

COMPOSITIONS AND METHODS FOR IMPROVING THE SOLUBILITY OF INSULIN, INSULIN ANALOGS, AND A1C OR GLUCOSE REGULATORY COMPOUNDS

TECHNICAL FIELD

[0001] Disclosed are water-soluble complexes of a non-nutritive sugar such as a diterpene glycoside (DTG), diterpene di-glycoside (“DDG”) or other non-nutritive sugar and/or a surfactant with a drug compound, which may or may not be poorly soluble, that is involved in regulating blood glucose and/or A1C levels in subjects, wherein the complex significantly enhances the solubility of compounds. Also disclosed are methods for making such complexes and pharmaceutical compositions comprising such water-soluble sugar-drug complexes.

REFERENCE TO RELATED APPLICATIONS

[0002] This International PCT Application claims benefit of and priority to U.S. Provisional Applications 63/539,788, 63/613,443, 63/662,263, and 63/673,012, filed respectively on September 21, 2023, December 21, 2023, June 20, 2024, and July 18, 2024, the contents of each of which are incorporated herein for all purposes.

BACKGROUND

[0003] The solubility of many compounds can play a critical role in their commercial utility, especially in the pharmaceutical industry. Compound solubility plays an important role in the compound’s effectiveness as a drug, especially in a number of essential pharmacokinetic properties. Poor drug solubility can lead directly to insufficient uptake, poor C_{max} properties (e.g., maximum blood concentration and time until maximum blood concentration), and the like. If a drug is not sufficiently soluble, it may not be fully absorbed into a subject’s blood circulation, which leads to insufficient C_{max} to be efficacious (e.g., Ganesan et al., “Solubility: a speed-breaker on the drug discovery highway,” *Bioequiv. Availab.* 3(3): 56-8, 2017, Editorial).

[0004] Insulin is an essential drug for many insulin-dependent diabetics without which these patients lack control of their blood sugar and ultimately die. Human insulin is now available from several manufacturers and, in all cases, must be stored with refrigeration to prevent protein degradation. Conventional insulin is delivered by injection which can occur

several times a day resulting in an increased risk of injection site infection. Recently, orally-deliverable insulin has been introduced which is stabilized against degradation in the gastrointestinal tract. A possible system for oral insulin delivery in the colon has been described (Martínez-López et al. “Arabinoxylans-Based Oral Insulin Delivery System Targeting the Colon: Simulation in a Human Intestinal Microbial Ecosystem and Evaluation in Diabetic Rats.” *Pharmaceuticals (Basel)*. 2022 Aug 26; 15(9): 1062). A recent review describes advances in material design for materials that might be useful for oral insulin delivery (Ji, K., et al. “Material design for oral insulin delivery.” *Med-X 1*, 7 (2023)). However, there appears to be no long-acting, orally deliverable insulin especially such a formulation of insulin that exhibits stability at room temperature for over 24 hours or more.

[0005] The use of long-acting insulin to maintain a basal level of the drug in the patient requires both refrigeration of the insulin, as well as patient injection for administration. The ability to provide long-acting insulin in an orally deliverable form, as well as without the need to refrigerate the insulin during at least the day it is to be administered, would present a significant improvement over currently available commercial insulin products.

[0006] Identifying a methodology that renders drug compounds, including poorly soluble drug compounds, such as insulin and insulin analogs (e.g., human insulin and human homologs such as HUMALOG®), substantially more soluble in aqueous environments remains needed.

[0007] Other compounds contemplated herein for creating more soluble complexes are those compounds that can reduce blood glucose and/or A1C levels in a subject. Such compounds include agonists of the glucagon-like peptide-1 (GLP-1) and also the glucose-dependent insulinotropic polypeptide (GIP) as well as GLP-1/GIP dual agonists. Additional compounds are amylin agonists and glucagon regulatory agents. Such agonists need improvement for their solubility whether they are in their free form, salt forms, or another related form of the compounds.

