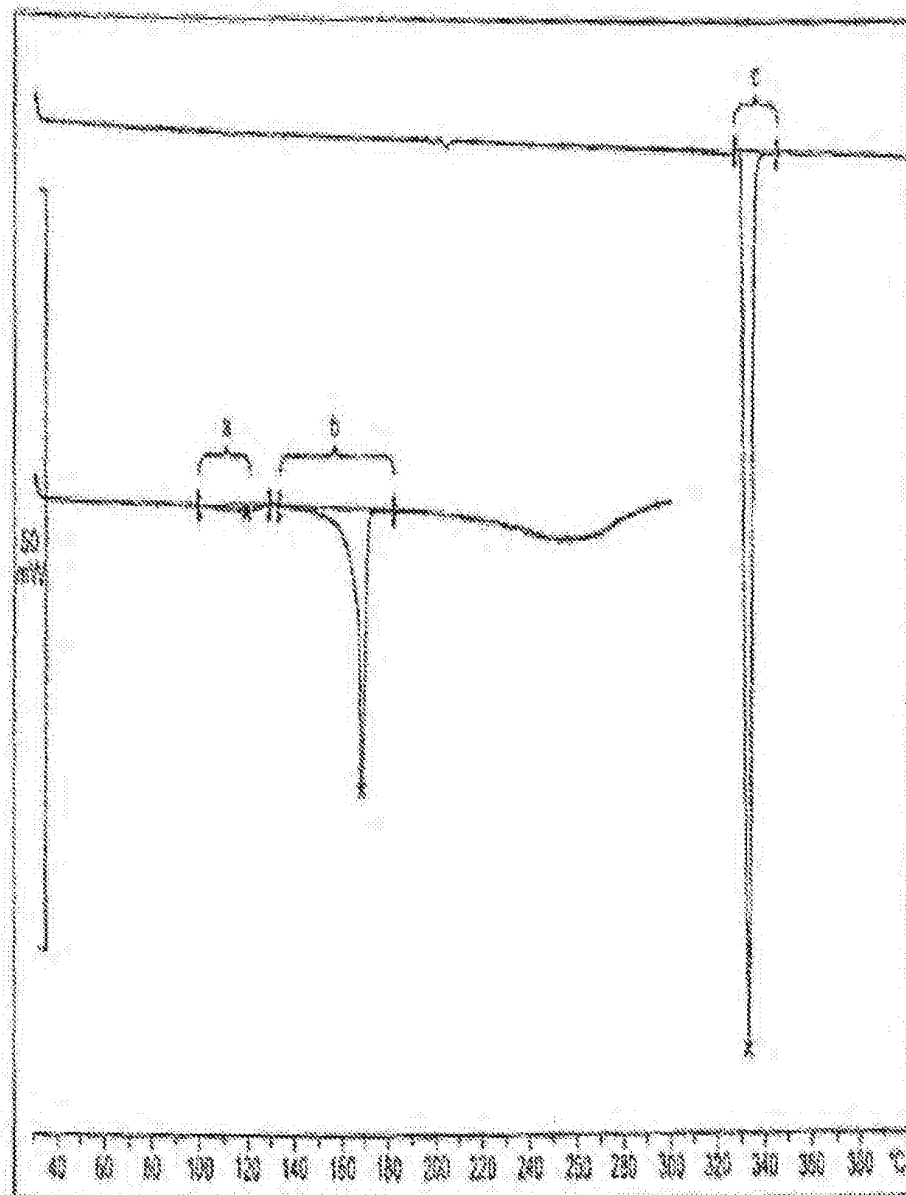
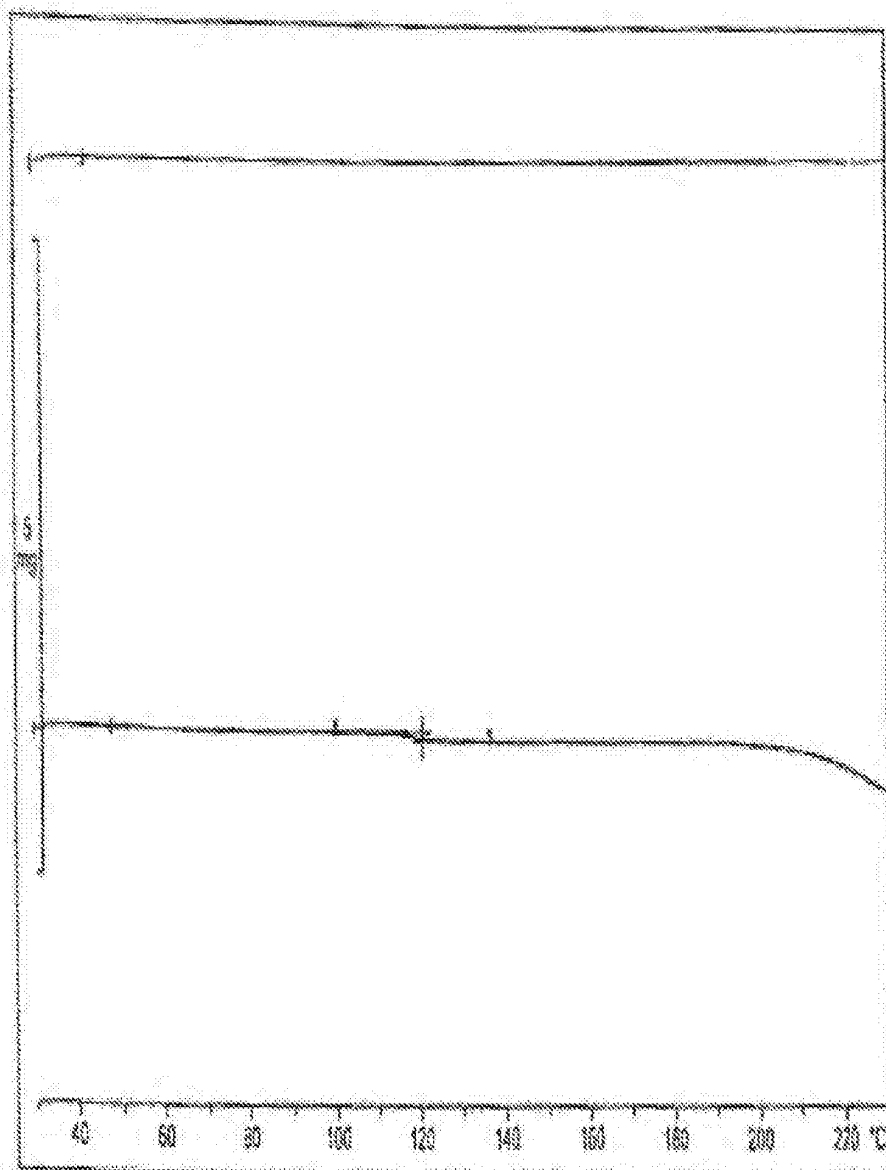


FIG. 11



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FIG. 12

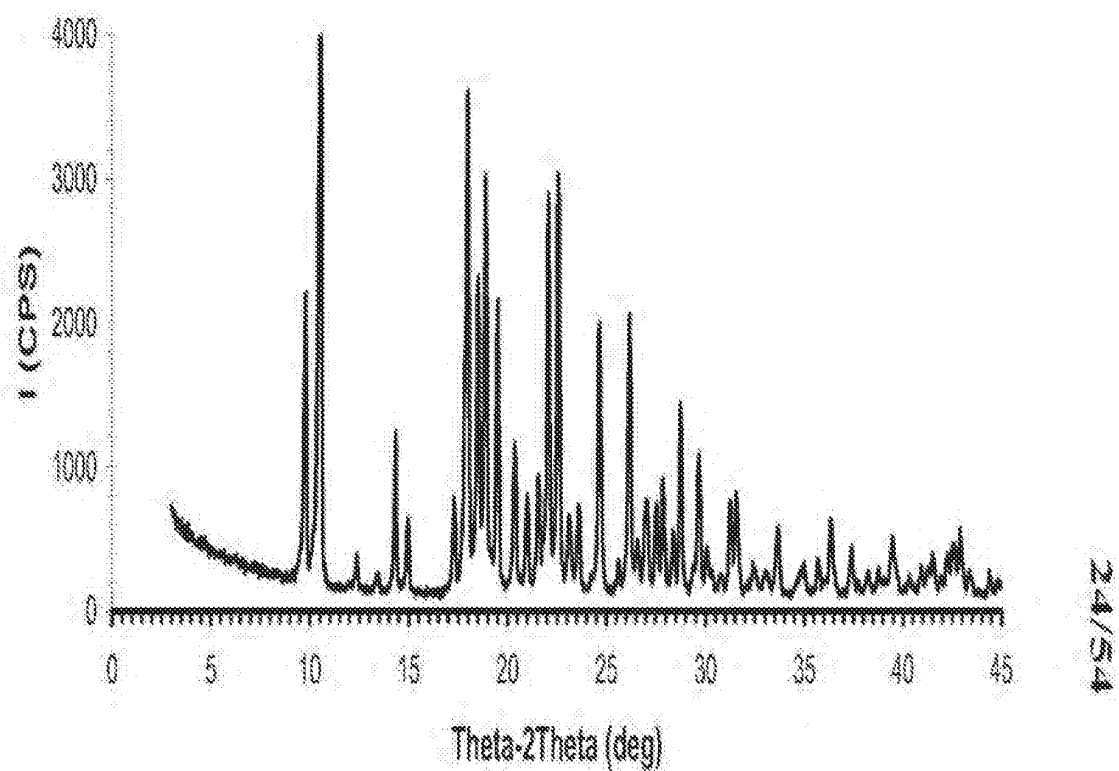


FIG. 13A

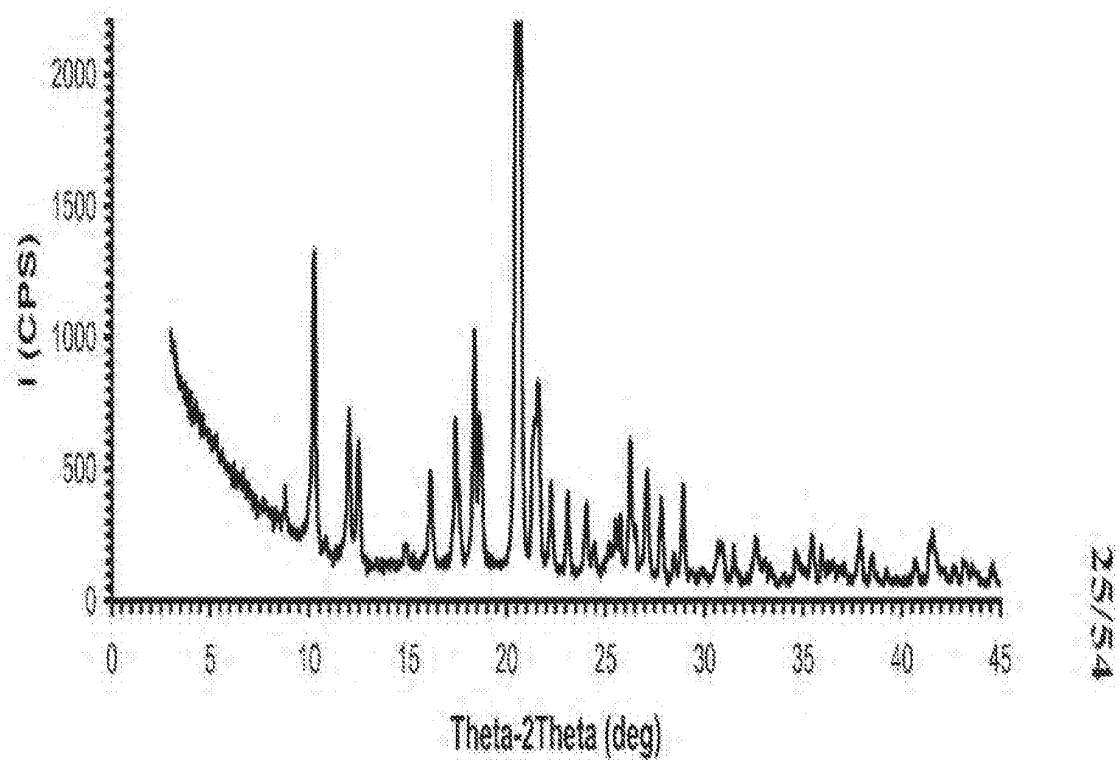


FIG. 13B

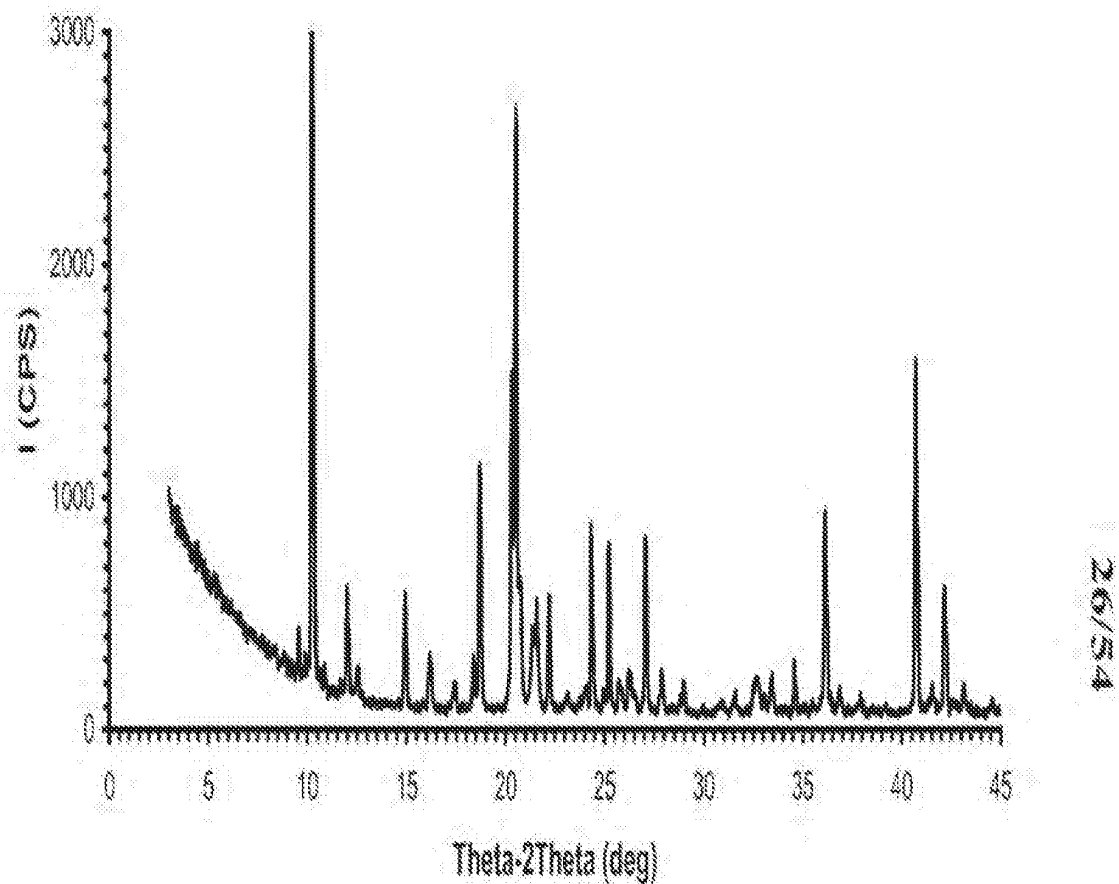


FIG. 13C

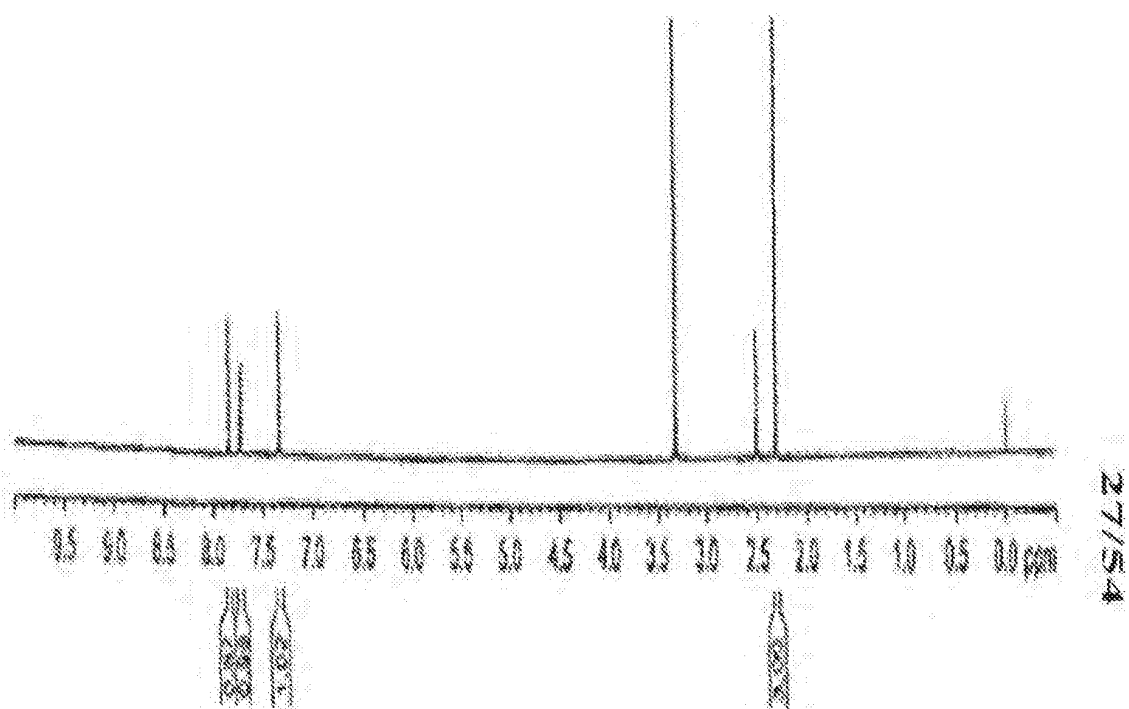
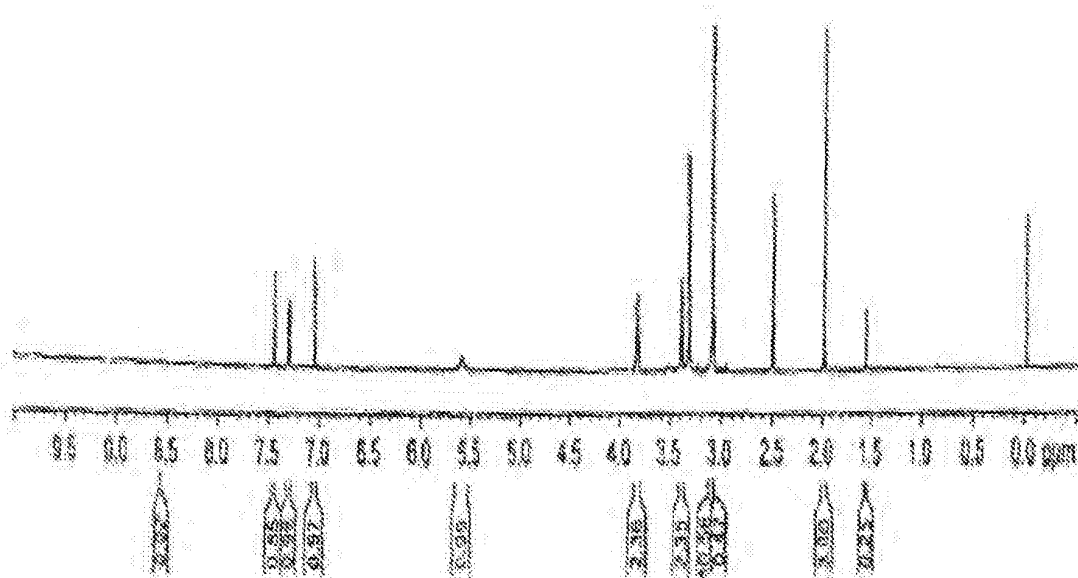


FIG. 14A



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FIG. 148

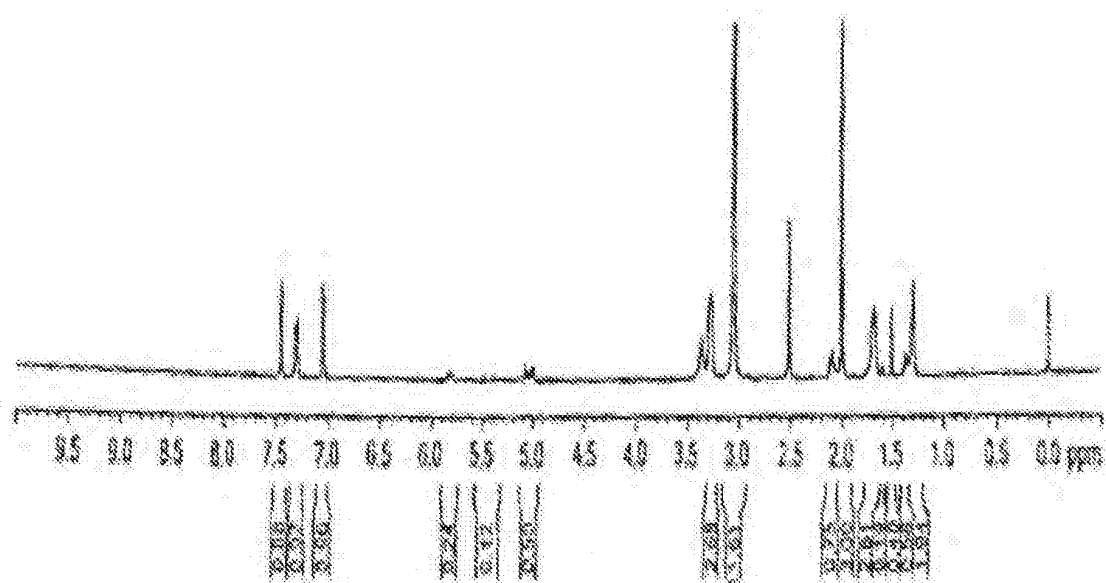
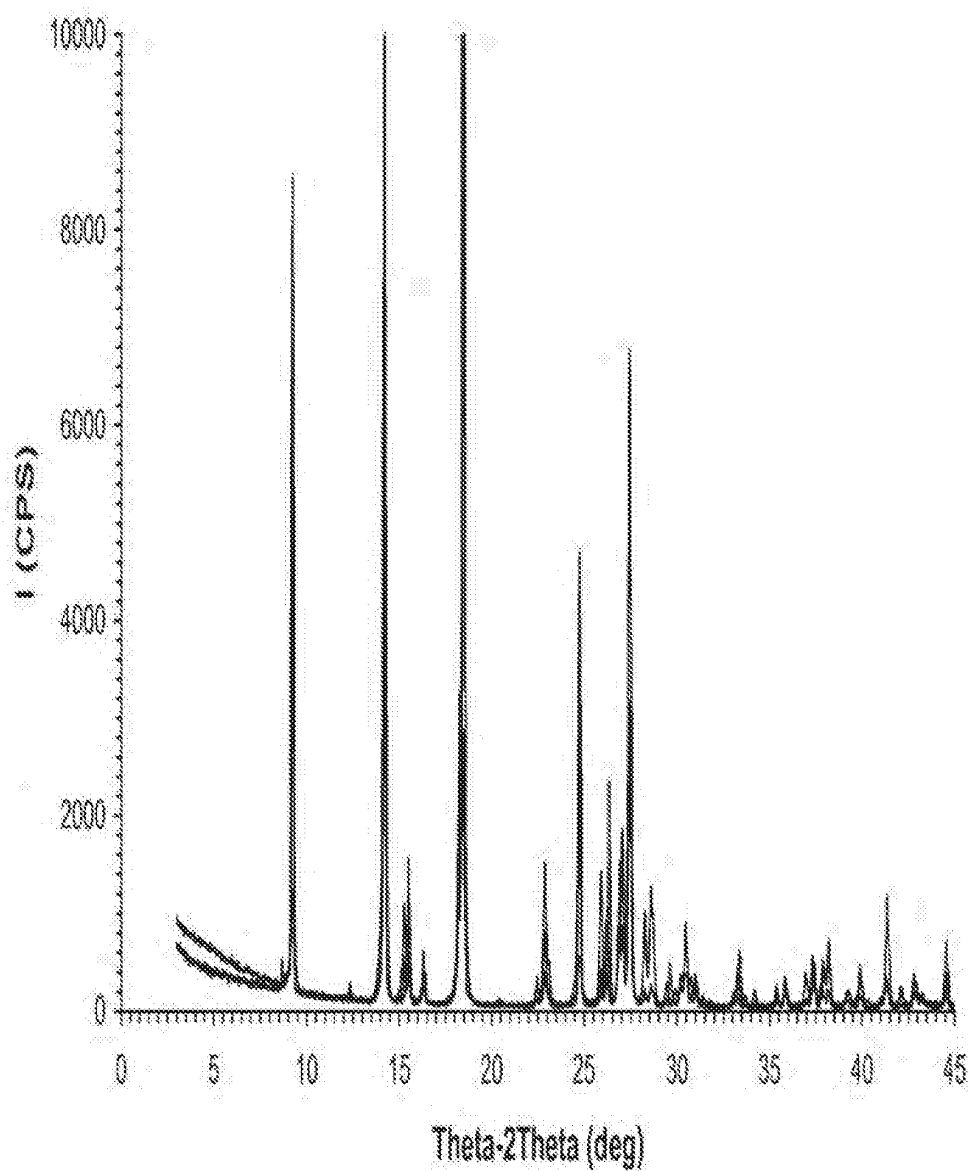