SUMMARY

[0008] Provided herein are complexes (sometimes also referred to in a related provisional application as an aggregate) of one or more diterpene glycosides which includes diterpene di-glycosides (DDG) with a drug compound wherein the drug is insulin or an insulin analog, and wherein the solubility of the complex is significantly enhanced as compared to the drug compound alone (e.g., not in the complex). The water-soluble complexes described herein

employ drug compounds which are generally pharmaceutical compounds having at least one heteroatom capable of forming a hydrogen bond with the DTG, DDG, or other non-nutritive sugar (and optionally with a surfactant in the complex as discussed herein). Not to be bound by a theory, it is believed that upon aggregation (e.g., complexation) of the sugar (and optionally with a surfactant in the complex as discussed herein) with the drug compound, a stable complex (e.g., complex) occurs, presumably by non-covalent hydrogen bonding and optionally hydrophobic-hydrophobic interactions, such as van der Waal forces. Insulin is characterized as insoluble in water at a physiological pH but dissolves relatively rapidly in plasma. Insulin is known to form zinc-containing hexamers, which are insoluble. Human insulin in mature form consists of two peptide chains – A chain and B chain, that are linked to each other by disulfide bonds (UniProt P01308 INS-HUMAN).

[0009] As is well known, the sugar portion of a DTG, DDG or non-nutritive sugar has a plurality of hydroxyl functionality capable of forming hydrogen bonds. In some cases, certain sugars may also contain a carboxyl group (e.g., sialic acid, glucuronic acid, etc.), an amino group (e.g., glucosamine), or a N-acetyl group (e.g., N-acetylglucosamine), each of which is capable of forming hydrogen bonds. The presence of such functionality allows DTGs, DDGs, or non-nutritive sugars to participate in hydrogen bonding with a drug compound containing at least one heteroatom that is capable of forming hydrogen bonds with the DTGs, DDGs, or other non-nutritive sugar.

[0010] Without being limited by any theory, the contemplated mode of action utilizes the plurality of hydroxyl groups on the sugar units in the DTG, DDGs, or other non-nutritive sugar to create a multiplicity of points for aggregation and/or complexation between the hydroxyl functionality of the sugar units on the DTGs or other non-nutritive sugars and heteroatoms of the drug that individually do not create sufficient adhesion to maintain a stable complex. Through aggregation, a cumulative amount of adhesion is achieved which provides for a stable complex. In addition, the diterpene glycoside and the listed other sugars are believed to use hydrophobic-hydrophobic interactions with the drug compound that provides for regions of hydrophobic and hydrophilic binding elements. It is further contemplated that these hydrophobic and hydrophilic regions will partition into the hydrophobic interactions being maintained in the interior of the complex while the exterior of the complex displays hydrophilic interactions rendering the complex soluble in aqueous solutions.

[0011] Disclosed are water-soluble complexes of a diterpene di-glycoside (“DDG”) with human insulin or insulin analog wherein the complexes are capable of oral delivery to

patients who are insulin-dependent, which is a subset of DTGs. The complexes are stable at room temperature for at least about 24 hours or more, at least 48 hours, or at least 96 hours. In one embodiment, methods are provided to maintain a basal level of insulin (or insulin analog) in an insulin-dependent patient using the complexes disclosed herein. In another embodiment, methods are provided wherein the complexes are used to control the patient's glycosylated hemoglobin by maintaining a basal level of insulin or insulin analog.

[0012] One embodiment discloses a water-soluble complex comprising a sugar (and optionally with a surfactant in the complex as discussed herein) and a drug compound, which water-soluble complex comprises: a molar ratio of up to about 12 moles of the sugar for each mole of the drug compound, wherein the sugar is one or more of rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A, provided that the water-soluble complex has at least a two (2), three (3), four (4) or five (5) fold increase in the water solubility of the drug compound at 20 °C. as compared to the water solubility of the drug compound not in the water-soluble complex; and further, provided that a maximum amount of the sugar in a daily unit dose of the water-soluble complex is no more than about 10 mg/kg, wherein the drug compound is peptide or small compound for reducing blood glucose in a subject and/or blood A1C, wherein the drug compound is insulin, an insulin analog, a natural insulin variant, a GLP-1 receptor agonist, an incretin mimetic, a GIP agonist, an amylin agonist, a glucagon agonist, or a salt thereof.