FIG. 14C

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FIG. 15A

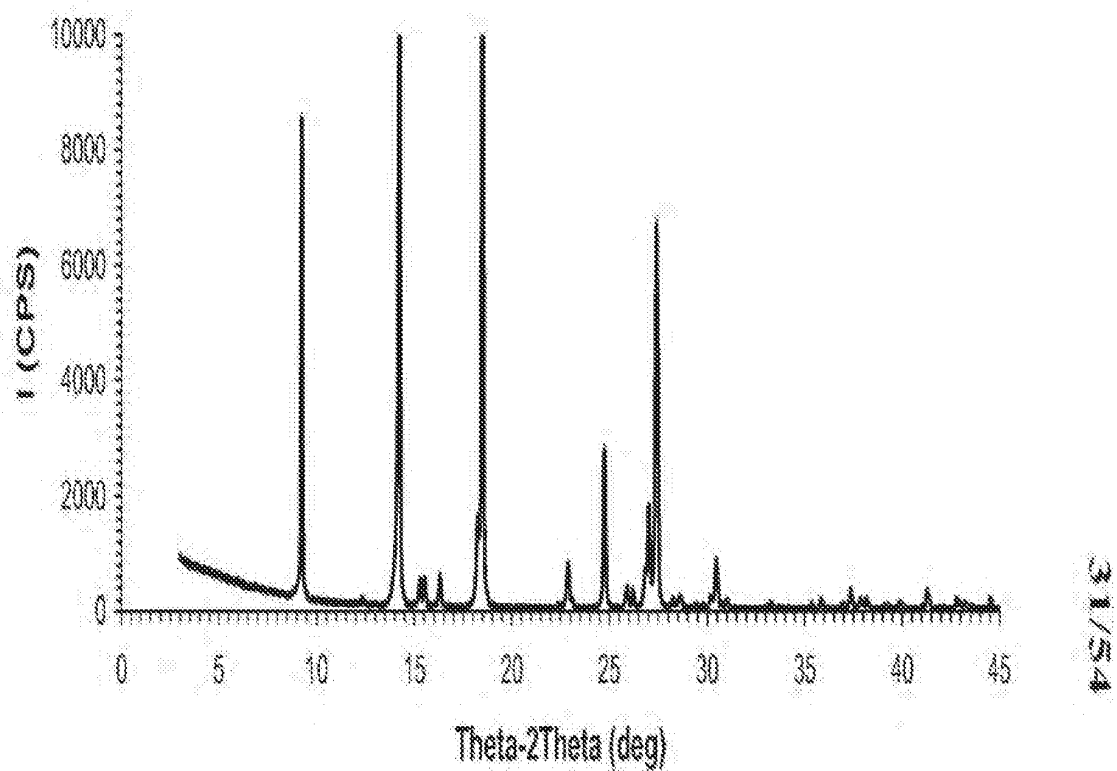
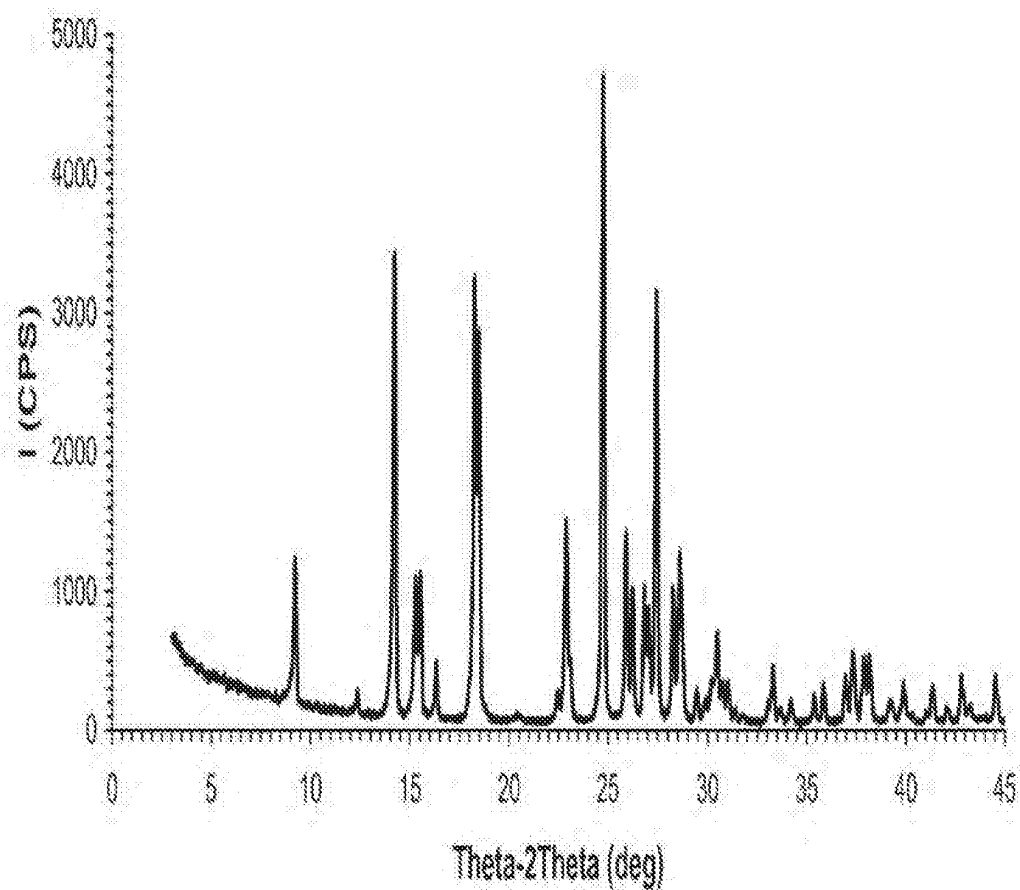


FIG. 15B



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FIG. 15C

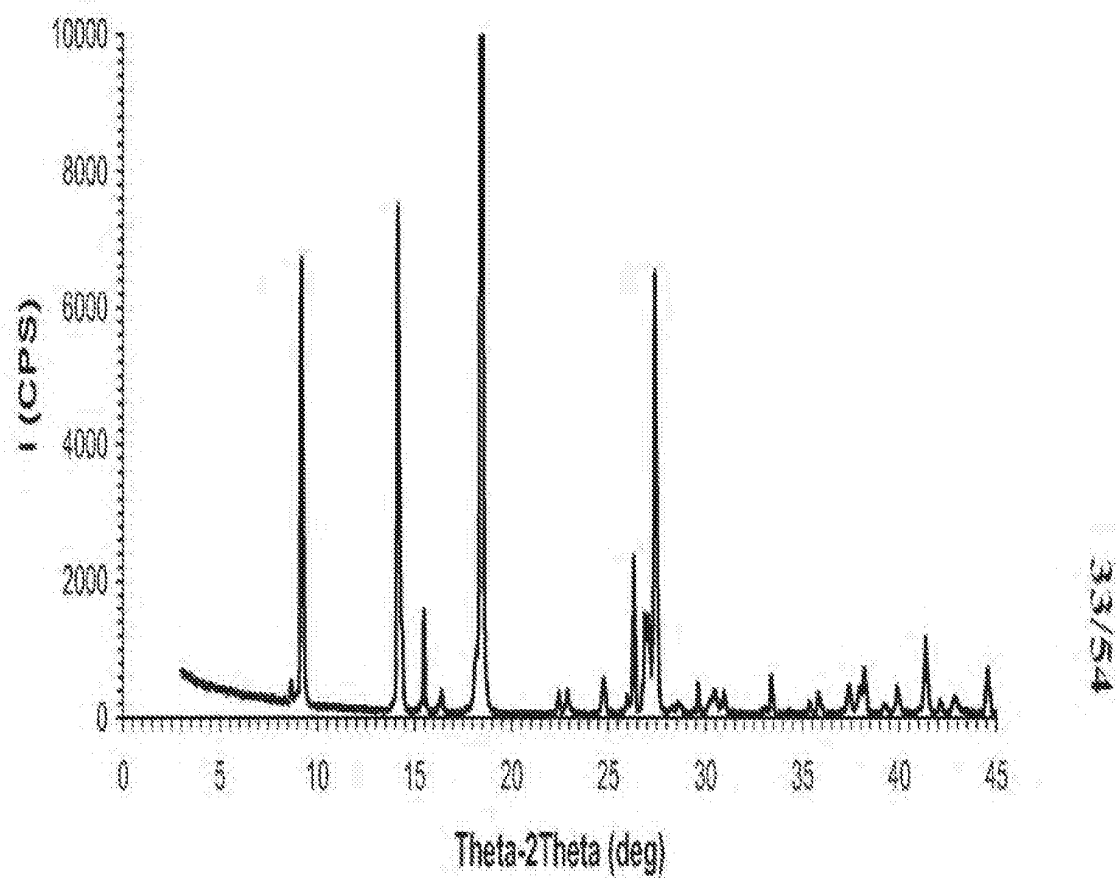
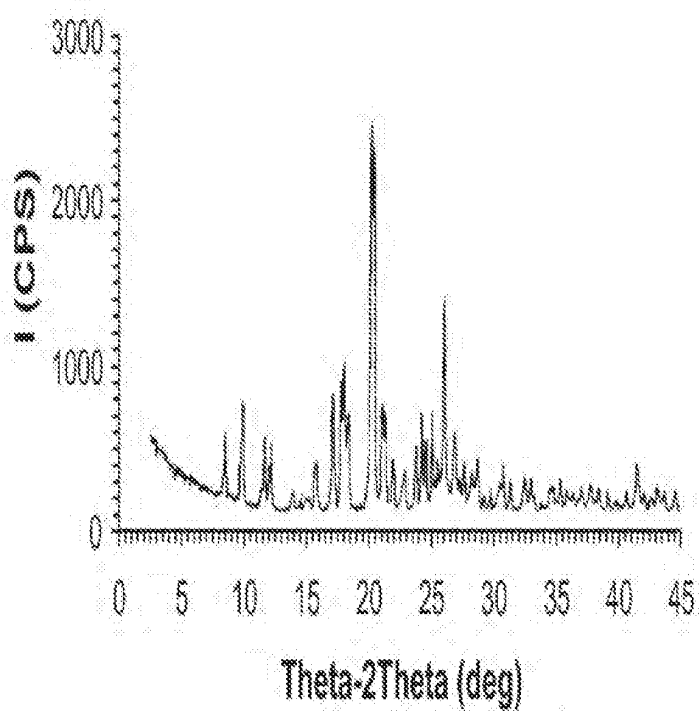


FIG. 15D



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FIG. 16A

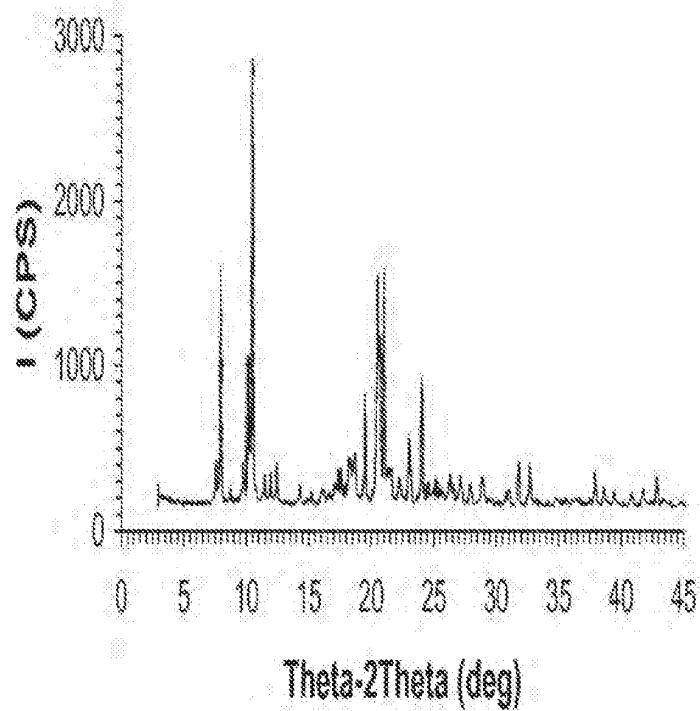


FIG. 16B

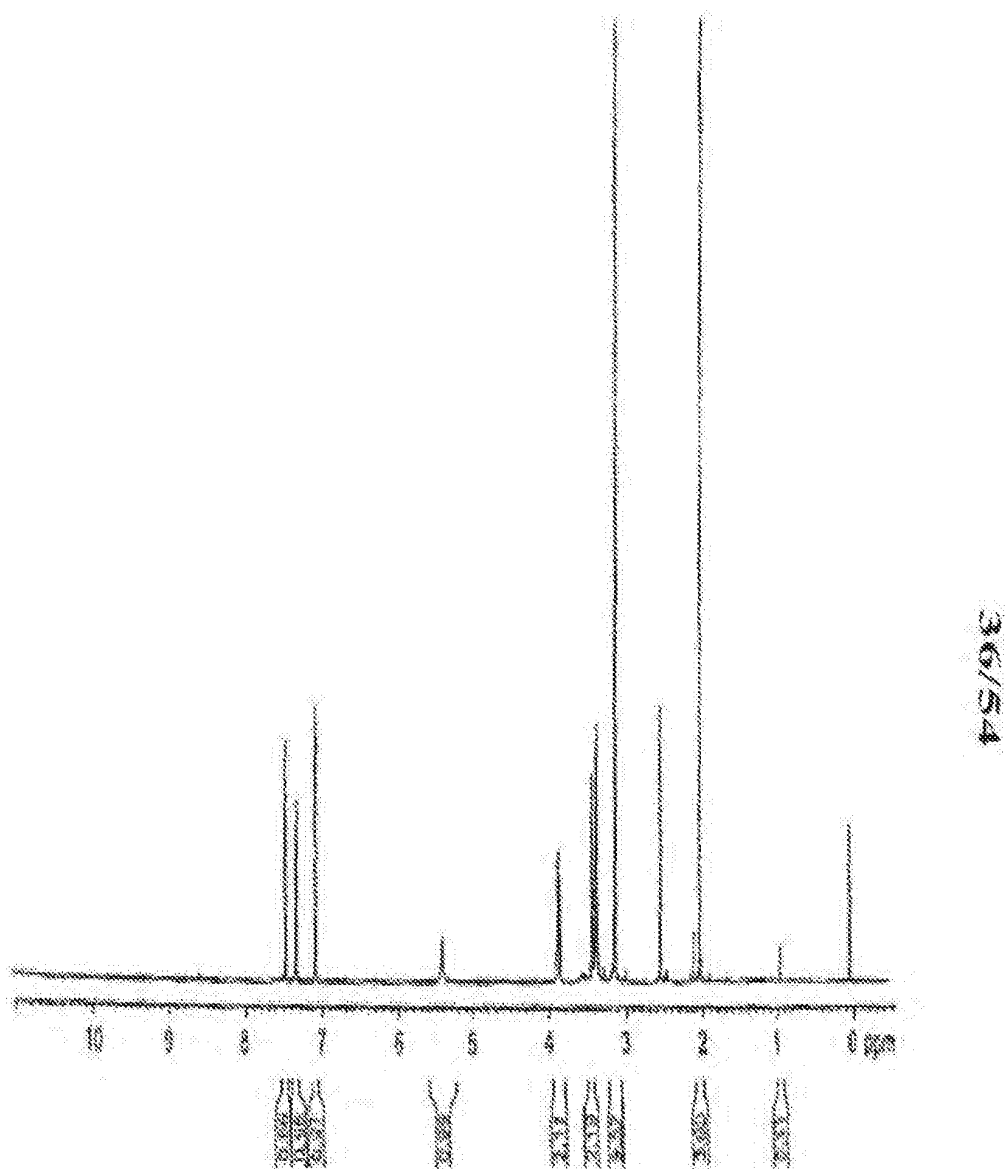
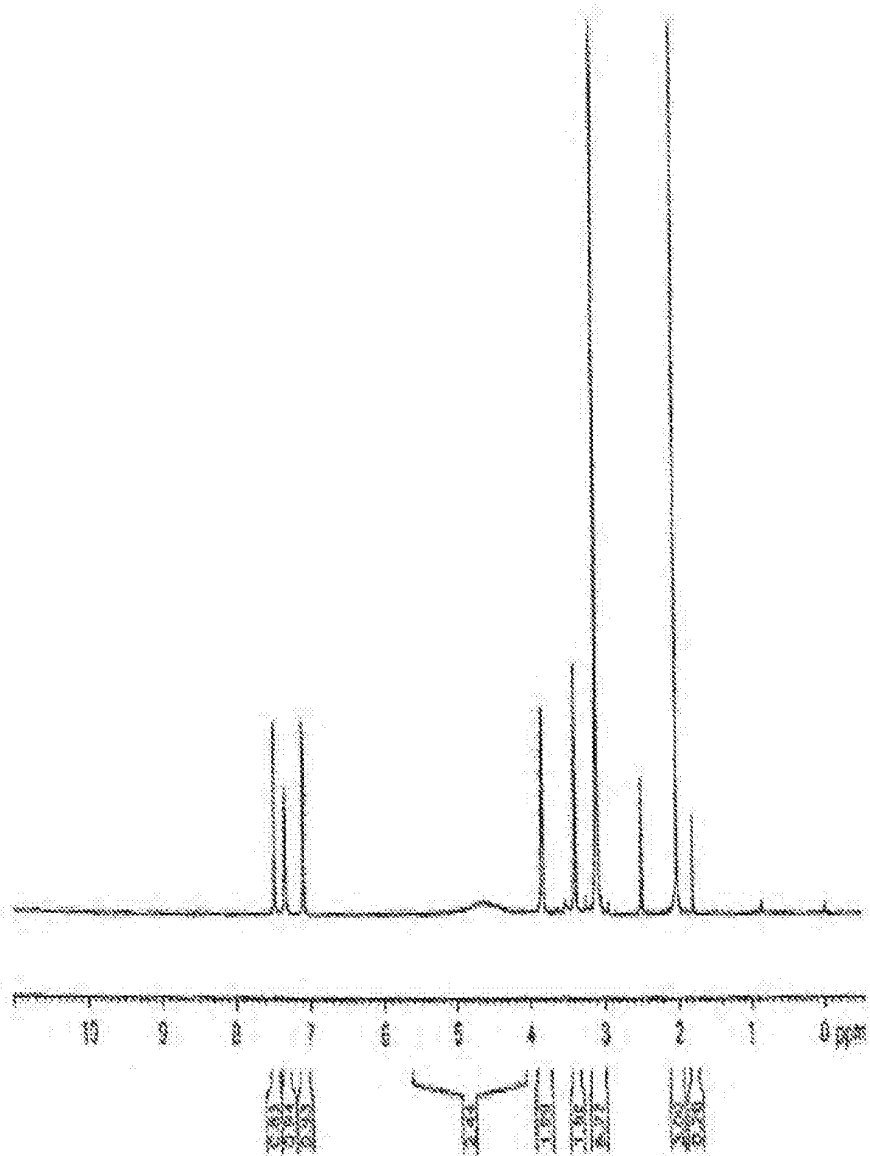
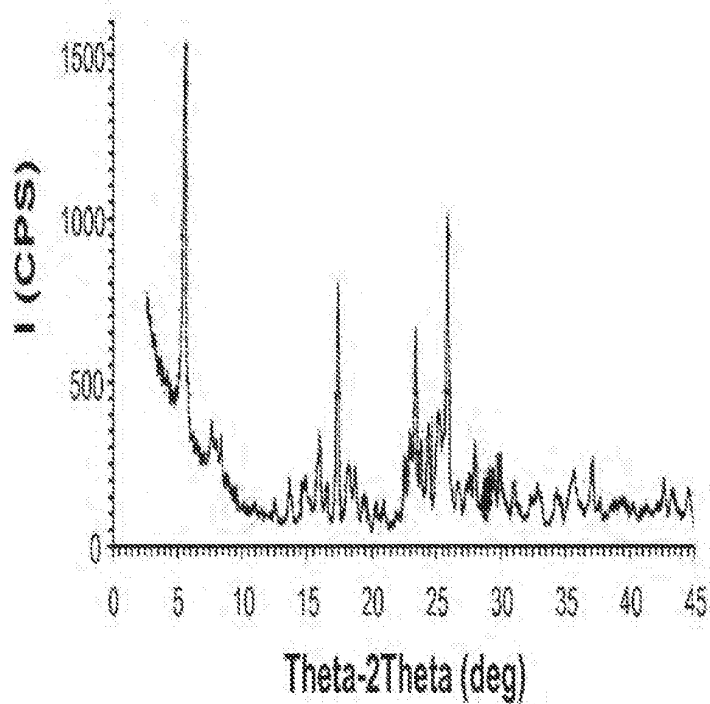


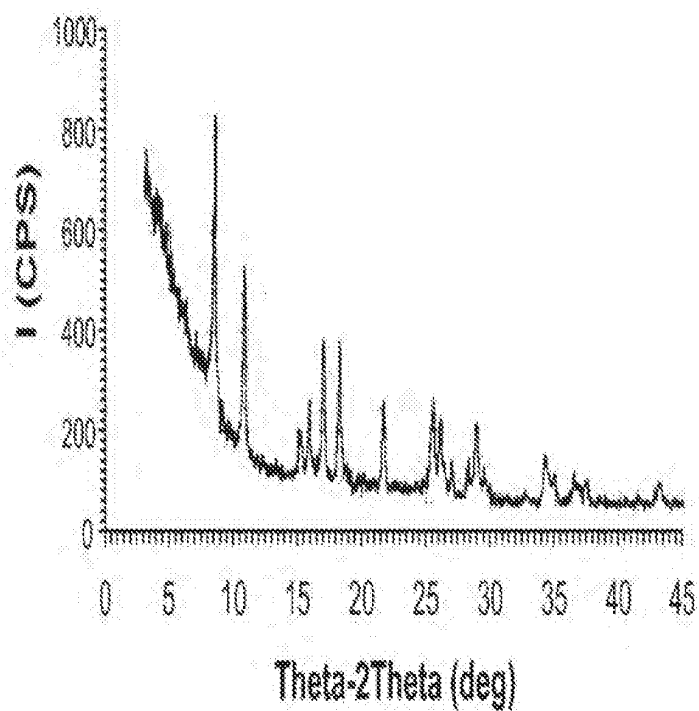
FIG. 17A





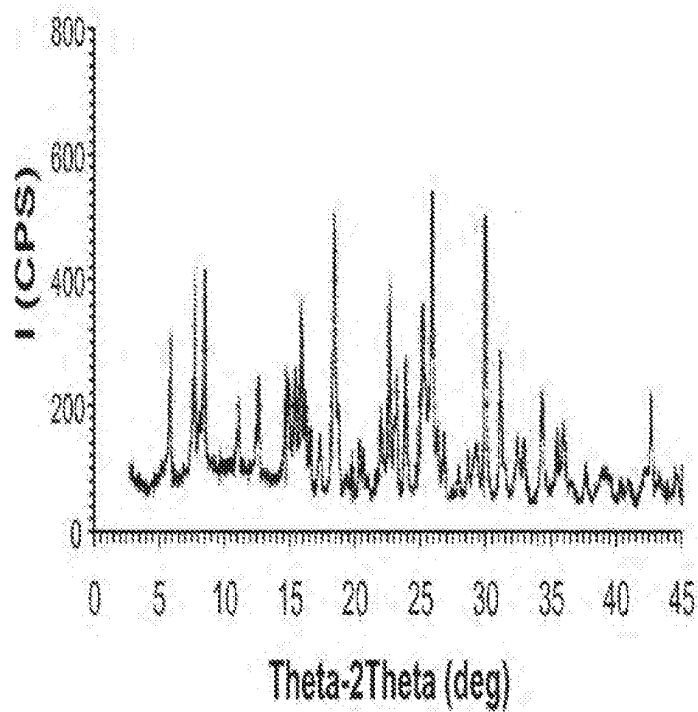
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FIG. 18A



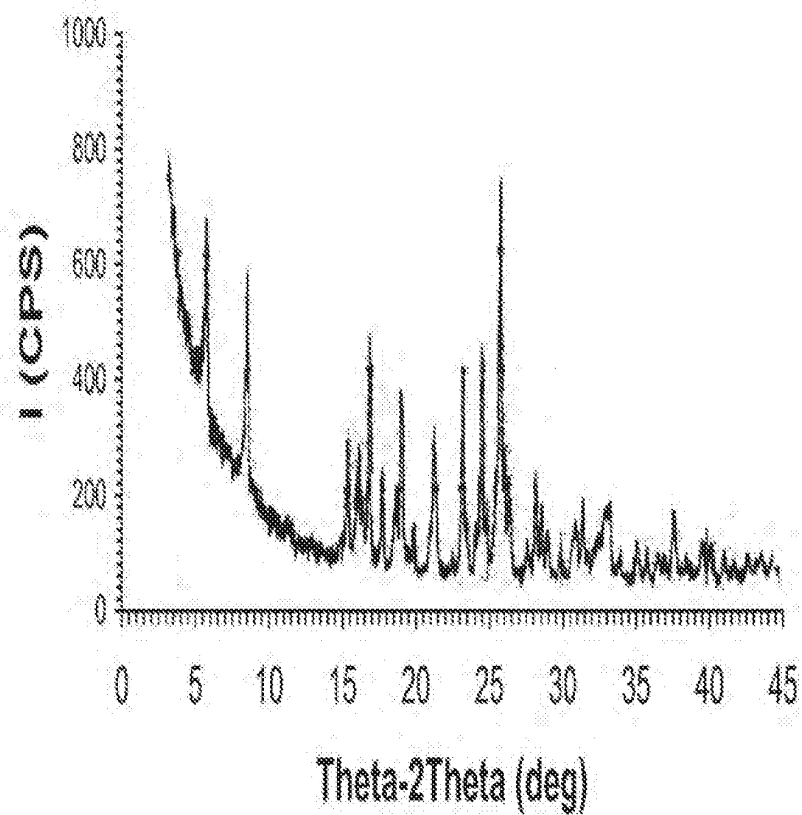
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FIG. 18B



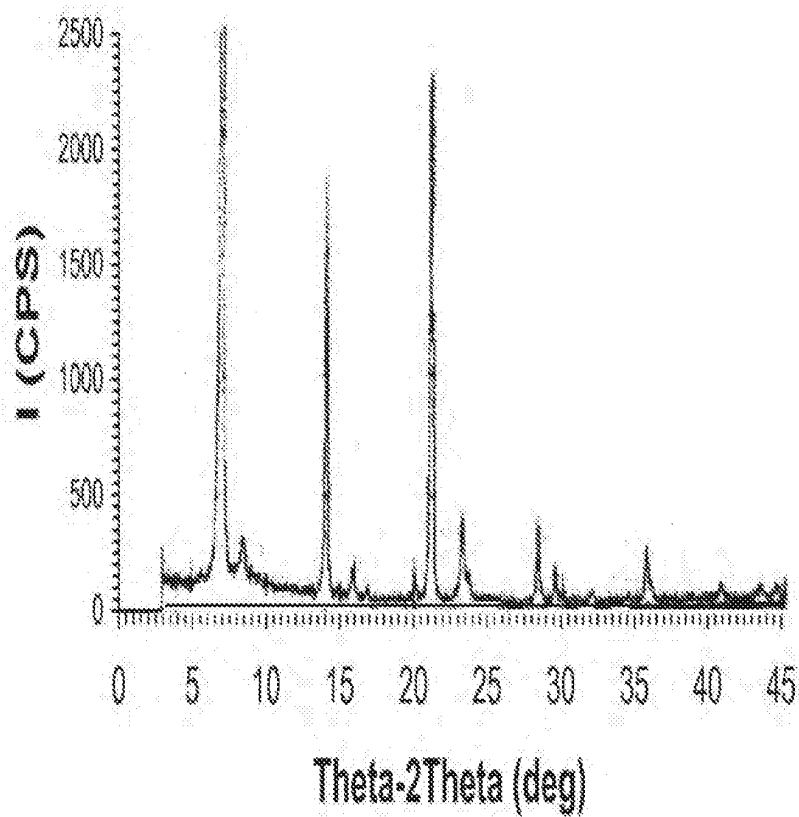
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FIG. 18C



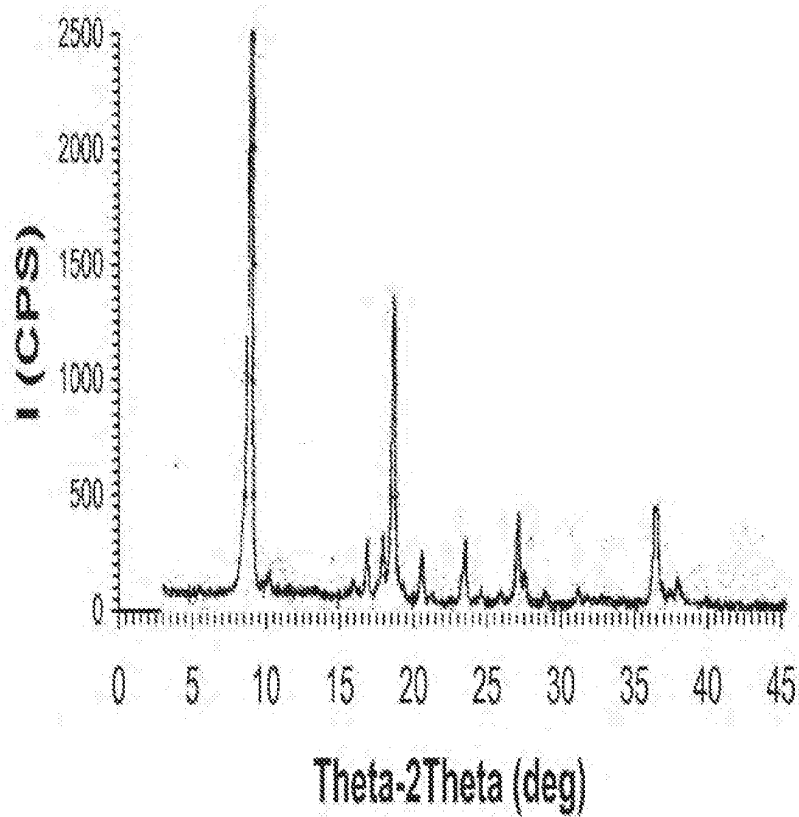
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FIG. 19A



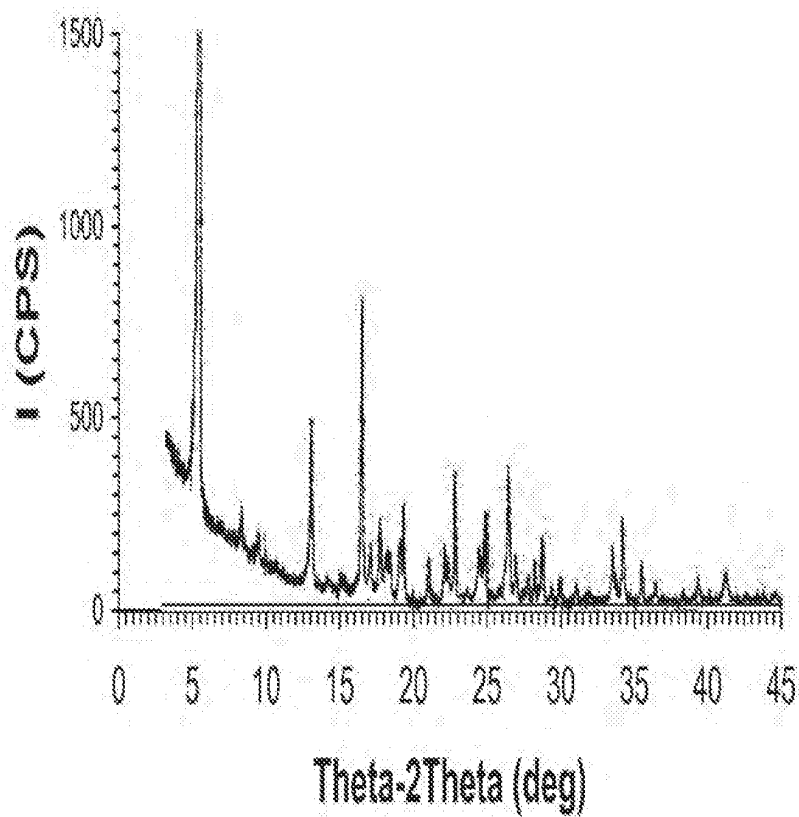
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FIG. 19B



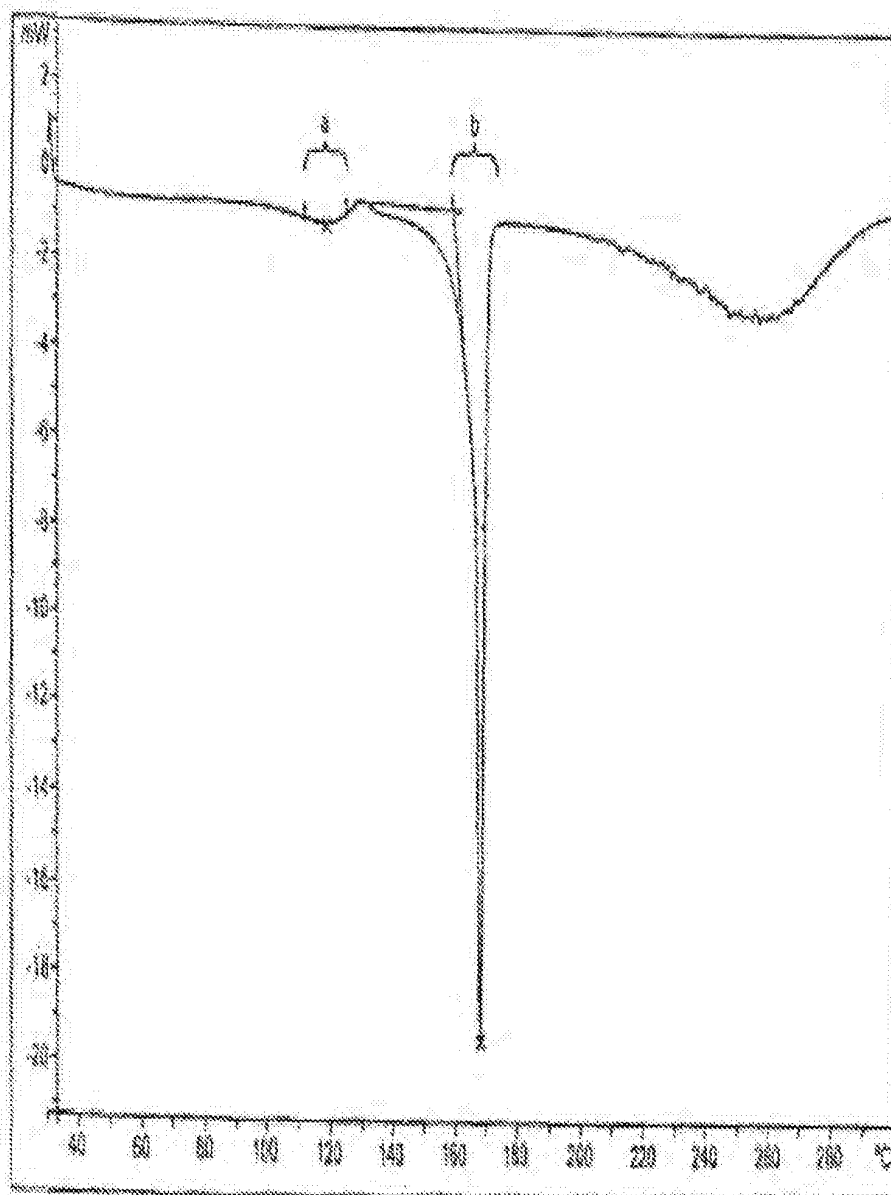
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FIG. 19C



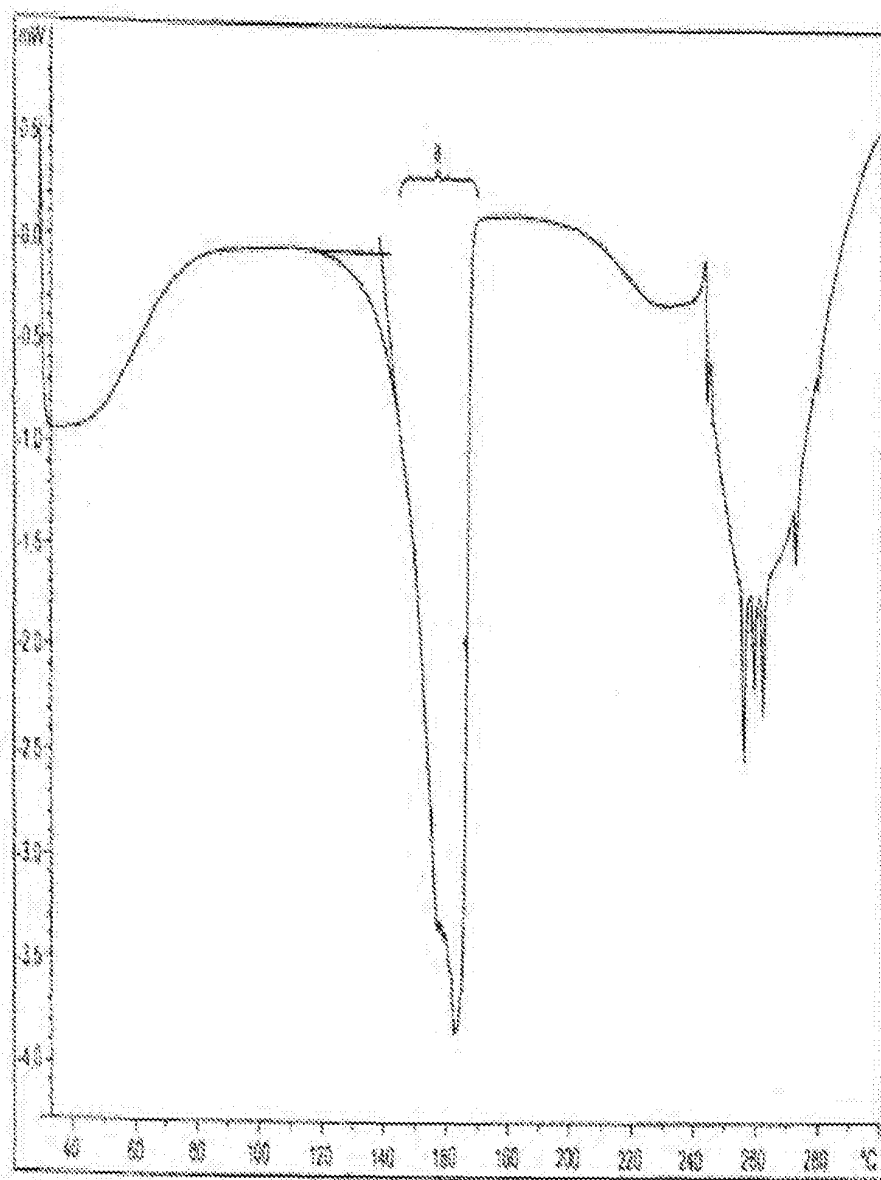
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FIG. 19D