[0013] When the drug compound in the water-soluble complex is an insulin analog, it can be any of insulin lispro, insulin aspart, insulin glulisine, admelog, NPH insulin, insulin isophane, insulin glargine, insulin detemir, or insulin degludec. The drug compound can also be an A1C-regulating drug compound. If the drug compound is an insulin or insulin analog it can be rapid-acting insulin, short-acting insulin, intermediate-acting insulin, long-acting insulin, or an ultra-long-acting insulin. Generally, ultra-long-acting insulin reaches the bloodstream in 6 hours, does not peak, and lasts about 36 hours or longer (e.g., glargine U-300, Toujeo). A long-acting insulin starts to work after 30 minutes to about 4 hours and lasts up to 16-24 hours. Regular insulin is considered shorting-acting insulin; onset after administration is usually within 1 hour and peaks at around 2 to about 4 hours after administration. An intermediate-acting insulin is one that generally reaches the bloodstream about 2 to about 4 hours after injection, peaks about 12 hours later, and is effective for 12 to 18 hours. These insulins can be insulin analogs, natural insulins, or natural insulin as would be known to the skilled artisan.

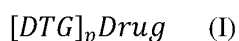
[0014] In another embodiment, when the drug compound in the water-soluble complex is a GLP-1 receptor agonist, the GLP-1 receptor agonist is semaglutide, tirzepatide, amycretin, orforglipron, albiglutide, beinaglutide, cagrilintide, CagriSema, CT996, danuglipron, efinopegdutide, HM15211, lixisenatide, pemvidutide, retratrutide, SCO-094, survodutide, WK2735, mazdutide, PEG-loxenatide (PEX168), liraglutide, dulaglutide, exenatide, or a salt, cocrystal, hydrate solvate, or polymorph thereof.

[0015] In another embodiment, when the drug compound in the water-soluble complex is a GIP agonist, the GIP agonist is HM15211, retratrutide, SCO-094, tirzepatide, WK2735, ZP6590, or a salt, cocrystal, hydrate, solvate, or polymorph thereof.

[0016] In another embodiment, when the drug compound in the water-soluble complex is a glucagon agonist, the glucagon agonist is efinopegdutide, HM15211, mazdutide, pemvidutide, survodutide, or a salt, cocrystal, hydrate, solvate, or polymorph thereof.

[0017] In another embodiment, when the drug compound in the water-soluble complex is an amylin agonist, the amylin agonist is AZD6234, cagrilintide, CagriSema, CT388, a long-acting amylin agonist, amycretin, ZP8396, or a salt, cocrystal, hydrate, solvate, or polymorph thereof.

[0018] In one embodiment, the complexes described herein can be represented by formula I as follows:



where DTG (includes DTG, DDG, or other non-nutritive sugar/sweetener) and drug compound (e.g., insulin or an insulin analog or A1C regulating compound) are as defined herein and p is an integer from 1.5 to 12. The formula can also include a surfactant. The surfactant is preferably a non-ionic surfactant. The Drug to non-ionic surfactant ratio can be 1:10, 1:5, and 1:0.5, and any 0.1 value for the surfactant between about 0.5 and 10.0.

[0019] As defined below, DTGs include diterpene di-glycosides (DDGs) and other non-nutritive sugars when referenced as “DTG” in the formulas. Such DTGs include stevioside and rubusoside, as well as other related compounds.

[0020] Disclosed herein and contemplated is a water-soluble complex comprising a non-nutritive sugar (and/or a surfactant) and a drug compound, which complex comprises: a molar ratio of up to about 12 moles of the non-nutritive sugar for each mole of the drug compound, wherein the sugar is one or more of rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A, provided that the water-soluble complex has at least a two (2), three (3), four (4) or five (5) fold increase in the water solubility of the drug

compound at 20° C as compared to the water solubility of the drug that is not in the water-soluble complex form; and further, provided that a maximum amount of the sugar in a daily unit dose of the complex is no more than about 10 mg/kg. The non-nutritive sugar used to make the water-soluble complex can be rubusoside or stevioside.