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FIG. 20



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FIG. 21

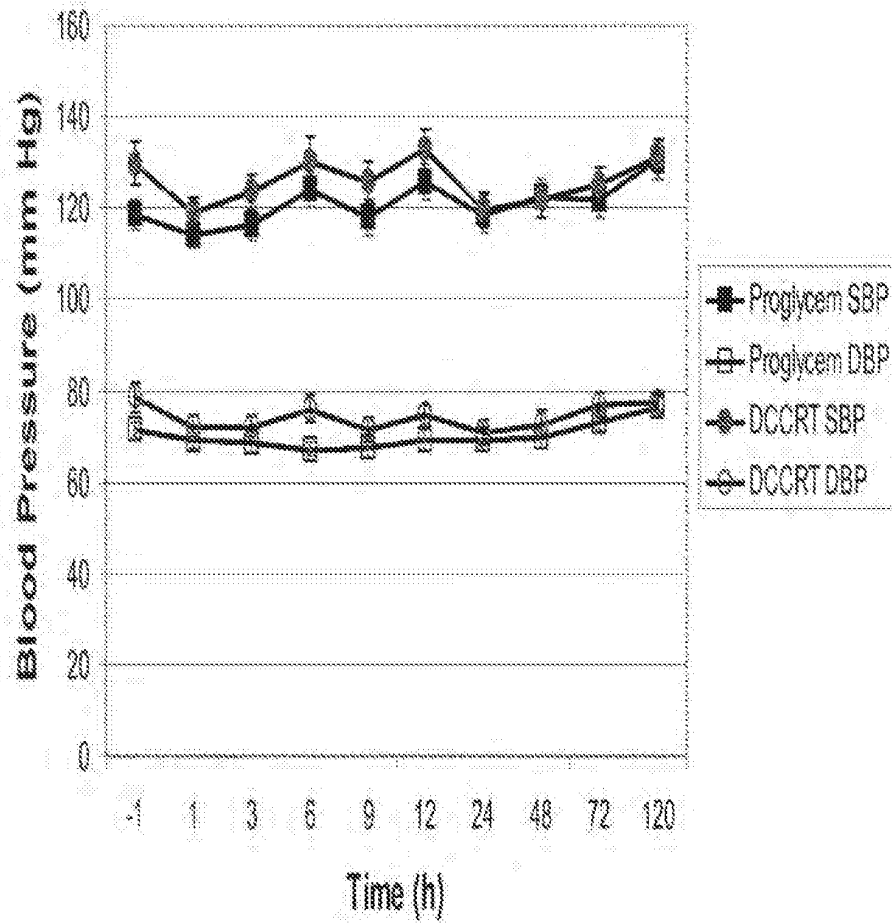


FIG. 22

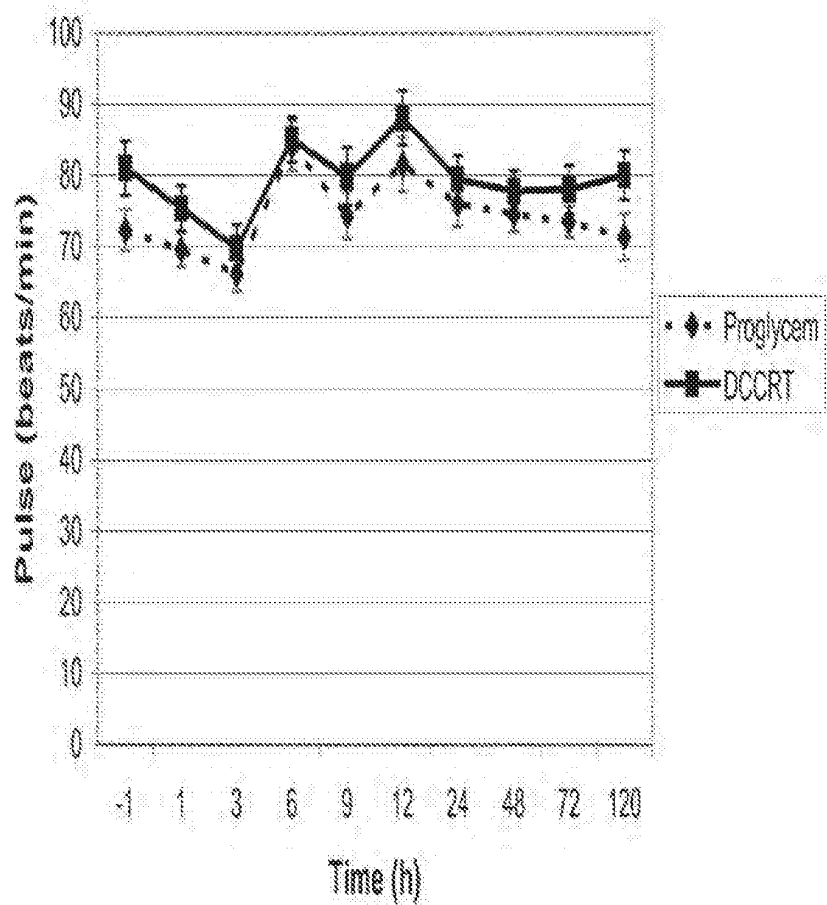


FIG. 23

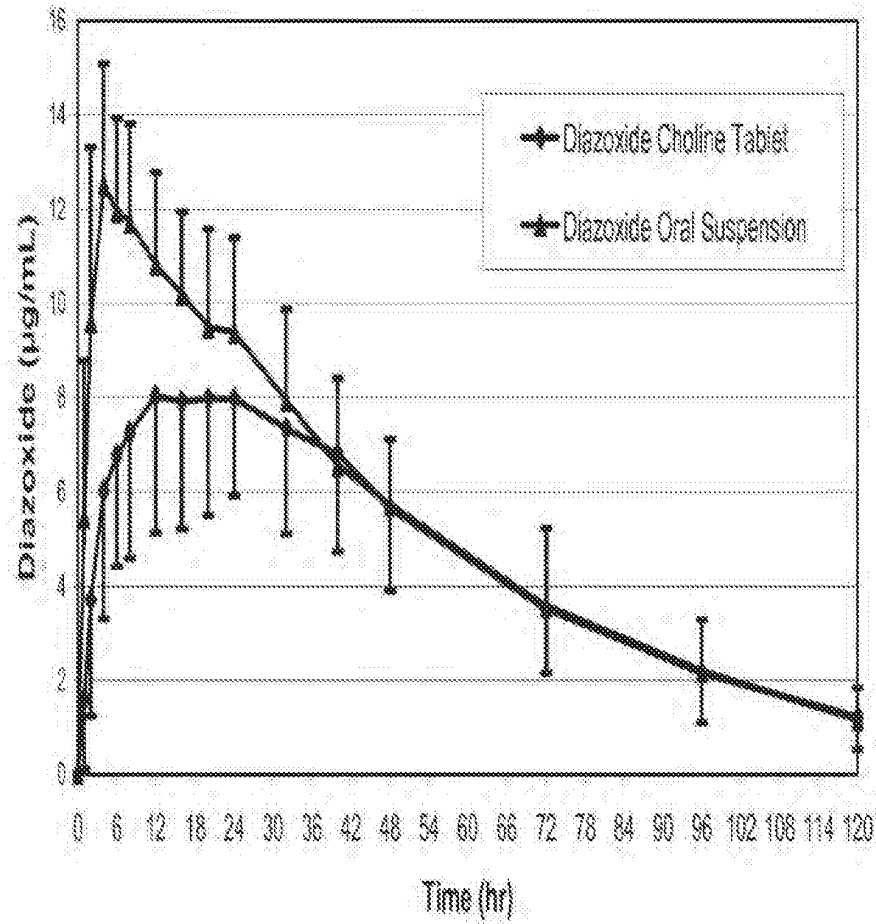
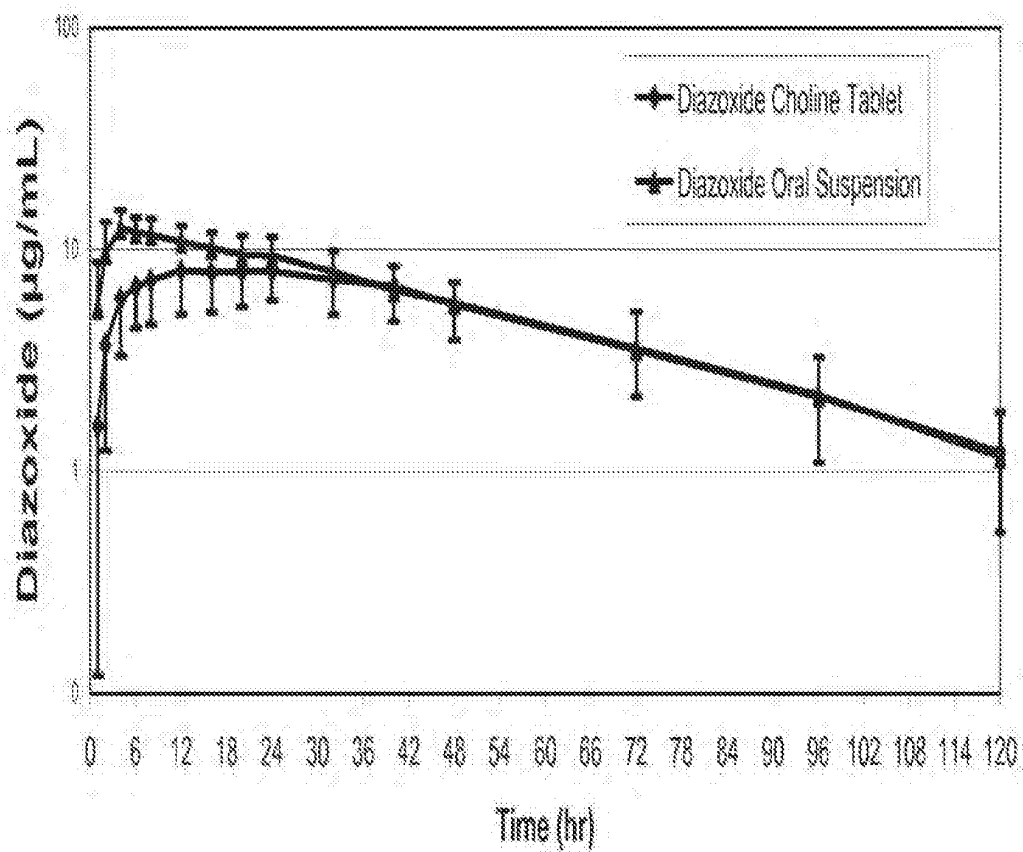


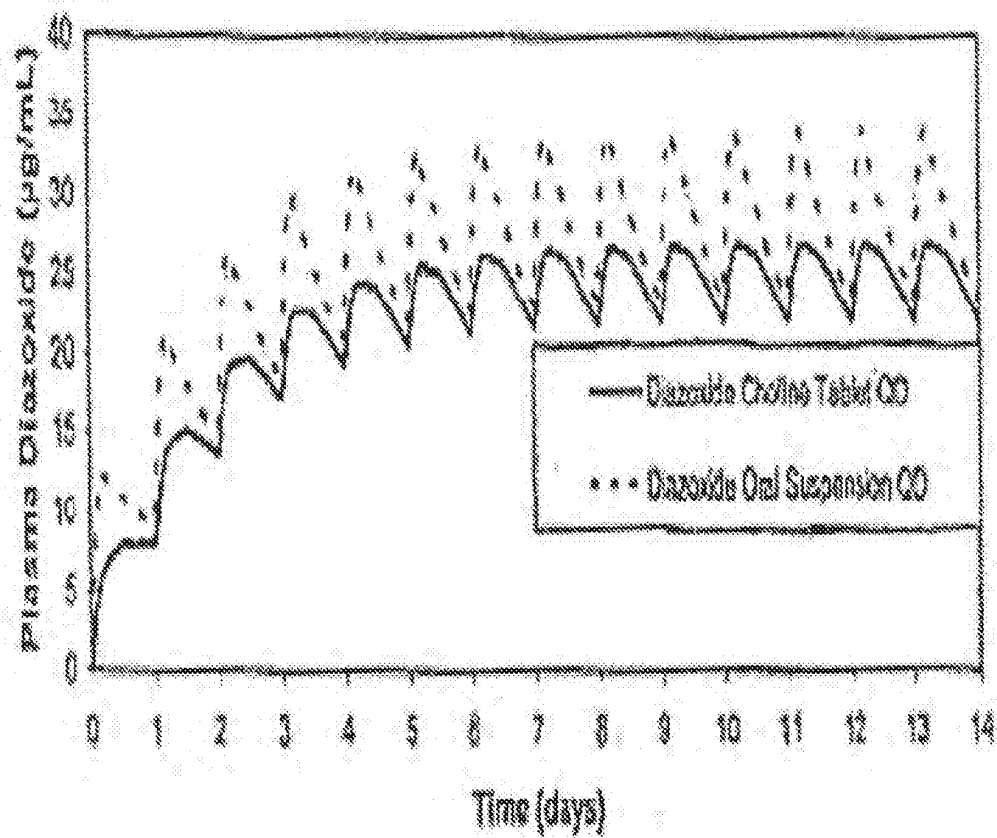
FIG. 24



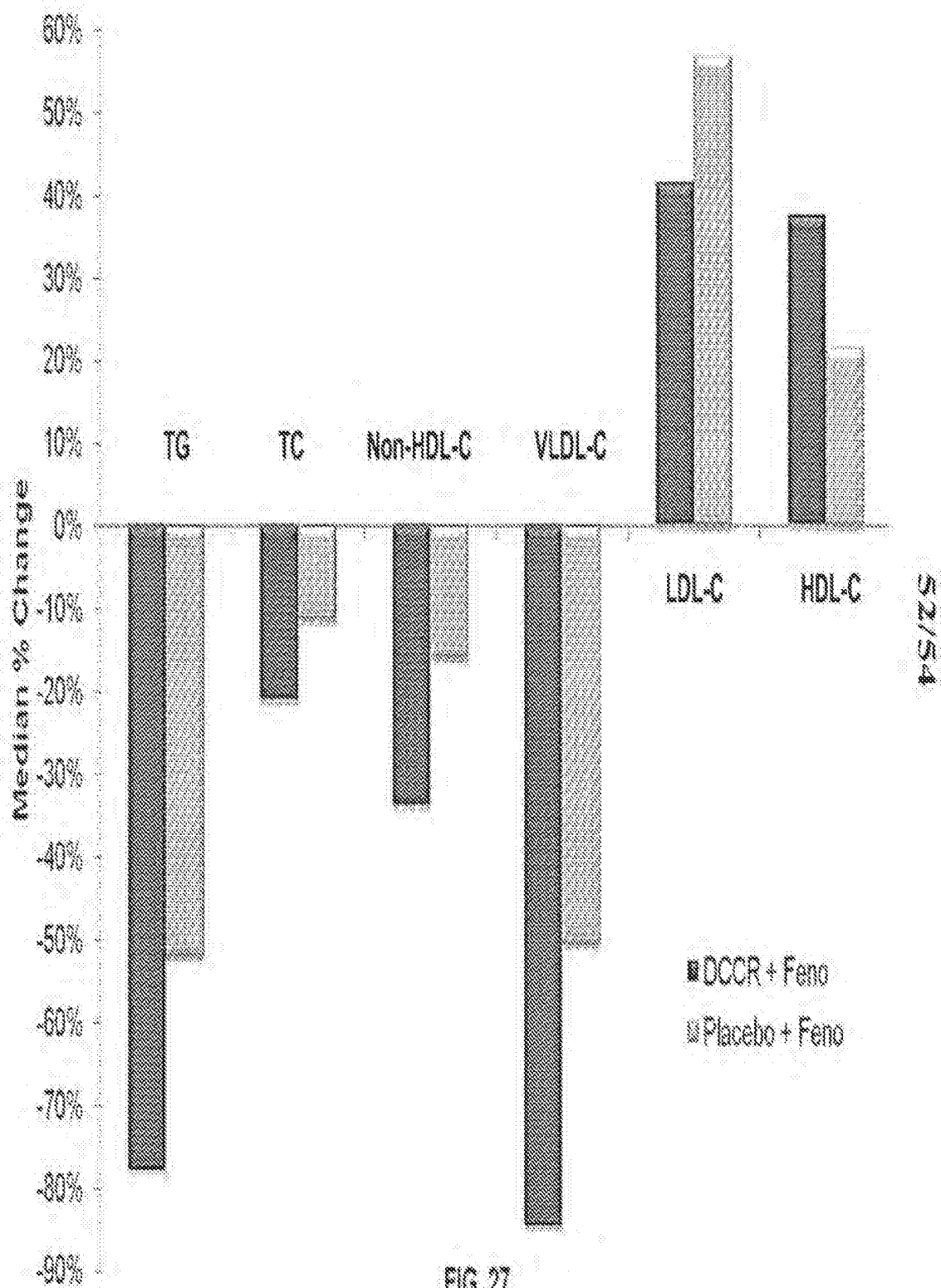
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FIG. 25

FIG. 26



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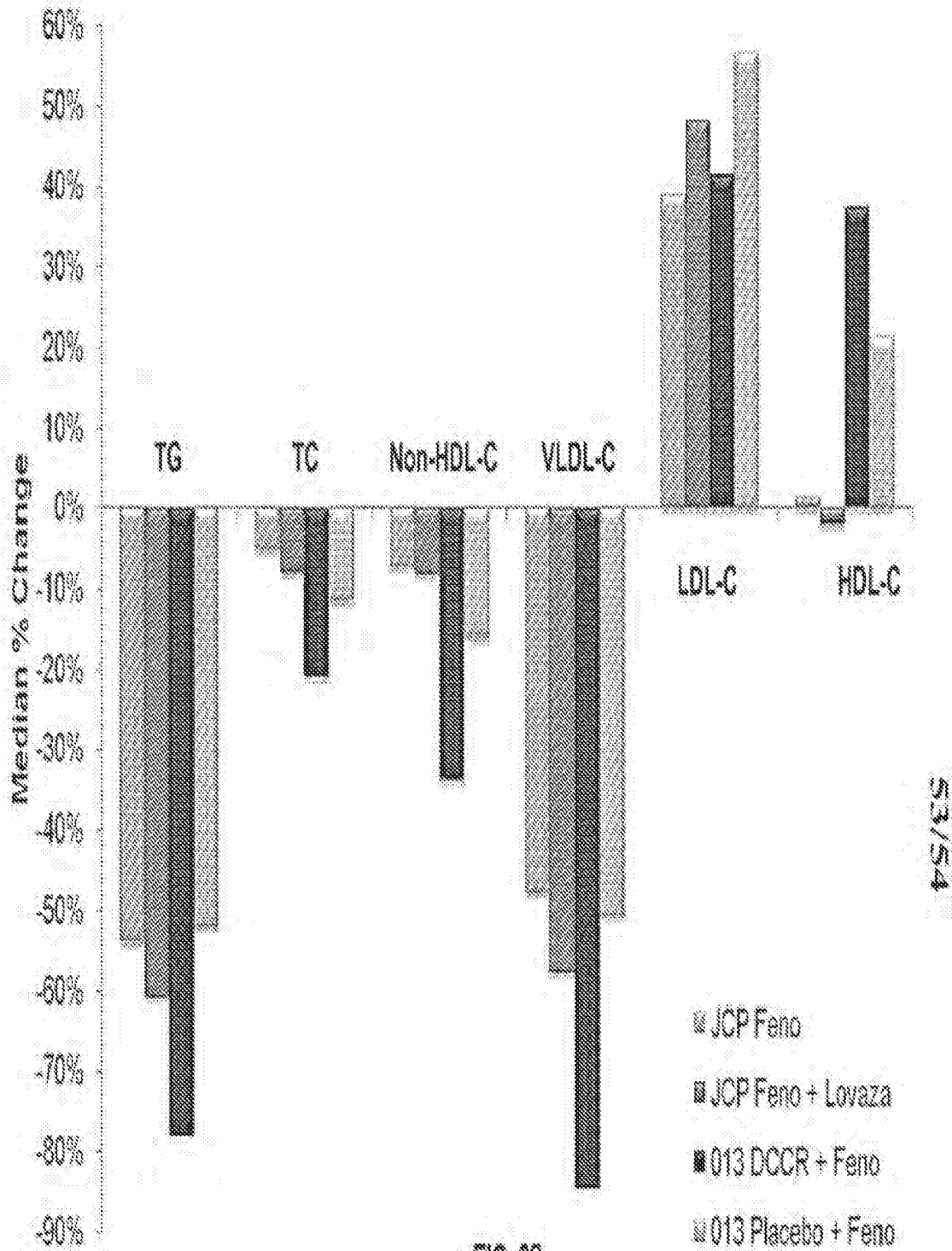


FIG. 28

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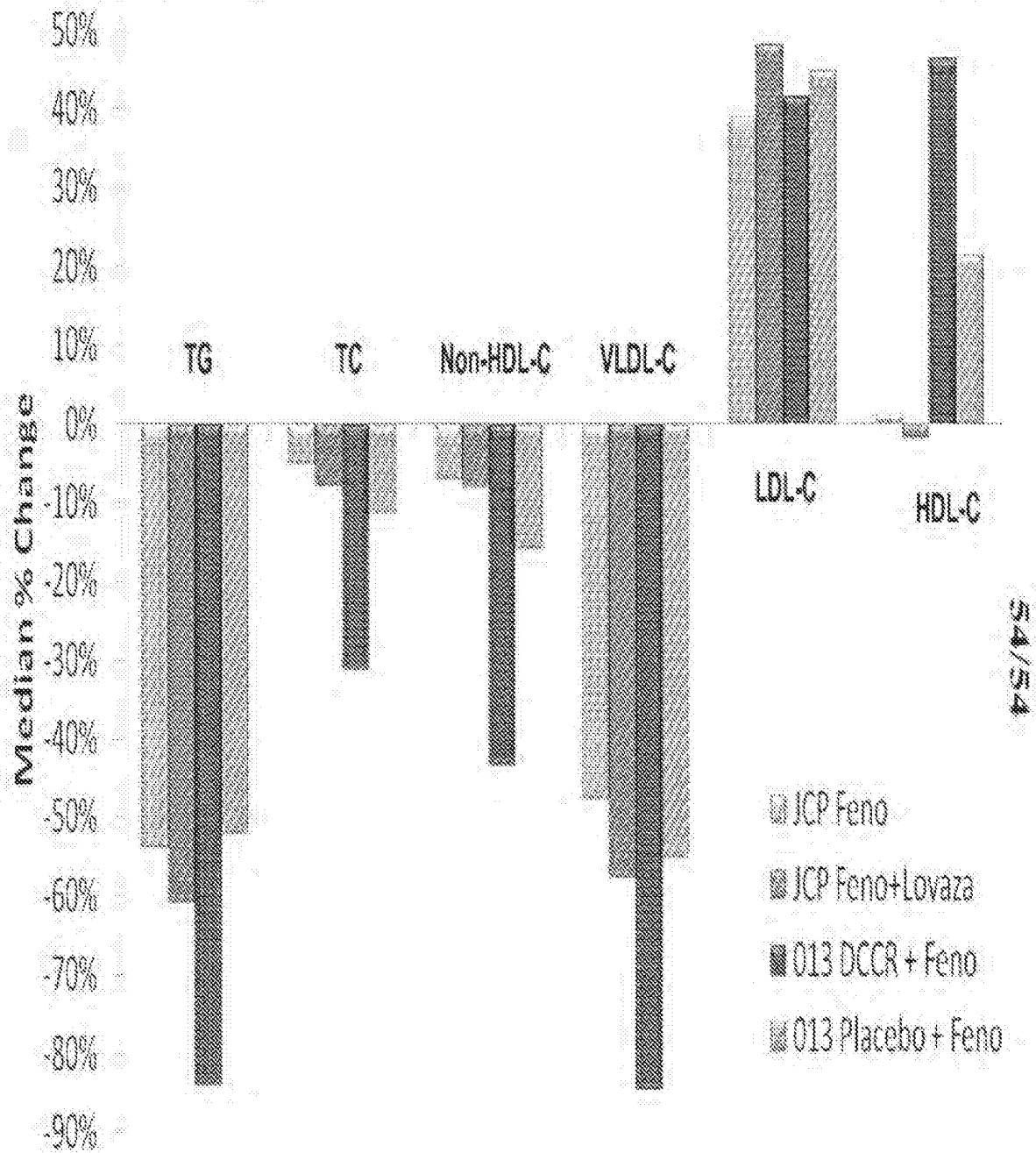


FIG. 29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/027676

A. CLASSIFICATION OF SUBJECT MATTER		
A61K 31/549(2006.01)I, A61K 31/38(2006.01)I, A61P 3/00(2006.01)I, A61P 9/00(2006.01)I		
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) A61K 31/549; C12N 5/06; A61K 31/498; A61K 31/517; C12Q 1/68; A61P 3/04		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Korean utility models and applications for utility models Japanese utility models and applications for utility models		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) eCOMPASS(KIPO internal) & Keywords: potassium channel opener, fibrate, blister card, kit, fibrinase dosage		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003-0032264 A1 (COHEN et al.) 05 March 2003 See paragraphs [0121] and [0201] and claims 13 and 16.	35-37, 44
A	YORIOAMA et al., 'Effects of KRS4884, a novel pirinixincarboxamide (type K1ATP) channel opener, on serum triglyceride levels in rats', British Journal of Pharmacology, 1997, Vol. 120, pp. 1471-1478. See abstract; pages 1474 and 1475; and Figure 3.	35-37, 44
A	US 2004-0072216 A1 (JOHNSON et al.) 15 April 2004 See abstract; and paragraphs [0219], [0223], [0229], and [0234].	35-37, 44
A	US 2006-0149451 A1 (COHEN, N. S.) 11 June 2006 See abstract and claim 49.	35-37, 44
A	US 2003-0145045 A1 (HAMANAKA et al.) 07 August 2003 See paragraphs [0734] and [0735]; and claims 165 and 166.	35-37, 44
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* 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 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 "I" 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 21 June 2013 (21.06.2013)		Date of mailing of the international search report 21 June 2013 (21.06.2013)
Name and mailing address of the ISA/KR Korean Intellectual Property Office 189 Changwon-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea Facsimile No. 82-42-472-7140		Authorized officer CHOI, Sung Hee Telephone No. 82-42-481-8740

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/027676**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.: 1-34, 45-52
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 1-34 and 45-52 are directed to a treatment method of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required to search under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT.
2. ☒ Claims Nos.: 7, 18, 24, 30, 31, 33, 34, 39
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:
Claims 7, 18, 24, 30, 31, 33, 34, and 39 are unclear, since they either directly or indirectly refer to one of claims which are not drafted in accordance with PCT Rule 6.4(a) (PCT Article 6).
3. ☒ Claims Nos.: 6, 8-11, 15-17, 19-23, 25-29, 32, 38, 40-43, 49-52
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 an additional fee, this Authority did not invite payment of any additional fee.
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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2013/027676

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		WO 99-43663 A1	02.09.1999

(10) International Publication Number
WO 2016/077629 A1(43) International Publication Date
19 May 2016 (19.05.2016)

(51) International Patent Classification:

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A61K 31/54 (2006.01) C07D 285/22 (2006.01)

(21) International Application Number:

PCT/US2015/060455

(22) International Filing Date:

12 November 2015 (12.11.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

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62/138,245 25 March 2015 (25.03.2015) US
62/170,035 2 June 2015 (02.06.2015) US
62/221,359 21 September 2015 (21.09.2015) US

(71) Applicant: ESSENTIALIS, INC. [US/US]; 7915 Corie
Caudio, Carlsbad, California 92009 (US).(72) Inventor: COWEN, Neil M.; 7915 Corie Caudio, Carlsbad,
California 92009 (US).(74) Agent: REITER, Stephen E.; Kilpatrick Townsend &
Stockton LLP, Two Embarcadero Center, Eighth Floor,
San Francisco, California 94111 (US).(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, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, 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, SA, 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, ST, 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, ME, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,

[Continued on next page]

(54) Title: METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

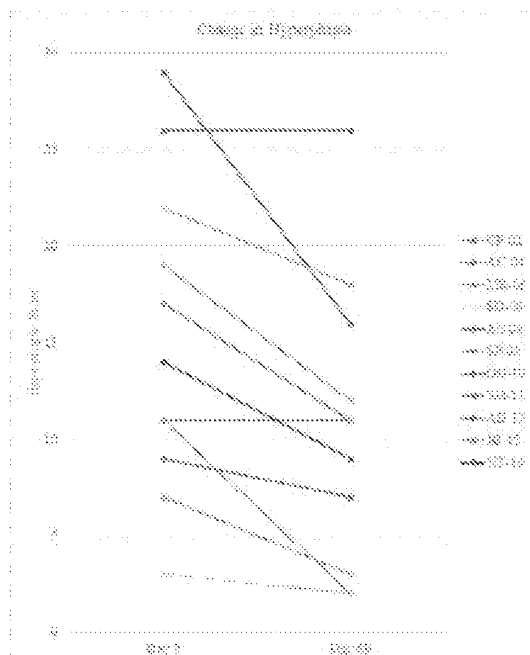


Figure 1

(57) Abstract: Provided are immediate or prolonged admin-
istration of certain potassium ATP (K_{ATP}) channel openers,
optionally in combination with growth hormone, to a subject
to achieve novel pharmacodynamic, pharmacokinetic, thera-
peutic, physiological, metabolic and compositional outcomes
in the treatment of diseases or conditions involving K_{ATP}
channels. Also provided are pharmaceutical formulations,
methods of administration and dosing of K_{ATP} channel open-
ers that achieve these outcomes and reduce the incidence of
adverse effects in treated individuals. Further provided are
methods of co-administering K_{ATP} channel openers with other
drugs (e.g., in combination with growth hormone) to treat
diseases of humans and animals (e.g., Prader-Willi Syndrome
(PWS), Smith-Magenis syndrome (SMS), and the like.



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

Published:

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

METHODS FOR TREATING SUBJECTS WITH PRADER-WILLI SYNDROME OR SMITH-MAGENIS SYNDROME

FIELD OF THE INVENTION

[0001] The present invention relates to pharmaceutical formulations of potassium ATP (K_{ATP}) channel openers and their use for treatment of various diseases and conditions such as Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like.

BACKGROUND OF THE INVENTION

[0002] The following description of the background of the invention is provided simply 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 B-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. 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-operated Ca²⁺ channels (VOCs) 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 kEur 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 C₈H₇ClN₂O₂S), 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 this use, diazoxide acts to open potassium channels in vascular smooth muscle, stabilizing the membrane potential at the resting level, and preventing vascular smooth muscle contraction.

[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.

[0008] 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 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 6,361,795).

[0009] Current oral formulations of diazoxide are labeled for dosing two or three times per day at 8 or 12 hour intervals. Most patients receiving diazoxide are dosed three times per day. Commercial and experimental formulations of diazoxide are characterized by rapid drug release following ingestion with completion of release in approximately 2 hours.

[0010] 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 current packaging insert for the Proglycem). Oral treatment with diazoxide is used in individuals experiencing serious disease where failing 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 patients at doses within the labeled range of 3 to 8 mg/kg per day.

[0011] The effect of diazoxide in animal models of diabetes and obesity (e.g. obese and lean Zucker rats) has been reported. See e.g. Alemzadeh et al. (*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 and Tushaus (*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)).

[0012] The effect of diazoxide in humans with obesity or diabetes has been reported. See e.g., Wigand and Blackard (*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), Orqvist 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), Björk 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)).

[0013] 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.

[0014] U.S. Patent No. 6,197,765 describes administration of diazoxide as a treatment for syndrome-X, and resulting complications, that include hyperlipidemia, hypertension, central obesity, hyperinsulinemia and impaired glucose intolerance. 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.

[0015] U.S. Patent No. 2,986,573 describes diazoxide and alkali metal salts for the treatment of hypertension.

[0016] U.S. Patent no. 5,629,045 describes diazoxide for topical ophthalmic administration.

[0017] WO 98/10786 describes use of diazoxide in the treatment of X-syndrome including obesity associated therewith.

[0018] U.S. Patent publication no. 2003/0035106 describes diazoxide-containing compounds for reducing the consumption of fat-containing foods.

[0019] U.S. Patent publication no. 2004/0204472 describes the use of a Cox-2 inhibitor plus diazoxide in the treatment of obesity.

[0020] U.S. Patent publication no. 2002/0035106 describes the use of K_{ATP} channel openers including diazoxide and metal salts for reducing the consumption of fat containing food.

SUMMARY OF THE INVENTION

[0021] Provided herein are pharmaceutical formulations of K_{ATP} channel openers and their use (optionally in combination with growth hormone) for treatment of various diseases and conditions, including Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like. 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 SUR1/Kir6.2 potassium channels; (2) binding to the SUR1 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 above preferably have the structure of compounds of Formulas I-VII as set forth below.

[0022] In accordance with one aspect of the present invention, it has been discovered that one or more K_{ATP} channel opener(s) (optionally in combination with growth hormone) is effective for the treatment of a subject having Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like, and is especially effective for increasing the lean body mass of such subjects. Therefore, in one aspect of the present invention, there are provided methods of increasing the lean body mass of a subject having Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like, said method comprising administering to said subject for at least 4 weeks an effective amount of a K_{ATP} channel opener (optionally in combination with growth hormone).

[0023] In some embodiments, the lean body mass of said subject is increased by at least 1%. In some embodiments, the lean body mass of said subject is increased by at least 2%. In some embodiments, the lean body mass of said subject is increased by at least 3%. In some embodiments, the lean body mass of said subject is increased by at least 4%. In some embodiments, the lean body mass of said subject is increased by at least 5%.

[0024] In addition to increasing the lean body mass of a subject, in some embodiments, invention methods also reduce the hyperphagia of a subject. In some embodiments, the hyperphagia of said subject is reduced by at least 10%. In some embodiments, the hyperphagia of said subject is reduced by at least 20%. In some embodiments, the hyperphagia of said subject is reduced by at least 30%.

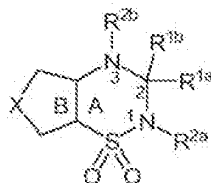
[0025] In addition to increasing the lean body mass of a subject, in some embodiments, invention methods also reduce the body fat of a subject. In some embodiments, the body fat

of said subject is reduced by at least 1%. In some embodiments, the body fat of said subject is reduced by at least 3%. In some embodiments, the body fat of said subject is reduced by at least 5%.

[0026] In another aspect, the present invention provides a method of increasing the lean body mass of a subject having Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like, wherein said subject is already being treated by administration thereto of growth hormone, said method comprising co-administering to said subject an effective amount of a K_{ATP} channel opener in addition to said growth hormone.

[0027] In yet another aspect, the present invention provides a method of increasing the lean body mass of a subject having Prader-Willi Syndrome (PWS), Smith-Magenis syndrome (SMS), and the like, wherein said subject is already being treated by administration thereto of an effective amount of a K_{ATP} channel opener, said method comprising co-administering to said subject an effective amount of growth hormone in addition to said K_{ATP} channel opener.

[0028] K_{ATP} channel openers defined by Formula I are as follows:



Formula I

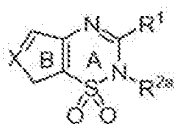
wherein:

- R^{1a} and R^{1b} , when present, are independently selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted amino;
- R^{2a} and R^{2b} , when present, are independently 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 or nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy, cycloalkyl, substituted cycloalkyl, substituted lower alkoxy, amino, or substituted amino;
- wherein rings A and B are each independently saturated, monounsaturated, polyunsaturated or aromatic;

and all bioequivalents including salts, prodrugs and isomers thereof.

[0029] In particular embodiments, compounds of Formula I may include a double bond between either positions 1 and 2 or positions 2 and 3 of Ring A. When a double bond is present between positions 1 and 2 of Ring A, R^{2a} is absent and one of R^{1a} and R^{1b} are absent. When a double bond is present between positions 2 and 3 of Ring A, R^{2b} is absent and one of R^{1a} and R^{1b} are absent. In a preferred embodiment, R^{1a} and R^{1b} are not amino. In another preferred embodiment, Ring B does not include any heteroatoms.

[0030] K_{ATP} channel openers defined by Formula II being a subgenera of Formula I are as follows:



Formula II

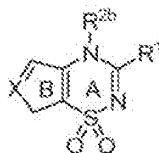
wherein:

- R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted amino;
- 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 or nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy, cycloalkyl, substituted cycloalkyl, substituted lower alkoxy, amino, or substituted amino;
- wherein ring B is saturated, monounsaturated, polyunsaturated or aromatic;
- and all bioequivalents including salts, prodrugs and isomers thereof.

[0031] 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, 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 amino, substituted amine, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, and the like. In a

preferred embodiment, R^1 is not amino. In another preferred embodiment, Ring B does not include any heteroatoms.

[0032] K_{ATP} channel openers defined by Formula III being a subgenera of Formula I are as follows:



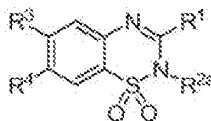
Formula III

wherein:

- R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted amino;
- 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 or nitrogen, and each atom is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, lower alkoxy, cycloalkyl, substituted cycloalkyl, substituted lower alkoxy, amino, or substituted amino;
- wherein ring B is saturated, monounsaturated, polyunsaturated or aromatic;
- and all bioequivalents including salts, prodrugs and isomers thereof.

[0033] In particular embodiments of Formula III, 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 amino, substituted amine, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino, and the like. In a preferred embodiment, R^1 is not amino. In another preferred embodiment, Ring B does not include any heteroatoms.

[0034] K_{ATP} channel openers defined by Formula IV being a subgenera of Formula I are as follows:



Formula IV

wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, amino, and substituted lower amino;

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, lower alkyl, substituted lower alkyl, amino, and substituted amino;

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

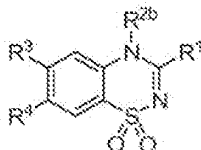
and all bioequivalents including salts, prodrugs and isomers thereof.

[0035] In particular embodiments of Formula IV, R^1 is a lower alkyl (preferably ethyl or methyl); R^{2a} is hydrogen; and R^3 and R^4 are each independently halogen.

[0036] In a preferred embodiment of Formula IV, R^1 is not amino.

[0037] In another embodiment of Formula IV, R^1 is methyl; 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.

[0038] K_{ATP} -channel openers defined by Formula V being a subgenera of Formula I are as follows:



Formula V

wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, amino, and substituted lower amino;

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, lower alkyl, substituted lower alkyl, amino, and substituted amino;

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

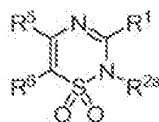
and all bioequivalents including salts, prodrugs and isomers thereof.

[0039] In particular embodiments of Formula V, R^1 is a lower alkyl (preferably ethyl or methyl); R^{2b} is hydrogen; and R^3 and R^4 are each independently halogen.

[0040] In a preferred embodiment of Formula V, R^1 is not amino.

[0041] In another embodiment of Formula V, R^1 is methyl; R^{2b} 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.

[0042] K_{ATP} channel openers defined by Formula VI are as follows:



Formula VI

wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted lower amino, or R^1 can cooperate with R^5 or R^6 to form an additional ring;

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

R^5 is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, and sulfonylamino, or R^5 can cooperate with R^1 or R^6 to form an additional ring;

R^6 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, and sulfonylamino, or R^6 can cooperate with R^1 or R^5 to form an additional ring;

wherein the ring formed by the cooperation of R^1 and R^5 , or R^1 and R^6 , or R^5 and R^6 is saturated, monounsaturated, polyunsaturated or aromatic;

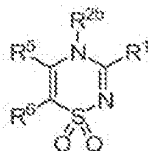
wherein the ring formed by the cooperation of R^1 and R^5 , or R^1 and R^6 , or R^5 and R^6 is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, or sulfonylamino;

and all bioequivalents including salts, prodrugs and isomers thereof.

[0043] In a preferred embodiment, R^1 is not an amino substituent.

[0044] In another embodiment of Formula VI, R^5 and R^6 combine to form a 6 membered ring. In another embodiment, R^5 and R^6 combine to form a 6 membered ring wherein at least one nitrogen is present. Preferably, the ring formed by R^5 and R^6 does not include any heteroatoms.

[0045] K_{ATP} channel openers defined by Formula VII are as follows:



Formula VII

wherein:

R^1 is selected from the group consisting of hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, amino, and substituted lower amino, or R^1 can cooperate with R^5 or R^6 to form an additional ring;

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

R^5 is selected from the group consisting of hydrogen, halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, and sulfonylamino, or R^5 can cooperate with R^1 or R^6 to form an additional ring;

R^6 is selected from the group consisting of hydrogen, halogen, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, and sulfonylamino, or R^6 can cooperate with R^1 or R^5 to form an additional ring;

wherein the ring formed by the cooperation of R^1 and R^5 , or R^1 and R^6 , or R^5 and R^6 is saturated, monounsaturated, polyunsaturated or aromatic;

wherein the ring formed by the cooperation of R^1 and R^5 , or R^1 and R^6 , or R^5 and R^6 is optionally substituted with halogen, hydroxyl, lower alkyl, substituted lower alkyl, amino, substituted amino, sulfonyl, aminosulfonyl, or sulfonylamino;

and all bioequivalents including salts, prodrugs and isomers thereof.

[0046] In a preferred embodiment, R^1 is not an amino substituent.

[0047] In another embodiment of Formula VI, R^5 and R^6 combine to form a 6 membered ring. In another embodiment, R^5 and R^6 combine to form a 6 membered ring wherein at least one nitrogen is present. Preferably, the ring formed by R^5 and R^6 does not include any heteroatoms.

[0048] Unless otherwise indicated, reference in this application to K_{ATP} channel openers should be understood to refer to K_{ATP} channel opener(s) having one or more and preferably all three of the following properties: (1) opening SUR1/Kir6.2 potassium channels; (2) binding to the SUR1 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 Formulae I-VII, or more preferably Formulae I-VII where R^1 is not amino and also where ring B or its equivalent does not include any heteroatoms, or more preferably, any of the compounds of Formulae II or III, or more preferably, any of the compounds of Formulae II or III where R^1 is not amino and also where ring B or its equivalent does not include any heteroatoms, or more preferably, the

structure is diazoxide. Structural variants or bioequivalents of the compounds of any of Formulae I-VII such as derivatives, salts, prodrugs or isomers are also contemplated. Other K_{ATP} channel openers that are contemplated for use herein include BPDZ62, BPDZ 73, NN414, BPDZ 154.

[0049] *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).

[0050] Provided herein are formulations, such as controlled release pharmaceutical formulations, of K_{ATP} channel openers and bioequivalents thereof. In one embodiment, the controlled release formulations are formulated for 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 K_{ATP} channel openers. In certain embodiments, the dosage of the K_{ATP} channel openers contained in a formulation may be determined based on the weight of the patient 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 patient's body weight, or between 0.1-0.5 mg of the K_{ATP} channel opener per kg of the patient's body weight; or between 0.5-1 mg of the K_{ATP} channel opener per kg of the patient's body weight; or between 1-2 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 2-5 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 5-10 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 10-15 mg of the K_{ATP} channel opener per kg of the patient's body weight, or between 15-20 mg of the K_{ATP} channel opener per kg of the patient's body weight.

[0051] Also provided herein are controlled release pharmaceutical formulations containing K_{ATP} channel openers obtained by at least one of the following: (a) particle size reduction involving comminution, spray drying, or other micronising techniques, (b) use of a pharmaceutical salt of the K_{ATP} channel opener, (c) use of an ion exchange resin, (d) use of inclusion complexes, for example cyclodextrin, (e) 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, (f) associating the K_{ATP} channel opener with a salt prior to formulation, (g) use of a solid dispersion of the K_{ATP}

channel opener, (h) use of a self emulsifying system, (i) addition of one or more surfactants to the formulation, (j) use of nanoparticles, or (k) combinations of these approaches.

[0052] Further provided herein are controlled release pharmaceutical formulations containing K_{ATP} channel openers 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 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, for example, U.S. Pharmacopeia, Chapter 711 (2005)).

[0053] Also provided are oral pharmaceutical formulations of K_{ATP} channel openers 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 co-polymer 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, (j) use of systems controlled by ion exchange resins, and (k) combinations of these approaches, wherein the pH sensitive polymer or co-polymer is resistant to degradation under acid conditions.

[0054] Also provided herein are controlled release pharmaceutical formulations of K_{ATP} channel openers, wherein the formulation includes at least one component that contributes to sustained release of a K_{ATP} channel opener 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 these approaches.

[0055] As used herein, an erodable matrix is the core of a tablet formulation that, upon exposure to an 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.

[0056] The above formulations may further comprise one or more additional pharmaceutically active agents (other than K_{ATP} channel openers) 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 comorbidities, ischemic and reperfusion injury, epilepsy, schizophrenia, mania, or other psychotic diseases.

[0057] Further provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener wherein administration to an obese, overweight or obesity prone individual 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, (e) inhibition of hyperphagia for about 24 hours, or (f) increase in lean body mass.

[0058] Additionally provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener wherein administration to an obese, overweight or obesity prone individual 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, (e) inhibition of hyperphagia for about 18 hours, or (f) increase in lean body mass.

[0059] Still further provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener which upon administration to an obese, overweight or obesity prone individual 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, (e) inhibition of hyperphagia for about 24 hours, or (f) increase in lean body mass.

[0060] Additionally provided is a controlled release pharmaceutical formulation of a K_{ATP} channel opener that upon administration to an obese, overweight or obesity prone individual 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, (e) inhibition of hyperphagia for about 18 hours, or (f) increase in lean body mass.

[0061] Provided herein is a method of treating hypoglycemia, the method comprising orally administering a controlled release formulation of a K_{ATP} channel opener, optionally in combination with growth hormone.

[0062] Further provided herein is a method of treating obesity associated co-morbidities in an obese, overweight or obesity prone individual, the method comprising administering a therapeutically effective amount of a solid oral dosage form of a K_{ATP} channel opener, or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0063] Yet further provided herein is a method of achieving weight loss in an obese overweight, or obesity prone individual, the method comprising administering a therapeutically effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. 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 individual 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.

[0064] Also provided is a method of maintaining a weight loss in an obese overweight, or obesity prone individual, the method comprising administering a therapeutically effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. It is preferable to maintain weight in an obese individual 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.

[0065] Further provided is a method of elevating energy expenditure in an overweight, obese or obesity prone individual, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. In certain embodiments, the individual 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.

[0066] Additionally provided is a method of elevating beta oxidation of fat in an overweight, obese or obesity prone individual, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours. In certain embodiments, the individual 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.

[0067] Yet further provided is a method of reducing visceral fat in an overweight, obese or obesity prone individual, the method comprising administering an effective amount of a solid oral dosage form of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0068] Still further provided is a method of delaying or preventing the transition to diabetes of a prediabetic individual comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0069] Additionally provided is a method of restoring normal glucose tolerance in a prediabetic individual comprising administering an effective amount of a K_{ATP} channel

opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0070] Further provided is a method of restoring normal glucose tolerance in a diabetic individual comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0071] Still further provided is a method of delaying or preventing progression of diabetes in an individual comprising administering an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0072] Also provided is a method to prevent or treat weight gain, impaired glucose tolerance or dyslipidemia associated with the use of anti-psychotics to treat patients comprising the co-administration of an effective amount of a K_{ATP} channel opener or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone. In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0073] Further provided is a method to increase lean body mass in a Prader-Willi Syndrome patient, in a Smith-Magenis syndrome patient, in 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 (optionally in combination with growth hormone) or a controlled release pharmaceutical formulation of a K_{ATP} channel opener (optionally in combination with growth hormone). In a preferred embodiment, administration is no more than two times per 24 hours, or once per 24 hours.

[0074] 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 or controlled release pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth

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

[0075] Also provided is a method of reducing the incidence of adverse effects from administration of a K_{ATP} channel opener 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 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.

[0076] 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, optionally in combination with growth hormone.

[0077] 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, optionally in combination with growth hormone.

[0078] 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, (h) hyperlipoproteinemia type I, II, III, and IV, or (i) Smith-Magenis syndrome (SMS), said method comprising administering a pharmaceutical formulation of a K_{ATP} channel opener, optionally in combination with growth hormone.

[0079] Further provided is a pharmaceutical formulation of a K_{ATP} channel opener 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 comorbidities, ischemic and reperfusion injury, epilepsy, schizophrenia, mania, and other psychotic condition.

[0080] The formulations containing K_{ATP} channel openers 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 with one or more additional pharmaceutically active agents that have complementary or similar activities or targets. Other pharmaceutical active agents that can be combined with K_{ATP} channel openers to treat obesity or to maintain weight loss in an obesity prone individual 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 individual once some weight loss has occurred when the alternative is to regain weight. Other pharmaceutically active agents that may be combined with K_{ATP} channel openers to treat type II diabetes, or prediabetes include acarbose, miglitol, metformin, repaglinide, nateglinide, rosiglitazone, proglitazone, ramipril, metaglidase, 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 agents that can be combined with K_{ATP} channel openers 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 individuals 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, infertility, and the like.

[0081] 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.

[0082] 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.

[0083] As used herein, the term “composition” refers to a formulation suitable for administration to an intended animal subject for therapeutic purposes; exemplary formulations contain at least one pharmaceutically active compound and at least one pharmaceutically acceptable carrier or excipient. Other terms as used herein are defined below.

[0084] Adipocyte: An animal connective tissue cell specialized for the synthesis and storage of fat.

[0085] 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.

[0086] About: is used herein to mean in quantitative terms plus or minus 10%.

[0087] Adipose tissue: Tissue comprised principally of adipocytes.

[0088] Adolescent: A person between 10 and 19 years of age.

[0089] 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.