[0021] Another water-soluble complex contemplates using the drug compound selected from the group consisting of insulin, such as human insulin, and variants thereof, i.e., insulin analogs. Exemplary insulins are those that have desired medicinal properties when administered to an animal. Exemplary insulins include but are not limited to, Insulin Lispro (e.g., Humalog®), Insulin aspart (e.g., NovoLog™), Insulin Beef, Insulin Degludec (e.g., Tresiba®), Insulin detemir (e.g., Levemir®), Insulin Glargine (e.g., Lantus™), Insulin glulisine (e.g., ApidraA®), Insulin Pork (e.g., Iletin® II), Insulin Regular (e.g., Humulin® R), Insulin porcine (e.g., vetsulin®/Caninsulin®), and Insulin isophane (e.g., Novolin® N). Further examples of commercial products include HUMALOG®, HUMALOG 50/50™, HUMALOG 75/25™, HUMULIN 50/50™, HUMALIN 75/25™, HUMALIN L™, HUMALIN N™, HUMALIN®, HUMALIN R U-500™, HUMALIN U™, ILETIN II LENTE™, ILETIN II NPH™, ILETIN II REGULAR™ LANTUS™, NOVOLIN 70/30™, NOVILIN N™, NOVILIN R™, NOVOLOG™, VELOSULIN BR™, and EXUBERA™. Lente insulin (vetsulin), ProZinc or glargine insulin can be used in cats.

[0022] The water-soluble complex and methods of making the complexes contemplated also contemplate creating complexes from GLP-1 agonists, GIP agonists, amylin agonists, incretin mimetics, and glucagon agonists, their salts, cocrystals, hydrates, polymorphs, and solvates, as well as drug compounds that have more than one such agonist activities.

[0023] The passage of food through the large intestine is a very slow process which can take up to as much as 36 hours. Without being bound by theory, it is contemplated that the complexes as described herein engulfed in the food entering the large intestine may be protected from the acid environment in the stomach. Again, without being bound by theory, it is believed that the improved solubility of the drug in the form of the complex may allow the drug to proceed through the body.

[0024] In certain embodiments, the water-soluble complex is comprised of a non-nutritive sugar selected from the group of ADVANTAME®, NEOTAME®, thaumatin, saccharin, sucralose, Lou Han Guo, aspartame, acesulfame potassium, allulose, rubusoside, dulcoside B, dodecyl-β-D-maltoside, stevioside, or rebaudioside A. In other embodiments, the

water-soluble complex is comprised of a non-nutritive sugar selected from the group consisting of rubusoside, rebaudioside A, dodecyl- β -D-maltoside, dulcoside B, stevioside, or any combination thereof. In still another embodiment, the complex may be formed using rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A, or combinations thereof. In another embodiment, the water-soluble complex uses either rubusoside, stevioside, or a combination thereof.

[0025] In a further embodiment, the amount of the non-nutritive sugar in the daily unit dose administered to a subject amounts to no more than about 5 mg/kg of subject weight. In another embodiment, the water-soluble complex comprises an amount of non-nutritive sugar in the daily unit dose of no more than about 280 mg.

[0026] In an embodiment, the water-soluble complex comprises a molar ratio (moles of drug compound) to moles of the non-nutritive sugar (and optionally with a surfactant in the complex as discussed herein); drug: non-nutritive sugar) of about 1:1 to about 1:12, about 1:1 to about 1:10, or about 1:1 to about 1:5 moles. In an embodiment, the water-soluble complex comprises about 3.0 moles of the non-nutritive sugar for each mole of the drug compound, i.e., about a 1:3 molar ratio.

[0027] In another embodiment, the water-soluble complex comprises a molar ratio of about 2 to about 5 moles of the non-nutritive sugar for each mole of the drug compound, i.e., molar ratio Drug: non-nutritive sugar of about 1:2 to about 1:5.

[0028] In another embodiment, the water-soluble complex comprises a molar ratio of about 2 to about 4.5 moles of the non-nutritive sugar for each mole of the drug compound, i.e., molar ratio Drug:sugar of about 1:2 to about 1:4.5.

[0029] Another embodiment contemplates the water-soluble complex being stable when dissolved in water at pH 8.5 for at least about 2 hours.

[0030] In a further embodiment, the water-soluble complex is stable when dissolved in water at pH 4 for at least about 2 hours.