- [0090] 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.
- [0091] Analog: a compound that resembles another in structure but differs by at least one atom.
- [0092] 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.
- [0093] Atherosclerotic Plaque: A buildup of cholesterol and fatty material within a blood vessel due to the effects of atherosclerosis
- [0094] Bariatric Surgery: a range of surgical procedures which are designed to aid in the management or treatment of obesity and allied diseases.
- [0095] Beta cell rest: Temporarily placing beta cells in a condition in which there is reduced metabolic stress due to suppressed secretion of insulin.
- [0096] Bilaminate: A component of a pharmaceutical dosage form that consists of the lamination of two distinct materials.
- [0097] 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.
- [0098] 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 (C_{max}) of the drug, using statistical criteria.

[0099] 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.

[00100] 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 collections. It can be a mixture thereof, such as a single mixture of the two or more items, or any variation thereof.

[00101] Composition: refers to any mixture. It can be a solution, a suspension, liquid, powder, a paste, aqueous, non-aqueous or any combination thereof.

[00102] Compression tablet: Tablet formed by the exertion of pressure to a volume of tablet matrix in a die.

[00103] Compression coated tablet: A tablet formed by the addition of a coating by compression to a compressed core containing the pharmaceutical active.

[00104] Derivative: a chemical substance derived from another substance by modification or substitution.

[00105] 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.

[00106] Diazoxide: 7-chloro-3-methyl-2-H-1,2,4-benzothiadiazine 1,1 dioxide with the empirical formula C₈H₇ClN₂O₂S and a molecular weight of 230.7.

[00107] 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.

[00108] 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.

[00109] Fatty acid synthase: The central enzyme of a multienzyme complex that catalyses the formation of palmitate from acetylcoenzyme A, malonylcoenzyme A, and NADPH.

[00110] Gastric Lipase: An enzyme secreted into the gastrointestinal tract that catalyzes the hydrolysis of dietary triglycerides.

[00111] Glidant: An inactive component of a pharmaceutical formulation that prevents caking of the matrix during processing steps.

[00112] Growth hormone: also known as somatotropin or somatropin, is a peptide hormone that stimulates growth, cell reproduction and regeneration in humans and other animals. It is a type of mitogen which is specific only to certain kinds of cells. Growth hormone is a 191-amino acid, single-chain polypeptide that is synthesized, stored, and secreted by somatotrophic cells within the lateral wings of the anterior pituitary gland. GH is a stress hormone that raises the concentration of glucose and free fatty acids. It also stimulates production of IGF-1.

[00113] Hyperinsulemia: 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.

[00114] Hyperinsulinism: Excessive secretion of insulin by the pancreatic islets.

[00115] Hyperlipidemia: A general term for elevated concentrations of any or all of the lipids in the plasma, such as cholesterol, triglycerides and lipoproteins.

[00116] Hyperphagia: Ingestion of a greater than optimal quantity of food.

[00117] 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, water, non-aqueous solvents, and flavorings.

[00118] IGF-1, also called somatomedin C, is a protein that in humans is encoded by the *IGF1* gene. IGF-1 is a hormone similar in molecular structure to insulin. It plays an important role in childhood growth and continues to have anabolic effects in adults. IGF-1

consists of 70 amino acids in a single chain with three intramolecular disulfide bridges, and has a molecular weight of 7,649 daltons.

[00119] Insulin resistance: A condition in which the tissues of the body are diminished in their response to insulin.

[00120] 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.

[00121] Ketoacidosis: Acidosis accompanied by the accumulation of ketone bodies (ketosis) in the body tissue and fluids, as in diabetic acidosis.

[00122] 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.

[00123] Kir: Pore forming subunit of the K_{ATP} channel. Also known as the inwardly rectifying subunit of the K_{ATP} channel. Typically existing as Kir6.x and infrequently as Kir2.x subspecies.

[00124] K_{ATP} 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.

[00125] Lean body mass: Lean Body Mass is a component of body composition, calculated by subtracting body fat weight from total body weight: total body weight is lean plus fat. In equations:

Lean Body Mass equals Body Weight minus Body Fat ($LBM = BW - BF$)

Lean Body Mass plus Body Fat equals Body Weight ($LBM + BF = BW$)

The percentage of total body mass that is lean is usually not quoted – it would typically be 60–90%. Instead, the body fat percentage, which is the complement, is computed, and is typically 10–40%. The Lean body mass (LBM) has been described as an index superior to total body weight for prescribing proper levels of medications and for assessing metabolic disorders, as body fat is less relevant for metabolism.

[00126] 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.

[00127] Lipogenesis: The generation of new lipids, primarily triacylglycerides. It is dependent on the action of multiple distinct enzymes and transport molecules.

[00128] Lipolysis: The breakdown of fat by the coordinated action of multiple enzymes.

[00129] Lipoprotein lipase: An enzyme of the hydrolase class that catalyses the reaction of triacylglycerol 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.

[00130] Lubricant: An inactive component of a pharmaceutical formulation that provides for the flow of materials in various processing steps, particularly tableting.

[00131] Microparticle: A small particulate formed in the process of developing pharmaceutical formulations that may be coated prior to producing the final dosage form.

[00132] 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.

[00133] Obesity Prone: Individuals who because of genetic predisposition or prior history of obesity are at above average risk of becoming obese.

[00134] Obesity related co-morbidities: any disease or condition of animals or humans that are increased incidence in obese or overweight individuals. Examples of such conditions include hypertension, prediabetes, type 2 diabetes, osteoarthritis and cardiovascular conditions.

[00135] 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.

[00136] Overweight: an individual 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/m^2) an overweight individual has a BMI between 25 and 30.

[00137] 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.

[00138] Pharmaceutical composition: refers 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."

[00139] 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.

[00140] Pharmacodynamic: An effect mediated by drug action.

[00141] Pharmacokinetic: Relating to the absorption, distribution, metabolism and elimination of the drug in the body.

[00142] Polymorph: A compound that shares the same chemistry but a different crystal structure.

[00143] Prader-Willi syndrome (PWS): A complex neurobehavioral/metabolic disorder which is due to the absence of normally active, paternally expressed genes from the chromosome 15q11-q13 region. PWS is an imprinted condition with 70–75% of the cases due to a de novo deletion in the paternally inherited chromosome 15 11-q13 region, 20–30% from maternal uniparental disomy 15 (UPD), and the remaining 2–5% from either microdeletions or epimutations of the imprinting center (i.e., imprinting defects) (Bittel and Butler, *Expert Rev Mol Med* 7(14):1-20 (2005); Cassidy and Driscoll, *Eur J Hum Genet* 17(1):3-13(2009)).

[00144] The clinical manifestations of the condition begin in utero with diminished fetal activity (Miller *Am J Med Genet A* 155A(5):1-10 (2011)). Low lean body mass and

hypotonia are universal in PWS and present throughout life (Brambilla *Am J Clin Nutr* 65(5):1369-1374 (1997), Lloret-lineras *Int J Obes* 37:1198-1203 (2013)). Mental retardation occurs to varying degrees with the average IQ being 70 (PWSUSA). PWS patients present with a range of behavioral complications including autistic-spectrum-disorder-like behaviors, compulsive behaviors, self-injurious behaviors, and aggressive, threatening and destructive behaviors. About 80% of PWS patients are growth hormone deficient (Goldstone, *Trends Endocrinol Metab* 15:12-120 (2004); Davies et al., *Front Neuroendocrinol* 29:413-427 (2008); Cassidy and Driscoll, 2009, *supra*). Nearly all PWS patients are hypogonadal, requiring sex hormone supplementation (Goldstone, 2004, *supra*; Davies et al., 2008, *supra*; Cassidy and Driscoll, 2009, *supra*). These patients have hypothalamic insufficiency/dysfunction (Goldstone *Am J Clin Nutr* 75(3):468-475 (2002)).

[00145] The accumulation of excess body fat may begin about age 2 and can continue into adulthood (Miller 2011, *supra*). The vast majority of body fat in PWS is subcutaneous (Brambilla 1997, *supra*; Sode-Carlson, *Growth hormone and IGF research* 20:179-184 (2010), Bedogni *J Endocrinol Invest* DOI 10.1007/s40618-015-0266-y (2015)). Obesity is not universal in PWS, unlike the universality of low lean body mass and hypotonia. For example, Sode-Carlson et al. (2010), *supra*, evaluated 46 adult PWS patients, 25 women and 21 men. The average BMI in these adult PWS patients was 27.2 kg/m². Thus, on average, these patients were overweight rather than obese, suggesting that more than half are not, in fact, obese by the best metric. Similarly, Brambilla et al. *Nutr Metab Cardiovasc Dis* 21(4):269-276 (2011) studied a population of 109 children with PWS. They found that 54% were not classified as obese by the best metric. Thus, both in adults and in children with PWS, obesity is not only not universal, but may, in fact, occur in less than half of the population. Subcutaneous fat makes up a greater percentage of total fat in PWS than it does in obese controls at all ages (Sode-Carlson 2010, *supra*).

[00146] Hyperphagia with the associated problematic food related behaviors begins on average about age 8 (Miller 2011, *supra*). These patients sense they are starving when they are not. Upon the onset of hyperphagia, PWS patients will eat any food in the line of sight, get up at night to eat, dig through the trash for food, steal food, consume frozen food, pet food, spoiled food and even consume non-food items (Miller 2011, *supra*). They will become angry or throw tantrums if denied food. At this stage and thereafter throughout life, access to

food is strictly limited, with cabinets and refrigerators being locked. To limit food related anxiety, meal times and meal composition are strictly regimented.

[00147] The mortality rate for PWS patients is three times that of the general population at all ages (Cassidy *Genet Med* 14(1):10-26 (2012)), with the average age at death being about 29 years (PWSUSA mortality database, n=488). In contrast, being obese, but not morbidly obese has little impact on life expectancy (Anon (2011) National Research Council Panel on Understanding Divergent Trends in Longevity in High-Income Countries; Crimmons, EM, Preston, SH, Cohen, B, editors. National Academies Press).

[00148] Prader-Willi patients expend less energy and are more sedentary than either the general population, obese controls or patients with similar intellectual disabilities. Butler et al. *Am J Med Genet A* 143A(5):449-459 (2007)) compared the energy expenditure and total work of a group of 48 PWS patients with a group of 24 obese controls. Compared to the controls, PWS patients had significantly decreased total energy expenditure (-20%), resting energy expenditure (-16%) and mechanical work (-35%). After adjusting for group differences in lean body mass, the difference remained significant for mechanical work.

[00149] In a study by van Mil et al., *Int J Obes Relat Metab Disord* 24(4):429-434 (2000), the authors measured basal metabolic rate (BMR), average daily metabolic rate (ADMR), activity induced energy expenditure (AEE), and ADMR/BMR (PAL) in a group of PWS patients and matched controls. ADMR, AEE and PAL were significantly lower ($P < 0.01$) in the PWS group compared with the control group -28.2%, -58.2%, and -14.2%, respectively).

[00150] De Lind van Wijngaarden et al., *J Clin Endocrinol Metab* 95(4):1758-1766 (2010) evaluated cardiovascular and metabolic risk factors in children with PWS. They showed that 63% of infants and 73% of pre-pubertal children with PWS have at least one cardiovascular risk factor, defined as dyslipidemia or hypertension. Thus, the cardiometabolic risk in PWS is elevated even in younger children.

[00151] Preadipocyte: A progenitor cell to adipocytes.

[00152] 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.

[00153] 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 metabolism, 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.

[00154] 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).

[00155] Quick dissolving formulation: a pharmaceutical formulation which upon oral administration may release substantially all of the drug active from the formulation within 10 minutes.

[00156] 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.

[00157] 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.

[00158] 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.

[00159] Salt: the neutral, basic or acid compound formed by the union of an acid or an acid radical and a base or basic radical.

[00160] Smith–Magenis syndrome (SMS; OMIM #182290, *607642): A complex, generally sporadic, genetic disorder caused by haploinsufficiency of the retinoic acid induced 1 (RAI1) gene, caused by either a 17p11.2 deletion encompassing the retinoic acid-induced 1 (RAI1) gene or a mutation of RAI1 (see, for example, Burns et al., in *Human Molecular Genetics*, 2010, Vol. 19, No. 20, pp. 4026–4042).

[00161] Smith–Magenis syndrome is characterized by a clinically recognizable phenotype that includes physical, developmental, neurological, and behavioral features. Short stature (<5th percentile) was observed in ~67% of young patients. Short stature resolves over time with most individuals reaching the 10–25th percentile by adulthood (see, for example, Burns et al. supra). A majority of children with SMS also have significant early-onset obesity (see, for example, *European Journal of Human Genetics* (2008) 16, 412–421). Obesity in teens and adults is common, typically with broad chests and truncal obesity. RAI1 haploinsufficiency represents a single-gene model of obesity with hyperphagia, abnormal fat distribution and altered hypothalamic gene expression associated with satiety, food intake, behavior and obesity.

[00162] Hearing loss is variable and is often associated with chronic ear infections. Ophthalmologic features are present in >60% of SMS patients and include myopia, iris anomalies, strabismus, microcornea, and, rarely, retinal detachment (often resulting from violent behaviors).

[00163] Prenatal history of SMS is notable for significantly decreased fetal movement in 50% of pregnancies. Early infancy is complicated by feeding difficulties leading to failure to thrive, marked oral sensory motor dysfunction with poor suckling reflex, gastroesophageal reflux, and hypotonia.

[00164] Most SMS individuals have mild-to-moderate mental retardation. IQ decreases as the child ages, ultimately placing the individual in the mild mental retardation range by adulthood. Delayed speech with or without hearing loss occurs in 96% of SMS patients. In addition, delayed fine/gross motor skills, problems with sensory integration, and poor adaptive function are seen. Other neurological features include pes cavus or pes planus, an abnormal ‘festinating’ gait, balance problems, and a decreased sensitivity to pain, which is often observed in association with self-injury in this disorder.

[00165] Sleep disturbance has been reported in 75–100% of SMS cases. Infants typically experience hypersomnolence during the first year of life. Sleep disturbances in older children include difficulties falling asleep, diminished REM sleep, reduced 24-h and night sleep, fragmented and shortened sleep cycles with frequent nocturnal and early-morning awakenings, and excessive daytime sleepiness.

[00166] Behavioral issues are one of the unique characteristic features of SMS. Maladaptive behaviors are a cause of major concern and include frequent outbursts/temper tantrums, attention seeking, aggression, disobedience, distraction, and self-injurious behaviors. Self-injurious behaviors include head banging, skin picking, wrist biting, onychotillomania and polyembolokoilomania. The behavioral phenotype of SMS escalates with age, typically with the onset of puberty. Age, degree of developmental delay, severity of any associated systemic disorder, and degree of sleep disturbance have a strong influence on maladaptive behaviors. Individuals also have a lack of respect for personal space during a conversation and are emotionally volatile.

[00167] SMS patients share many characteristics in common with PWS patients. These include: (1) diminished fetal activity; (2) hypotonia; (3) feeding difficulties in early infancy; (4) short stature; (5) early onset obesity which may include hyperphagia; (6) developmental delays; (7) mental retardation; (8) temper outbursts; (9) aggressive behavior; (10) self-injurious behavior; (11) hypersomnolence in infancy and similar sleep disturbances in older children and adults; (12) frequent ear infections; (13) scoliosis; and (14) strabismus. While the underlying genetic basis for these disorders is quite distinct, the presentation and natural history of the disease is very similar.

[00168] Solid oral dosage form: pharmaceutical formulations designed for oral administration including capsules and tablets.

[00169] Subject: refers to animals, including mammals, such as human beings.

[00170] Sulfonylurea receptor: A component of the K_{ATP} channel responsible for interaction with sulfonylurea, other K_{ATP} channel antagonists, diazoxide and other K_{ATP} channel agonists.

[00171] 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.

[00172] Thermogenesis: The physiological process of heat production in the body.

[00173] 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.

[00174] Treatment: means any manner in which the symptoms of a condition, disorder or disease or other indication, are ameliorated or otherwise beneficially altered.

[00175] Triglyceride: Storage fats of animal and human adipose tissue principally consisting of glycerol esters of saturated fatty acids.

[00176] Type 1 diabetes: A chronic condition in which the pancreas makes little or no insulin because the beta cells have been destroyed.

[00177] Uncoupling protein: A family of proteins that allow oxidation in mitochondria to proceed without the usual concomitant phosphorylation to produce ATP.

[00178] Visceral fat: Human adipose tissues principally found below the subcutaneous fat and muscle layer in the body.

BRIEF DESCRIPTION OF THE FIGURES

[00179] Figure 1 summarizes the change in hyperphagia score for all subjects who participated in clinical study PC025.

[00180] Figure 2 summarizes the percent change in lean body mass for all subjects who participated in clinical study PC025.

[00181] Figure 3 summarizes the percent change in body fat mass for all subjects who participated in clinical study PC025.

[00182] Figure 4 summarizes the percent change of the lean body mass/fat mass ratio for all subjects who participated in clinical study PC025.

DETAILED DESCRIPTION OF THE INVENTION

[00183] Provided herein are pharmaceutical formulations of particular K_{ATP} channel openers that when administered to subjects achieve novel pharmacodynamic, pharmacokinetic, therapeutic, physiological, and metabolic outcomes. Also provided are pharmaceutical formulations, methods of administration and dosing of particular K_{ATP} channel openers, optionally in combination with growth hormone, that achieve therapeutic outcomes while reducing the incidence of adverse effects.

[00184] In particular, pharmaceutical formulations 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.

[00185] Compounds of formulas II and III, formulas IV and V, and formulas VI and VII, such as for example, diazoxide (shown below) can be 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 nitrogen substituent is hydrogen, the two isomeric chemical structures may be used interchangeably.

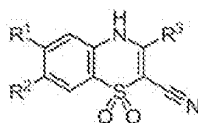


[00186] The particular K_{ATP} channel openers that can be used in the invention formulations include any of those within formulae I to VII. Exemplary such compounds include diazoxide, BPDZ62, BPDZ 73, NN414 and BPDZ 154 (see, for example, Schou, et al., *Bioorg. Med. Chem.*, 13, 141-155 (2005)). Compound BPDZ 154 also is an effective K_{ATP} 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).

[00187] Analogs of diazoxide include 3-isopropylamino-7-methoxy-4H-1,2,4-benzothiadiazine 1,1-dioxide, which is a selective $K_{ir6.2/SUR1}$ channel opener (see

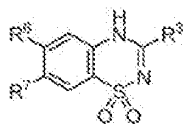
Dabrowski, et al., *Diabetes*, 51, 1896-1906 (2002)). 2-alkyl substituted diazoxides are included (see, for example, Ouedraogo, et al., *Biol. Chem.*, 383, 1759-1768 (2002)); these channel openers show decreased activity in the inhibition of insulin release and increased activity in vascular smooth muscle tissue. Furthermore, 2-alkyl substituted diazoxides generally do not function as traditional potassium channel activators, but instead show potential as Ca^{2+} blockers.

[00188] Other diazoxide analogs are described in Schou, et al., *Bioorg. Med. Chem.*, 13, 141-155 (2005), and are shown below.



R^1 , R^2 and R^3 are:
a) H, Cl, $\text{NHCH}(\text{CH}_3)_2$
b) CF_3 , H, $\text{NHCH}(\text{CH}_3)_2$
c) H, Cl, $\text{NHCH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$
d) H, Cl, NH-cyclobutyl

[00189] Diazoxide analogs having different alkyl substituents at the 3 position of the molecule (identified as R^5 shown below) are described in Bertolino, et al., *Receptors and Channels*, 1, 267-278 (1993).



R^5 , R^6 and R^7 are:

a) H, H, CH_3	i) nC_7H_{15} , H, Cl
b) H, H, Cl	j) nC_3H_7 , Cl, H
c) CH_3 , Cl, H	k) nC_6H_5 , Cl, H
d) CH_2Cl , H, Cl	l) nC_9H_{19} , Cl, H
e) NH_2 , H, H	m) nC_7H_{15} , Cl, H
f) $\text{CH}_2\text{CH}_2\text{Cl}$, H, Cl	n) nC_7H_{15} , Cl, Cl
g) nC_6H_5 , H, Cl	o) nC_6H_5 , Cl, Cl
h) nC_9H_{19} , H, Cl	p) nC_9H_{19} , Cl, Cl
	q) nC_7H_{15} , Cl, Cl
	r) H, Cl, H

[00190] K_{ATP} channel activity of formulae I – VII 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).

[00191] 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 K_{ATP} 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).

[00192] Activation of recombinant K_{ATP} channels by K_{ATP} channel openers can be examined by monitoring macroscopic currents of inside-out membrane patches from *Xenopus* oocytes coexpressing 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).

[00193] Binding experiments can be used to determine the ability of K_{ATP} channel openers to bind SUR1, SUR2A and SUR2B. See, for example, Schwanstecher, et al., *EMBO J.*, 17, 5529-5535 (1998).

[00194] 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).

[00195] 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).

[00196] "Halo" and "halogen" refer to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[00197] "Hydroxyl" and "hydroxy" refer to the group -OH.

[00198] "Substituted oxy" refers to the group -OR^f, where R^f is alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aralkyl, substituted aralkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

[00199] "Substituted thiol" refers to the group -SR, where R is alkyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aralkyl, substituted aralkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

[00200] "Alkyl" refers to an alkane-derived radical containing from 1 to 10, preferably 1 to 6, carbon atoms. Alkyl includes straight chain alkyl, branched alkyl and cycloalkyl, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. Straight chain or branched alkyl groups contain from 1-10, preferably 1 to 6, more preferably 1-4, yet more preferably 1-2, carbon atoms. The alkyl group is attached at any available point to produce a stable compound.

[00201] 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.

[00202] "Lower alkyl" refers to an alkyl group having 1-6 carbon atoms.

[00203] 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.

[00204] "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. "Cycloalkylene" is a divalent cycloalkyl.

[00205] "Alkoxy" denotes the group $-OR^f$, where R^f is lower alkyl.

[00206] "Substituted alkoxy" denotes the group $-OR^f$, where R^f is substituted lower alkyl.

[00207] "Alkylthio" or "thioalkoxy" refers to the group $-S-R$, where R is lower alkyl.

[00208] "Substituted alkylthio" or "substituted thioalkoxy" refers to the group $-S-R$, where R is substituted lower alkyl.

[00209] "Sulfinyl" denotes the group $-S(O)-$.

[00210] "Sulfonyl" denotes the group $-S(O)_2-$.

[00211] "Substituted sulfinyl" denotes the group $-S(O)-R$, where R is lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

[00212] "Substituted sulfonyl" denotes the group $-S(O)_2-R$, where R is lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, cycloalkylalkyl, substituted cycloalkylalkyl, heterocyclyl, substituted heterocyclyl, heterocyclylalkyl, substituted heterocyclylalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

[00213] "Sulfonylamino" denotes the group $-NRS(O)_2-$ where R is hydrogen or lower alkyl.

[00214] "Substituted sulfonylamino" denotes the group $-NR^a S(O)_2-R^b$, where R^a is hydrogen or lower alkyl and R^b is lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaralkyl, substituted heteroaralkyl, aralkyl or substituted aralkyl.

[00215] "Amino" or "amine" denotes the group $-NH_2$. A "divalent amine" denotes the group $-NH-$. A "substituted divalent amine" denotes the group $-NR-$ wherein R is lower alkyl, substituted lower alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, sulfonyl or substituted sulfonyl.

[00216] "Substituted amino" or "substituted amine" denotes the group $-NR^i R^j$, wherein R^i and R^j are independently hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, substituted acyl, sulfonyl, substituted sulfonyl, or cycloalkyl provided, however, that at least one of R^i and R^j is not hydrogen. $R^i R^j$ in combination with the nitrogen may form an optionally substituted heterocyclic or heteroaryl ring.

[00217] "Alkylsulfinyl" denotes the group $-S(O)R^p$, wherein R^p is optionally substituted alkyl.

[00218] "Alkylsulfonyl" denotes the group $-S(O)_2R^p$, wherein R^p is optionally substituted alkyl.

[00219] "Alkylsulfonylamino" denotes the group $-NR^qS(O)_2R^p$, wherein R^p is optionally substituted alkyl, and R^q is hydrogen or lower alkyl.

[00220] Pharmaceutical formulations containing K_{ATP} channel openers include the free base of the drug or a salt of the drug. Such salts 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 K_{ATP} channel opener upon exposure to simulated or actual gastric and duodenal conditions, (5) release K_{ATP} channel opener 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 K_{ATP} 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 K_{ATP} channel opener, (12) have limited hygroscopicity to improve stability, or (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.

[00221] K_{ATP} channel openers can be 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.

[00222] Pharmaceutically acceptable salts 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 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.

[00223] Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chlorprocaine, 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 can be prepared using the appropriate corresponding bases.

[00224] Pharmaceutically acceptable salts 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.

[00225] The pharmaceutically acceptable salt of the different compounds 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.

[00226] Salts of K_{ATP} channel openers, and particular salts of diazoxide, may include, but are not limited to acetate, acetonide, acetyl, adipate, aspartate, besylate, biacetate, bitartrate, bromide, butoxide, butyrate, calcium, camsylate, caproate, carbonate, citrate, cypionate, decaroate, diacetate, dimeglumine, dinitrate, dipotassium, dipropionate, disodium, disulfide, edisylate, enanthate, estolate, etabonate, ethylsuccinate, fumarate, furoate, gluceptate, gluconate, hexacetonide, hippurate, hyclate, hydrobromide, hydrochloride, isethionate, lactobionate, malate, maleate, meglumine, methylbromide, methylsulfate, metrizoate, nafate, napsylate, nitrate, oleate, palmitate, pamoate, phenpropionate, phosphate, pivalate, polistirex, polygalacturonate, probutate, propionate, saccharate, sodium glycinate, sodium phosphate, sodium succinate, state, succinate, sulfate, sulfonate, sulfosalicylate,

tartrate, tebutate, terephalate, terephthalate, tosylate, trifluate, trihydrate, trisilicate, tromethamine, valerate, xinafolate, or the like.

[00227] Formulations provided herein exhibit some or 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 K_{ATP} channel opener over a sustained time frame such that the circulating concentration of the K_{ATP} 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 individuals, and (7) they delay release until gastric transit is complete or nearly complete.

[00228] Formulations designed for oral administration can be provided, for example, as capsules or tablets. Capsule or tablet formulations include a number of distinguishing components. One is a component to improve absorption of the K_{ATP} channel opener. Another sustains release of the drug over more than 2 hours. A third delays substantial release of the drug until gastric transit is completed.

[00229] The formulations disclosed herein exhibit improved solubility and absorption of the K_{ATP} channel opener 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 a pharmaceutical salt of the K_{ATP} channel opener, (3) using an ion exchange resin in the formulation, (4) using inclusion complexes, for example using a cyclodextrin, (5) compaction of the K_{ATP} channel opener with a solubilizing agent including low viscosity hypromellose, low viscosity methylcellulose or similarly functioning excipient and combinations thereof, (6) associating the K_{ATP} channel opener with a salt prior to formulation, (7) using a solid dispersion of the K_{ATP} channel opener, (8) using a self emulsifying system, (9) adding one or more surfactants to the formulation, (10) using nanoparticles in the formulation, or (11) combinations of these approaches. Preferably, when the K_{ATP} channel opener is a salt of diazoxide, the salt is not a sodium salt.

[00230] Release of K_{ATP} channel opener over a sustained period of time (2-24 hours) is 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, or (7) the use of a compression coated tablet, or (8) combinations of these approaches.

[00231] Delay of release of K_{ATP} channel openers from the formulation until gastric transit is complete is achieved in the formulations provided herein by any of several mechanisms. A pH sensitive polymer or co-polymer is 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 L100, S100 or L100-55 solids, L30 D-55 or FS 30D dispersions, or the L12,5 or S12,5 organic solutions.

[00232] 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 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."

[00233] Accordingly, delay of release of K_{ATP} channel openers from the invention formulations until after gastric transit is complete is achieved in the formulations provided herein 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 co-polymer 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.

[00234] Formulations are provided that are designed for administration once daily (per 24 hours). These can contain between 25 and 500 mg of K_{ATP} channel openers. Formulations intended for administration twice daily (per 24 hours) are also provided. These can contain between 25 and 250 mg of K_{ATP} channel openers.

[00235] 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, abdominal pain, diarrhea and ileus. Second, by sustaining release of the active drug over 2 or more hours 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.

[00236] Also provided herein are controlled release formulations of K_{ATP} channel openers, 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
	500-2000mg
C. Dosing	Once daily (24 hours)
	Twice daily (24 hours)
D. Release time:	2-4 hrs
	4-8 hrs
	8-24 hours

[00237] For example, a controlled release composition can be a tablet containing 25-100 mg of a K_{ATP} channel opener, such tablet administered 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.

[00238] In addition, any of the above formulations from Table 1 can include at least one feature that improves the solubility or absorption of the K_{ATP} channel opener.

[00239] The controlled release formulations provided herein comprise the active compound (e.g., K_{ATP} channel opener, optionally in combination with growth hormone) and a matrix which comprises a gelling agent that swells upon contact with aqueous fluid. The active compound(s) entrapped within the gel is(are) slowly released into the body upon dissolution of the gel. The active compound(s) 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.

[00240] 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 xanthan 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, hydroxypropyl 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).

[00241] 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 crosslinking agent such as 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.

[00242] 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, dextrans, calcium phosphate, calcium sulphate; and lubricants: stearic acid, magnesium stearate, calcium stearate, Precirol™ and flow aids for example talc or colloidal silicon dioxide.

[00243] 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 co-polymers derived from acrylic or methacrylic acid esters, co-polymers 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, cetoeryl 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.

[00244] 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.

[00245] 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 (co-polymers of acrylic and methacrylic acid esters having a low content (e.g., 1:20 or 1:40) of quaternary ammonium compounds).

[00246] 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.

[00247] 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.

[00248] 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 co-polymer (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 co-polymer, Eudragit RL30D and Eudragit RS30D, carboxyvinyl polymers, polyvinylalcohols, glucans scleroglucans, mannans, and xanthans.

[00249] 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 Aquacoat brand hydroxypropyl methylcellulose acetate succinate. Most of these dispersions are latex, pseudolatex powder or micronized powder mediums.

[00250] 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.

[00251] 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.

[00252] 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, 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.

[00253] The specified tablet or capsule formulations of Table 1 may include co-formulation with an obesity treating drug (in addition to the K_{ATP} channel opener). 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 K_{ATP} channel opener is one half the amount included in the once daily formulation and the coformulated obesity treating drug is half of the amount specified. Alternative obesity treating drugs may include: 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 include protein-tyrosine phosphatase-1B inhibitors, peroxisome proliferator activated receptor- receptor antagonists, short-acting bromocriptine (ergose), somatostatin agonists (octreotide), and adiponectin, gastrointestinal-neural pathway agents, including those that increase cholecystokinin activity, increase glucagon-like peptide-1 activity (extendin 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, phytostanol analogues, amylase inhibitors, growth hormone fragments, synthetic analogues of dehydroepiandrosterone sulfate, antagonists of adipocyte 11 β hydroxysteroid dehydrogenase type 1 activity, corticotropin releasing hormone agonists, inhibitors of fatty acid synthesis, carboxypeptidase inhibitors, indanones/indanols, aminosterols, and other gastrointestinal lipase inhibitors.

[00254] The specified tablet or capsule formulations of Table 1 may include co-formulation with a diabetes treating drug (in addition to the K_{ATP} channel opener). 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), metaglidase (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 the K_{ATP} channel opener is half the amount included in the once daily formulation and the co-formulated diabetes treating drug is half of the amount specified.

[00255] 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 or simvastatin or atorvastatin or fluvastatin or rosuvastatin or lovastatin (all at 10 to 80 mg/unit). These formulations are preferably used once daily. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably 25 to 200 mg/unit and the coformulated cholesterol lowering drug is half of the amount specified.

[00256] 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 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 K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated depression treating drug is half of the amount specified.

[00257] 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), benazepril hydrochloride (10 to 80 mg/unit), quinapril hydrochloride (10 to 80 mg/unit), perindopril 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 (all 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 K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated hypertension treating drug is half of the amount specified.

[00258] 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 (all at 10 to 50 mg/unit), tosemide (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), mythelothiazide (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 K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated diuretic is half of the amount specified.

[00259] 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), fenpropen 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 K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated diuretic is half of the amount specified.

[00260] The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat obesity associated comorbidities 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.

[00261] The specified tablet or capsule formulations of Table 1 may include co-formulation with an anti-psychotic drug the combination used to treat the psychotic condition and to treat or prevent weight gain, dyslipidemia or impaired glucose tolerance in the treated individual. Drugs for treating various psychotic conditions that may be used include, but are not limited to, lithium or a salt thereof (250 to 2500 mg/unit), carbamazepine or a salt thereof

(50 to 1200 mg/unit), valproate, valproic acid, or divalproex (125 to 2500 mg/unit), lamotrigine (12.5 to 200 mg/unit), olanzapine (5 to 20 mg/unit), clozapine (12.5 to 450 mg/unit), or risperidone (0.25 to 4 mg/unit). These coformulations are preferably intended for once per day administration. For a twice daily dosing, the amount of K_{ATP} channel opener is preferably half the amount included in the once daily formulation and the coformulated anti-psychotic is half of the amount specified.

[00262] The specified tablet or capsule formulations of Table 1 may include co-formulation with a drug to treat or prevent ischemic or reperfusion injury. Drugs for treating or preventing ischemic or reperfusion injury that may be used include, but are not limited to: low molecular weight heparins (dalteparin, enoxaparin, nadroparin, tinzaparin or danaparoid), anard, pentoxifylline, nimodipine, flunarizine, ebselen, tirilazad, clomethiazole, an AMPA agonist (GYKI 52466, NBQX, YM90K, zonanpanel, orMPQX), SYM 2081, selfotel, Ceresiat, CP-101,606, dextrophan, dextromethorphan, MK-801, NPS 1502, remacemide, ACEA 1021, GVL50526, eliprodil ifenprodil, lubeluzole, naloxone, nalfemene citicoline, acetyl-L-carnitine, nifedipine, resveratrol, a nitron derivative, clopidogrel, dabigatram, prasugrel, troxoprodil, AGY-94806, or KAI-9803.

[00263] Provided are formulations administered once or twice daily to an obese or overweight subject continuously to result in a circulating concentration of K_{ATP} channel opener sufficient to induce weight loss. Weight loss occurs by the preferential loss of body fat. Additional weight loss can occur when the formulation is administered in combination with a reduced calorie diet.

[00264] Provided are formulations of K_{ATP} channel openers administered as a single dose to an obese, overweight or obesity-prone subject that result in the inhibition of fasting or glucose stimulated insulin secretion for about 24 hours or for about 18 hours.

[00265] Provided are formulations of K_{ATP} channel openers administered as a single dose to an obese, overweight or obesity-prone subject that result in the elevation of energy expenditure for about 24 hours or for about 18 hours.

[00266] Provided are formulations of K_{ATP} channel openers administered as a single dose to an obese, overweight or obesity-prone subject that result in the elevation of beta oxidation of fat for about 24 hours or for about 18 hours.

[00267] Provided are formulations of K_{ATP} channel openers administered as a single dose to an obese, overweight or obesity-prone hyperphagic subject that result in the inhibition of hyperphagia for about 24 hours or for about 18 hours.

[00268] Provided are formulations administered once or twice daily (per 24 hours) to a subject continuously result in a circulating concentration of K_{ATP} channel opener sufficient to induce either beta-cell rest or improved insulin sensitivity or both. Such beta-cell rest and improvements in insulin sensitivity can contribute to effective treatment of type I diabetes, type II diabetes and prediabetes. Such beta-cell rest and improvements in insulin sensitivity can contribute to effective restoration of normal glucose tolerance in type II diabetic and prediabetic subjects.

[00269] The various pharmaceutical K_{ATP} channel opener formulations have a variety of applications, including, but not limited to: (1) treatment of obesity; (2) prevention of weight gain in individuals who are predisposed to obesity; (3) treatment of hyperinsulemia or hyperinsulinism; (4) treatment of hypoglycemia; (5) treatment of hyperlipidemia, (6) treatment of type II diabetes, (7) preservation of pancreatic function in type I diabetics; (8) treatment of metabolic syndrome (or syndrome X); (9) prevention of the transition from prediabetes to diabetes, (10) correction of the defects in insulin secretion and insulin sensitivity contributing to prediabetes and type II diabetes, (11) treatment of polycystic ovary syndrome, (12) prevention of ischemic or reperfusion injury, (13) treat weight gain, dyslipidemia, or impairment of glucose tolerance in subjects treated with antipsychotics drugs, (14) prevent weight gain, dyslipidemia, or impairment of glucose tolerance in subjects treated with antipsychotics drugs and (15) treatment of any disease where hyperlipidemia, hyperinsulemia, hyperinsulinism, hyperlipidemia, hyperphagia or obesity are contributing factors to the severity or progression of the disease, including but not limited to, Prader-Willi Syndrome, Smith-Magenis syndrome, Froelich's syndrome, Cohen syndrome, Summit Syndrome, Alstrom, Syndrome, Borjesen Syndrome, Bardet-Biedl Syndrome, hyperlipoproteinemia type I, II, III, and IV, and the like.

[00270] In one embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage once per 24 hours, optionally in combination with growth hormone, to induce weight loss. In further embodiments, the individual (a) is not a type I diabetic, (b) is not a type II diabetic, (c) is not experiencing chronic, recurrent or drug-

induced hypoglycemia, (d) does not have metabolic syndrome, or (e) is not experiencing malignant hypertension.

[00271] In one embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage twice per 24 hours, optionally in combination with growth hormone, to induce weight loss. This treatment can be the sole treatment to induce weight loss. In further embodiments, the overweight or obese individual (a) does not have an insulin secreting tumor, (b) is not suffering from Poly Cystic Ovary Syndrome, (c) is not a type I diabetic, (d) is not a type II diabetic, (e) does not have metabolic syndrome, (f) is not experiencing chronic recurrent or drug-induced hypoglycemia, (g) has not been treated for schizophrenia with haloperidol, or (h) is not experiencing malignant hypertension. In further embodiments, the overweight or obese adolescent (a) has not been diagnosed as being type I or type II diabetic, (b) is not experiencing chronic, recurrent or drug-induced hypoglycemia, or (c) has not been diagnosed as having metabolic syndrome.

[00272] In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage form three times per 24 hours, optionally in combination with growth hormone, to induce weight loss. This treatment can be the sole treatment to induce weight loss. In further embodiments, the overweight or obese individual (a) does not have an insulin-secreting tumor, (b) is not suffering from Poly Cystic Ovary Syndrome, (c) is not a type I diabetic, (d) is not a type II diabetic, (e) does not have metabolic syndrome, or (f) is not experiencing chronic, recurrent or drug-induced hypoglycemia.

[00273] In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese adolescent as a solid oral dosage form three times per 24 hours, optionally in combination with growth hormone, to induce weight loss. This treatment can be the sole treatment to induce weight loss. In further embodiments, the overweight or obese adolescent is (a) is a type I or type II diabetic, (b) is not experiencing chronic, recurrent or drug-induced hypoglycemia or (c) does not have metabolic syndrome.

[00274] In another embodiment, a K_{ATP} channel opener is administered as a solid oral dosage form three times per 24 hours, optionally in combination with growth hormone, to induce weight loss to an overweight or obese adult who (a) is not simultaneously receiving glucagon injections, triiodothyroxin or furosemide, (b) is not being treated for schizophrenia with haloperidol, or (c) is not experiencing malignant hypertension.

[00275] In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage form four times per 24 hours, optionally in combination with growth hormone, to induce weight loss.

[00276] In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage form administered from one, two, three or four times per 24 hours, optionally in combination with growth hormone, to induce weight loss at a daily dose of 50 to 275 mg. In a further embodiment, the overweight or obese individual (a) is not type I diabetic, (b) is not type II diabetic, (c) is not suffering chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00277] In another embodiment, a K_{ATP} channel opener is administered to an overweight or obese individual as a solid oral dosage form administered from one, two, three or four times per 24 hours, optionally in combination with growth hormone, to induce weight loss at a daily dose of 130 to 275 mg. In a further embodiment, the overweight or obese individual (a) is not type I diabetic, (b) is not type II diabetic, (c) is not suffering chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00278] In another embodiment, a K_{ATP} channel opener is administered to an overweight or obesity prone individual as a solid oral dosage form one, two, three or four times per 24 hours, optionally in combination with growth hormone, to maintain a weight loss, as it is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight. In a further embodiment, the administered daily dose of the K_{ATP} channel opener is 50 to 275 mg.

[00279] In other embodiments, a K_{ATP} channel opener is administered as a solid oral dosage form to an overweight, obese, or obesity prone individual, optionally in combination with growth hormone, to (a) elevate energy expenditure, (b) elevate beta oxidation of fat, or (c) reduce circulating triglyceride concentrations.

[00280] In other embodiments, a solid oral dosage of a K_{ATP} channel opener is administered on a prolonged basis to an individual in need thereof to induce the loss of 25%, 50%, or 75% of initial body fat.

[00281] In another embodiment, a solid oral dosage of a K_{ATP} channel opener is administered on a prolonged basis to an individual in need thereof, optionally in combination

with growth hormone, to induce (a) the preferential loss of body fat or (b) the preferential loss of visceral body fat.

[00282] In additional embodiments, a solid oral dosage of a K_{ATP} channel opener is administered on a prolonged basis one, two or three times per 24 hours at daily doses of 50 to 275 mg to an individual, optionally in combination with growth hormone, to (a) induce the loss of 25%, 50% or 75% of initial body fat, (b) induce the preferential loss of body fat, or (c) induce the preferential loss of visceral fat.

[00283] In another embodiment, a solid oral dosage of a K_{ATP} channel opener is administered to an individual, optionally in combination with growth hormone, to induce the preferential loss of body fat and to induce reduction in circulating triglycerides.

[00284] In another embodiment, a solid oral dosage of a K_{ATP} channel opener is co-administered with growth hormone.

[00285] In yet another embodiment, a solid oral dosage of a K_{ATP} channel opener is co-administered with growth hormone and optionally one or more of sibutramine, orlistat, rimonabant, an appetite suppressant, an anti-depressant, an anti-epileptic, a diuretic that is not furosemide, a drug that induces weight loss by a mechanism that is distinct from a K_{ATP} channel opener, a drug that induces weight loss by a mechanism that is distinct from a K_{ATP} channel opener but is not metformin, furosemide or triiodothyroxin, or a drug that lowers blood pressure, to induce weight loss and/or treat obesity associated comorbidities in an overweight, obese, or obesity prone individual. In further embodiments, the overweight, obese, or obesity prone individual (a) is a type I diabetic, (b) is not a type II diabetic, (c) is not suffering from chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00286] In another embodiment a solid oral dosage of a K_{ATP} channel opener is co-administered with growth hormone and optionally one or more of an anti-depressant, a drug that lowers blood pressure, a drug that lowers cholesterol, a drug that raises HDL, an anti-inflammatory that is not a Cox-2 inhibitor, a drug that lowers circulating triglycerides, to an overweight, obese, or obesity prone individual to induce weight loss and/or treat obesity associated comorbidities. In further embodiments, the overweight, obese, or obesity prone individual (a) is not a type I diabetic, (b) is not a type II diabetic, (c) is not suffering from chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00287] In another embodiment, a solid oral dosage of a K_{ATP} channel opener is co-administered with growth hormone and optionally one or more of a drug that lowers blood pressure, a drug that lowers cholesterol, a drug that raises HDL, an anti-inflammatory that is not a Cox-2 inhibitor, a drug that lowers circulating triglycerides, to maintain weight and/or treat obesity associated comorbidities in an overweight, obese, or obesity prone individual, as it is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight. In further embodiments, the overweight, obese, or obesity prone individual (a) is not a type I diabetic, (b) is not a type II diabetic, (c) is not suffering from chronic, recurrent or drug-induced hypoglycemia, or (d) does not have metabolic syndrome.

[00288] In additional embodiments, a tablet formulation of a K_{ATP} channel opener is used to administer a therapeutically effective dose of a K_{ATP} channel opener to an obese, overweight or obesity prone individual in need thereof to treat obesity, to (a) provide beta cell rest, (b) treat type I or type II diabetes, or (c) prevent the occurrence of diabetes.

[00289] In additional embodiments, a solid oral dosage form or tablet formulation of a K_{ATP} channel opener is co-administered with growth hormone and optionally one or more of Phentermine or a derivative thereof to an obese adult or adolescent to induce weight loss and/or treat obesity and obesity-associated co-morbidities. In further embodiments, a solid oral dosage form or tablet formulation of a K_{ATP} channel opener is co-administered with Phentermine or a derivative, optionally in combination with growth hormone, thereof to an obese adult or adolescent to treat metabolic syndrome in a patient in need thereof.

[00290] In further embodiments, a pharmaceutically acceptable formulation of a K_{ATP} channel opener at doses of 50 to 275 mg/day is co-administered with growth hormone and optionally one or more of Phentermine or a derivative thereof at daily doses of 15 to 37.5 mg to an overweight or obese individual to induce weight loss, to treat metabolic syndrome, or to induce weight loss and treat obesity-associated co-morbidities. In another embodiment, a tablet formulation is co-administered with growth hormone and optionally one or more of Phentermine or a derivative thereof to treat metabolic syndrome in a patient.

[00291] In another embodiment, a quick dissolving formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is used to provide a therapeutically effective dose to a patient in need thereof.

[00292] In further embodiments, a K_{ATP} channel opener is administered, optionally in combination with growth hormone, once per 24 hours at doses of 125 mg to 275 mg to an overweight or obese individual who is not type II diabetic and is not being treated for nighttime hypoglycemia.

[00293] In further embodiments, a K_{ATP} channel opener is formulated as a tablet or capsule for oral administration. The tablet or capsule may be co-formulated with metformin. In another embodiment, a K_{ATP} channel opener is formulated as an oral suspension, and the oral suspension may be further encapsulated in another embodiment.