[0031] A further embodiment contemplates that the dried form of the water-soluble complex is stable at 30 °C. for at least 90 days.

[0032] A further embodiment contemplates that the water-soluble complex is stable at room temperature for about 24 hours. Another embodiment contemplates that water-soluble complex does not require refrigeration for at least 24 hours.

[0033] Another embodiment contemplates the water-soluble complex in the form of a powder, a tablet, an orally disintegrating tablet, a capsule, a liquid, a gel, a thin film, a lozenge,

a chewable pill or gummy, an effervescent powder or tablet, or an emulsion. Alternatively, the water-soluble complex can be a formulation prepared for parenteral administration and can be administered intradermally, subcutaneously, intramuscularly, intraperitoneally, topically (e.g., transdermal patch, cream, lotion, or gel), or intravenously. A further embodiment contemplates the water-soluble complex formulated as a thin film, an effervescent powder or tablet, a syrup, a solution, an elixir, an emulsion, a chewing gum, a gummy, a lollipop, a sublingual drop, a soft gel, or a tincture.

[0034] Another embodiment contemplates a water-soluble complex comprising a non-nutritive sugar and a drug compound, wherein the water-soluble complex comprises: a molar ratio of about 3 moles of the non-nutritive sugar for each mole of the drug compound, wherein the non-nutritive sugar is one or more of ADVANTAME®, NEOTAME®, thaumatin, saccharin, sucralose, Lou Han Guo, aspartame, acesulfame potassium, allulose, rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A; wherein the water-soluble complex is stable in water at pH 8.5 and at pH 4.0 for at least 2 hours each; provided that the water-soluble complex has at least a two (2), three (3), four (4) or five (5) fold increase in the water solubility of the drug compound at 20 °C. as compared to the water solubility of the drug compound not in the water-soluble complex; and further provided that a maximum amount of the non-nutritive sugar in a daily unit dose of the water-soluble complex is no more than about 280 mg.

[0035] Another aspect contemplates a method of making a water-soluble complex comprising a non-nutritive sugar (and optionally with a surfactant in the complex as discussed herein) and a drug compound (wherein the drug compound may or may not be poorly water soluble), the method comprising the steps of admixing, in at least 85% ethanol (or at least 90% or 95%), the non-nutritive sugar with the drug compound in a molar ratio of from about 1.0 to about 5.0 moles of the sugar for each mole of the drug compound until solubilized thereby forming the water-soluble complex, wherein the formation of the water-soluble complex can be determined by nuclear magnetic resonance spectroscopy (NMR), and wherein the sugar is one or more of ADVANTAME®, NEOTAME®, thaumatin, saccharin, sucralose, Lou Han Guo, aspartame, acesulfame potassium, allulose, rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A, wherein the admixing step (step 1) is optionally performed with a pharmaceutically acceptable acid in the one or more solvents; the components of step 1 are dried and step 2 involves dissolving the components in water and optionally drying the water from the water-soluble complex. In another method, the non-nutritive sugar is

rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, rebaudioside, or a combination thereof. A further method contemplates that the sugar used in the method is rubusoside, stevioside, or a combination thereof. The drug compound (i.e., drug compound or poorly soluble drug compound) used in the method of making the water-soluble complex can be insulin or an A1C-regulating compound. The drug compound can be any insulin, such as wild-type insulin ("regular insulin") or any functional variant thereof, including naturally occurring variants and insulin analogs. Exemplary insulins include but are not limited to, Insulin Lispro (e.g., Humalog®), Insulin aspart (e.g., NovoLog™), Insulin Beef, Insulin Degludec (e.g., Tresiba®), Insulin detemir (e.g., Levemir®), Insulin Glargine (e.g., Lantus™), Insulin glulisine (e.g., ApidraA®), Insulin Pork (e.g., Iletin® II), Insulin Regular (e.g., Humulin® R), Insulin porcine (e.g., vetsulin), and Insulin isophane (e.g., Novolin® N). Further examples of commercial products include HUMALOG®, HUMALOG 50/50™, HUMALOG 75/25™, HUMULIN 50/50™, HUMALIN 75/25™, HUMALIN L™, HUMALIN N™, HUMALIN®, HUMALIN R U-500™, HUMALIN U™, ILETIN II LENTE™, ILETIN II NPH™, ILETIN II REGULAR™, LANTUS™, NOVOLIN 70/30™, NOVILIN N™, NOVILIN R™, NOVOLOG™, VELOSULIN BR™, and EXUBERA™. In another embodiment, the insulin analog can be insulin lispro, insulin aspart, insulin glulisine, admelog, NPH insulin, insulin isophane, insulin glargine, insulin detemir, or insulin degludec or a salt, hydrate, solvate, hydrate polymorph, or cocrystal thereof.