[00294] In another embodiment, a pharmaceutical salt of a K_{ATP} channel opener is formulated as a tablet or capsule for oral administration, or as an oral suspension or as an oral solution, or as an oral solution that is encapsulated. If the opener is diazoxide, the salt, is preferably not a sodium salt.

[00295] In another embodiment a K_{ATP} channel opener is co-formulated with hydrochlorothiazide, chlorothiazide, cyclothiazide, benzthiazide, metyclothiazide, bendroflumethiazide, hydroflumethiazide, trichlormethiazide, or polythiazide in a pharmaceutical formulation suitable for oral administration.

[00296] Upon administration of the formulations provided herein to humans or animals, some or all of the following effects are observed: (1) the production of lipoprotein lipase by adipocytes is reduced; (2) enhanced lipolysis by adipocytes; (3) expression of fatty acid synthase by adipocytes is reduced; (4) glyceraldehydes phosphate dehydrogenase activity of adipocytes is reduced; (5) little or no new triglycerides are synthesized and stored by adipocytes; (6) enhanced expression of β_3 Adrenergic Receptor (β_3AR) an improvement in the adrenergic function in adipocytes; (7) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (8) decreased insulinemia; (9) enhanced blood glucose levels; (10) increased expression of Uncoupling Protein 1 in adipocytes; (11) enhanced thermogenesis in white and brown adipose tissue; (12) reduction of plasma triglyceride concentration; (13) decrease in circulating leptin concentrations; (14) up-regulation of insulin receptors; (15) enhanced glucose uptake; (16) reduced adipocyte hyperplasia; (17) reduced adipocyte hypertrophy; (18) reduced rates of conversion of preadipocytes to adipocytes; (19) reduced rates of hyperphagia, (20) increased protection of CNS, cardiac and other tissues from ischemic or reperfusion injury, (21) improved insulin sensitivity, (22) elevated CSF insulin

concentrations, (23) elevated circulating adiponectin concentrations, (25) reduced circulating triglyceride concentrations, (26) enhancement of beta-cell rest, and/or (27) increase in lean body mass.

[00297] Threshold concentrations of the current invention include those circulating concentrations of K_{ATP} channel openers, optionally in combination with growth hormone, resulting from the administration of the drug as an i.v. formulation, an immediate release oral formulation, a controlled release formulation, a transdermal formulation, or an intranasal formulation to an overweight or obese individual which results in (1) measurable suppression of fasting insulin levels, (2) suppression of fasting insulin levels by at least 20% from the baseline measurement in the same individual prior to treatment with a K_{ATP} channel openers, (3) suppression of fasting insulin levels by at least 30% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (4) suppression of fasting insulin levels by at least 40% from the baseline measurement in the same individual prior to treatment with a K_{ATP} channel openers, (5) suppression of fasting insulin levels by at least 50% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (6) suppression of fasting insulin levels by at least 60% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (7) suppression of fasting insulin levels by at least 70% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (8) suppression of fasting insulin levels by at least 80% from the baseline measurement in the same individual prior to treatment with K_{ATP} channel openers, (9) loss of weight, (10) elevation of resting energy expenditure, or (11) elevation of the oxidation of fat or fatty acids.

[00298] Threshold effects of the current invention include those circulating concentrations of K_{ATP} channel openers resulting from the administration of an i.v. formulation of the drug, or an immediate release oral formulation of the drug, or a controlled release formulation of the drug, or a sustained release formulation, or a transdermal formulation, or an intranasal formulation of the drug to an obesity prone individual which result in (1) the loss of weight, and (2) the maintenance of weight.

[00299] Threshold effects of the current invention include those circulating concentrations of K_{ATP} channel openers resulting from the administration of an i.v. formulation of the drug, or an immediate release oral formulation of the drug, or a controlled release formulation of the drug, or a sustained release formulation, or a transdermal formulation, or an intranasal

formulation of the drug to a prediabetic individual which result in prevention of the transition to diabetes.

[00300] Threshold effects of the current invention include those circulating concentrations of K_{ATP} channel openers resulting from the administration of an i.v. formulation of the drug, or an immediate release oral formulation of the drug, or a controlled release formulation of the drug, or a sustained release formulation, or a transdermal formulation, or an intranasal formulation of the drug to a individual with type 1 diabetes which result in beta cell rest.

[00301] The mode of action by which weight is maintained or lost resulting from the prolonged administration of K_{ATP} channel openers to overweight, obese or obesity prone individuals as provided herein includes, but is not limited to one or more of (1) enhanced energy expenditure, (2) enhanced oxidation of fat and fatty acids, (3) the enhancement of lipolysis in adipose tissue, (4) enhanced glucose uptake by tissues, enhanced insulin sensitivity, (5) improved beta adrenergic response, and (6) increase in lean body mass. The mode of action by which weight is maintained or lost resulting from the prolonged administration of K_{ATP} channel openers to obese or obesity prone individuals as provided herein may also include the suppression of appetite.

[00302] Prolonged administration of pharmaceutical formulations of K_{ATP} channel openers to overweight or obese humans or animals, optionally in combination with growth hormone, results in substantial and sustained weight loss including some or all of the following effects: (1) preferential loss of body fat; (2) loss of greater than 25% of initial body fat mass; (3) loss of greater than 50% of initial body fat mass; (4) loss of greater than 75% of initial body fat mass; (5) significant increase in resting energy expenditure; (6) increase in the oxidation of fat and fatty acids; (7) reduction in blood pressure; (8) production of lipoprotein lipase by adipocytes is reduced; (9) enhanced lipolysis by adipocytes; (10) expression of fatty acid synthase by adipocytes is reduced; (11) glyceraldehydes phosphate dehydrogenase activity of adipocytes is reduced; (12) little or no new triglycerides are synthesized and stored by adipocytes; (13) enhanced expression of β_1 Adrenergic Receptor (β_1AR) and an improvement in the adrenergic function in adipocytes; (14) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (15) decreased insulinemia; (16) enhanced blood glucose levels; (17) increased expression of Uncoupling Protein 1 in adipocytes; (18) enhanced thermogenesis in white and brown adipose tissue; (19) reduction of plasma triglyceride concentration; (20) decrease in circulating leptin concentrations; (21) up-regulation of insulin receptors; (22)

enhanced glucose uptake; (23) reduced adipocyte hyperplasia; (24) reduced adipocyte hypertrophy; (25) reduced rates of conversion of preadipocytes to adipocytes; (26) reduced rates of hyperphagia; (27) the sequential loss first of the metabolically most active adipose tissue (visceral), followed by the loss of less metabolically active adipose tissue, (28) elevation of circulating adiponectin concentrations, (29) elevation of cerebrospinal fluid insulin levels, (30) enhanced islet insulin mRNA and insulin content, (31) enhanced metabolic efficiency of insulin, or (32) increase in lean body mass.

[00303] Prolonged administration of formulations of K_{ATP} channel openers, optionally in combination with growth hormone, to obesity prone humans or animals, including individuals who have undergone various types of bariatric surgery, results in sustained maintenance of weight including some or all of the following effects: (1) increased resting energy expenditure; (2) increase in the oxidation of fat and fatty acids; (3) reduction in blood pressure; (4) production of lipoprotein lipase by adipocytes is reduced; (5) enhanced lipolysis by adipocytes; (6) expression of fatty acid synthase by adipocytes is reduced; (7) glyceraldehyde phosphate dehydrogenase activity of adipocytes is reduced; (8) little or no new triglycerides are synthesized and stored by adipocytes; (9) enhanced expression of β_3 Adrenergic Receptor (β_3AR) and improvement in the adrenergic function in adipocytes; (10) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (11) decreased insulinemia; (12) enhanced blood glucose levels; (13) increased expression of Uncoupling Protein 1 in adipocytes; (14) enhanced thermogenesis in white and brown adipose tissue; (15) reduction of plasma triglyceride concentration; (16) decreased circulating leptin concentration; (17) up-regulation of insulin receptors; (18) enhanced glucose uptake; (19) reduced adipocyte hyperplasia; (20) reduced adipocyte hypertrophy; (21) reduced rates of conversion of preadipocytes to adipocytes; and (22) reduced rates of hyperphagia, (23) elevated circulating adiponectin concentration, (24) elevated cerebrospinal fluid insulin levels, (25) enhanced islet insulin mRNA and insulin content, or (26) enhanced metabolic efficiency of insulin.

[00304] Immediate or prolonged administration of formulations of K_{ATP} channel openers, optionally in combination with growth hormone, to prediabetic or type I diabetic humans or animals results in the prevention of beta cell failure, improved glycemic control, and prevention of the transition from prediabetes to diabetes including some or all of the following effects: (1) increase in resting energy expenditure; (2) increase in the oxidation of

fat and fatty acids; (3) reduction in blood pressure; (4) production of lipoprotein lipase by adipocytes is reduced; (5) enhanced lipolysis by adipocytes; (6) expression of fatty acid synthase by adipocytes is reduced; (7) glyceraldehyde phosphate dehydrogenase activity of adipocytes is reduced; (8) little or no new triglycerides are synthesized and stored by adipocytes; (9) enhanced expression of β_3 Adrenergic Receptor (β_3 AR) and an improvement in the adrenergic function in adipocytes; (10) reduced glucose stimulated secretion of insulin by pancreatic B-cells; (11) decreased insulinemia; (12) enhanced blood glucose levels; (13) increased expression of Uncoupling Protein 1 in adipocytes; (14) enhanced thermogenesis in white and brown adipose tissue; (15) reduction of plasma triglyceride concentration; (16) decreased circulating leptin concentrations; (17) up-regulation of insulin receptors; (18) enhanced glucose uptake; (19) reduced adipocyte hyperplasia; (20) reduced adipocyte hypertrophy; (21) reduced rates of conversion of preadipocytes to adipocytes; (22) reduced rates of hyperphagia, (23) elevated circulating adiponectin concentrations, (24) elevated cerebrospinal fluid insulin levels, (25) enhanced islet insulin mRNA and insulin content, or (26) enhanced metabolic efficiency of insulin.

[00305] Immediate or prolonged administration of formulations of K_{ATP} channel openers, optionally in combination with growth hormone, to humans or animals that are at risk for myocardial infarct, or stroke or undergoing a surgical procedure that restores blood flow to heart or brain results in improved therapeutic outcomes post-surgically, or following the occurrence of myocardial infarct or stroke by improving the survival of tissue after blood flow is restored, reduced stunning of tissue, and altering the nature of the inflammatory responses.

[00306] Pharmaceutical formulations as provided herein are designed to be used in the treatment of obesity, hyperlipidemia, hypertension, weight maintenance, type I diabetes, prediabetes, type II diabetes, or any condition where weight loss, reduction in circulating triglycerides or beta cell rest contributes to therapeutic outcomes provide for a range of critical changes in pharmacodynamic and pharmacokinetic responses to administered doses of K_{ATP} channel openers, optionally in combination with growth hormone, which changes include one or more of the following: (1) extending the pharmacodynamic effect of an administered dose to greater than 24 hours as measured by the suppression of insulin secretion, (2) providing for substantial uptake of the active pharmaceutical ingredient in the small intestine, (3) providing for substantial uptake of the active pharmaceutical ingredient in

the large intestine, (4) result in lowered C_{max} versus current oral suspension or capsule products for the same administered dose of active pharmaceutical ingredient, (5) provide for circulating concentrations of unbound active pharmaceutical ingredient above threshold concentrations for 24 or more hours from a single administered dose, and (6) provide for more consistent drug absorption by treated individuals as compared to existing capsule formulations.

[00307] Pharmaceutical co-formulations of the current invention designed to treat a range of conditions in humans and animals include the combination of K_{ATP} channel openers with growth hormone and optionally one or more of: (1) a diuretic, (2) a drug that lowers blood pressure, (3) a drug that suppresses appetite, (4) a cannabinoid receptor antagonist, (5) a drug that suppresses that action of gastric lipases, (6) any drug that is used to induce weight loss, (7) a drug that lowers cholesterol, (8) a drug that lowers LDL bound cholesterol, (9) a drug that improves insulin sensitivity, (10) a drug that improves glucose utilization or uptake, (11) a drug that reduces incidence of atherosclerotic plaque, (12) a drug that reduces inflammation, (13) a drug that is antidepressant, (14) a drug that is an anti-epileptic, or (15) a drug that is an anti-psychotic.

[00308] Treatment of humans or animals of the current invention using pharmaceutical formulations of K_{ATP} channel openers, optionally in combination with growth hormone, result in reduced incidence of adverse side effects including but not limited to edema, fluid retention, reduced rates of excretion of sodium, chloride, and uric acid, hyperglycemia, ketoacidosis, nausea, vomiting, dyspepsia, ileus and headaches. These reductions in frequency of adverse side effects are achieved by: (1) initiating dosing of individuals at subtherapeutic doses and in a step wise manner increasing the dose daily until the therapeutic dose is achieved where the number of days over which the step up in dose is effected is 2 to 10, (2) use of the lowest effective dose to achieve the desired therapeutic effect, (3) use of a pharmaceutical formulation that delays release of active until gastric transit is complete, (4) use of a pharmaceutical formulation that delays release of active until gastric transit is complete, (5) use of a pharmaceutical formulation that results in lower circulating peak drug levels as compared to an immediate release oral suspension or capsule formulation for the same administered dose, and (6) optimizing the timing of administration of dose within the day and relative to meals.

[00309] Treatment of patients suffering from Prader-Willi Syndrome, Smith-Magenis syndrome, Froelich's syndrome, Cohen syndrome, Summit Syndrome, Alstrom, Syndrome, Borjesen Syndrome, Bardet-Biedl Syndrome, and hyperlipoproteinemia type I, II, III, and IV with the current invention using pharmaceutical formulations of K_{ATP} channel openers, optionally in combination with growth hormone, result in some or all of the following therapeutic outcomes: (1) weight loss, (2) reduced rates of weight gain, (3) inhibition of hyperphagia, (4) reduced incidence of impaired glucose tolerance, prediabetes or diabetes, (5) reduced incidence of congestive heart failure, (6) reduced hypertension, and (7) reduced rates of all cause mortality.

[00310] Treatment of prediabetic subjects with the current invention using pharmaceutical formulations of K_{ATP} channel openers, optionally in combination with growth hormone, result in some or all of the following therapeutic outcomes: (1) weight loss, (2) restoration of normal glucose tolerance, (3) delayed rates of progression to diabetes, (4) reduced hypertension, and (5) reduced rates of all cause mortality.

[00311] Treatment of diabetic subjects with the current invention using pharmaceutical formulations of K_{ATP} channel openers, optionally in combination with growth hormone, result in some or all of the following therapeutic outcomes: (1) weight loss, (2) restoration of normal glucose tolerance, (3) delayed rates of progression of diabetes, (4) improvements in glucose tolerance, (5) reduced hypertension, and (6) reduced rates of all cause mortality.

[00312] Co-administration of drugs with formulations of K_{ATP} channel openers in the treatment of diseases of overweight, obese or obesity prone human and animal subjects involves the co-administration of a pharmaceutically acceptable formulation of K_{ATP} channel openers with an acceptable formulation of growth hormone and optionally one or more of: (1) Sibutramine, (2) orlistat, (3) Rimonabant, (4) a drug that is an appetite suppressant, (5) any drug used to induce weight loss in an obese or overweight individual, (6) a non-thiazide diuretic, (7) a drug that lowers cholesterol, (8) a drug that raises HDL cholesterol, (9) a drug that lowers LDL cholesterol, (10) a drug that lowers blood pressure, (11) a drug that is an anti-depressant, (12) a drug that improves insulin sensitivity, (13) a drug that improves glucose utilization and uptake (14) a drug that is an anti-epileptic, (15) a drug that is an anti-inflammatory, or (16) a drug that lowers circulating triglycerides.

[00313] Co-administration of drugs with formulations of K_{ATP} channel openers in the treatment or prevention of weight gain, dyslipidemia, or impaired glucose tolerance in subjects treated with antipsychotics drugs involve the co-administration of a pharmaceutically acceptable formulation of K_{ATP} channel openers with growth hormone and optionally one or more of an acceptable formulation of: lithium, carbamazepine, valproic acid and divalproex, and lamotrigine, antidepressants generally classified as monoamine oxidase inhibitors including isocarboxazid, phenelzine sulfate and tranylcypromine sulfate, tricyclic antidepressants including doxepin, clomipramine, amitriptyline, maprotiline, desipramine, nortriptyline, desipramine, doxepin, trimipramine, imipramine and protriptyline, tetracyclic antidepressants including mianserin, mirtazapine, maprotiline, oxaprotiline, desipramine, levoprotline, trifluorcarbine, setipiline, lortetiline, azipramine, aptazapine maleate and pirlindole, and major tranquilizers and atypical antipsychotics including paloproxidol, perphenazine, thioridazine, risperidone, clozapine, olanzapine and chlorpromazine.

[00314] In one embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to measurably reduce fasting insulin levels for a prolonged period. Preferably the K_{ATP} channel opener formulation reduces fasting insulin levels by at least 20%, more preferably by at least 30%, more preferably by at least 40%, more preferably by at least 50%, more preferably by at least 60% more preferably by at least 70%, and more preferably by at least 80%. Fasting insulin levels are commonly measured using the glucose tolerance test (OGTT). After an overnight fast, a patient ingests a known amount of glucose. Initial glucose levels are determined by measuring pre-test glucose levels in blood and urine. Blood insulin levels are measured by a blood is draw every hour after the glucose is consumed for up to three hours. In a fasting glucose assay individuals with plasma glucose values greater than 200 mg/dl at 2 hours post-glucose load indicate an impaired glucose tolerance.

[00315] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal

formulation or an intranasal formulation to reach and maintain the threshold concentration required to induce weight loss for a prolonged period.

[00316] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to elevate resting energy expenditure for a prolonged period.

[00317] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to elevate fat and fatty acid oxidation for a prolonged period.

[00318] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an obesity prone individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to induce weight loss for a prolonged period.

[00319] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an obesity prone individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain the threshold concentration required to maintain weight for a prolonged period.

[00320] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to induce weight loss for a prolonged period.

[00321] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal

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

[00322] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation for a prolonged period of time to preferentially reduce visceral fat deposits.

[00323] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation for a prolonged period of time to reduce visceral fat depots and other fat deposits.

[00324] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to a normoinsulemic overweight or obese individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to induce weight loss for a prolonged period.

[00325] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to a prediabetic individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to prevent the transition to diabetes for a prolonged period.

[00326] In another embodiment, a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to a type 1 diabetic individual as an oral suspension, or an immediate release capsule or tablet or a controlled release formulation or a transdermal formulation or an intranasal formulation to reach and maintain a drug concentration above the threshold concentration required to induce beta cell rest for a prolonged period.

[00327] In another embodiment, a single dose of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is

administered to an individual in need thereof that results in circulating concentration of active drug sufficient to diminish the secretion of insulin for 24 or more hours.

[00328] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to diminish the secretion of insulin on a continuous basis.

[00329] In another embodiment, a single dose of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an individual in need thereof that results in circulating concentration of active drug sufficient to elevate non-esterified fatty acids in circulation for 24 or more hours.

[00330] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to elevate non-esterified fatty acids in circulation on a continuous basis.

[00331] In another embodiment, a single dose of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an individual in need thereof that results in circulating concentration of active drug sufficient to treat hypoglycemia in circulation for 24 or more hours.

[00332] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to treat hypoglycemia on a continuous basis.

[00333] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to induce weight loss on a continuous basis.

[00334] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to maintain weight on a continuous basis, as it is preferable to maintain weight in an obese individual once some weight loss has occurred when the alternative is to regain weight.

[00335] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to reduce circulating triglyceride levels on a continuous basis.

[00336] In another embodiment, a single dose of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered to an individual in need thereof that results in circulating concentration of active drug sufficient to reduce or prevent ischemic or reperfusion injury in circulation for 24 or more hours.

[00337] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is administered over a prolonged basis to an individual in need thereof no more than once per 24 hours that results in circulating concentration of active drug sufficient to reduce or prevent ischemic or reperfusion injury on a continuous basis.

[00338] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of diazoxide or its derivatives that is administered to an individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached.

[00339] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener that is administered to an

individual in need thereof on a daily basis in which the active ingredient is not released from the formulation until gastric transit is complete.

[00340] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener that is administered to an individual in need thereof on a daily basis in which the active ingredient is not released from the formulation until gastric transit is complete.

[00341] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an individual in need thereof on a daily basis in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation.

[00342] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete and in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation.

[00343] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an overweight or obese individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the

administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 2.5 mg/kg/day.

[00344] In another embodiment, the adverse effects of frequent treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an overweight or obese individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 1.75 mg/kg/day.

[00345] In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide near zero order release for at least 12 hours.

[00346] In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide near zero order release for at least 18 hours.

[00347] In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 12 hours.

[00348] In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in

which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 18 hours.

[00349] In another embodiment, the treatment of an overweight or obese individual is optimized for weight loss by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to match the pattern of basal insulin secretion.

[00350] In another embodiment, the frequency of adverse effects upon treatment with a K_{ATP} channel opener is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an obesity prone individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 2.5 mg/kg/day.

[00351] In another embodiment, the frequency of adverse effects upon treatment with a K_{ATP} channel opener, optionally in combination with growth hormone, is reduced using a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, that is administered to an obesity prone individual in need thereof on a daily basis in which the first dose is known to be subtherapeutic and daily dose is subsequently increased stepwise until the therapeutic dose is reached, the active ingredient is not released from the formulation until gastric transit is complete, in which the maximum circulating concentration of active ingredient is lower than what would be realized by the administration of the same dose using an oral suspension or capsule formulation, and in which the maximum dose is less than 1.75 mg/kg/day.

[00352] In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide near zero order release for at least 12 hours.

[00353] In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide near zero order release for at least 18 hours.

[00354] In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 12 hours.

[00355] In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to provide a rising drug concentration in circulation for at least 18 hours.

[00356] In another embodiment, the treatment of an obesity prone individual is optimized for weight maintenance by administration of a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, once per 24 hours in which the release of the active ingredient from the formulation has been modified to match the pattern of basal insulin secretion.

[00357] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with sibutramine to an overweight or obese individual to induce weight loss.

[00358] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with orlistat to an overweight or obese individual to induce weight loss.

[00359] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with rimonabant to an overweight or obese individual to induce weight loss.

[00360] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with an appetite suppressant to an overweight or obese individual to induce weight loss.

[00361] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with an anti-depressant to an overweight or obese individual to induce weight loss.

[00362] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with anti-epileptic to an overweight or obese individual to induce weight loss.

[00363] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a non-thiazide diuretic to an overweight or obese individual to induce weight loss.

[00364] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that induces weight loss by a mechanism that is distinct from diazoxide to an overweight or obese individual to induce weight loss.

[00365] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that lowers blood pressure to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

[00366] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that lowers cholesterol to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.

[00367] In another embodiment, a pharmaceutically acceptable formulation of a K_{ATP} channel opener, optionally in combination with growth hormone, is co-administered with a drug that raises HDL associated cholesterol to an overweight, obesity prone or obese individual to induce weight loss and treat obesity associated comorbidities.