[0036] Another embodiment contemplates that the method of making a water-soluble complex comprising a non-nutritive sugar and a drug compound, the method comprising the steps of admixing, in at least 85% ethanol, the sugar with the drug compound in a molar ratio of from about 1 to about 12 moles of the sugar for each mole of the drug compound until solubilized thereby forming the water-soluble complex, wherein formation of the water-soluble complex can be determined by nuclear magnetic resonance spectroscopy (NMR), and wherein the sugar is one or more of rubusoside, rebaudioside A, dulcoside B, dodecyl- β -D-maltoside (DDM), or stevioside; and wherein the admixing step is optionally performed with a pharmaceutically acceptable acid; and drying the water-soluble complex and redissolving the water-soluble complex in water, wherein the drug compound is a peptide or small compound for reducing blood glucose and/or blood A1C in a subject, wherein the drug compound is insulin, an insulin analog, a natural insulin variant, a GLP-1 receptor agonist, an incretin mimetic, a GIP agonist, an amylin agonist, a glucagon agonist, or a salt thereof.

[0037] When the drug compound in the method of making the water-soluble complex is an insulin analog, it can be any of insulin lispro, insulin aspart, insulin glulisine, admelog, NPH insulin, insulin isophane, insulin glargine, insulin detemir, or insulin degludec. Alternatively, if the drug compound is an insulin or insulin analog it can be a rapid-acting insulin, short-acting insulin, intermediate-acting insulin, long-acting insulin, or an ultra-long-acting insulin (e.g., insulin detemir/Levemir, insulin glargine, and insulin degludec/Tresiba).

[0038] In another embodiment, when the drug compound in the method of making the water-soluble complex is a GLP-1 receptor agonist, the GLP-1 receptor agonist is semaglutide, tirzepatide, amycretin, orforglipron, albiglutide, beinaglutide, cagrilintide, CagriSema, CT996, danuglipron, efinopegdutide, HM15211, lixisenatide, pemvidutide, retratrutide, SCO-094, survodutide, WK2735, mazdutide, PEG-loxenatide (PEX168), liraglutide, dulaglutide, exenatide, or a salt thereof.

[0039] In another embodiment, when the drug compound in the method of making the water-soluble complex is a GIP agonist, the GIP agonist is HM15211, retratrutide, SCO-094, tirzepatide, WK2735, ZP6590, or a salt thereof.

[0040] In another embodiment, when the drug compound in the method of making the water-soluble complex is a glucagon agonist, the glucagon agonist is efinopegdutide, HM15211, mazdutide, pemvidutide, survodutide, or a salt thereof.

[0041] In another embodiment, when the drug compound in the method of making the water-soluble complex is an amylin agonist, the amylin agonist is AZD6234, cagrilintide, CagriSema, CT388, a long-acting amylin agonist, amycretin, ZP8396, or a salt thereof.

[0042] The method further can comprise drying the water-soluble complex to form a solid. The dried solid can be re-dissolved into a suitable liquid.

[0043] In some embodiments, the method of preparing the water-soluble complex may further require the presence of a pharmaceutically acceptable acid to be added in the admixing step (i.e., step 1) in the presence of a sufficient amount of a pharmaceutically acceptable acid to solubilize and render the reaction mixture homogeneous and clear. The pharmaceutically acceptable acid to be used in the method can be acetic acid, ascorbic acid, aspartic acid, citric acid, formic acid, fumaric acid, gluconic acid, glutamic acid, glutaric acid, glycolic acid, hydrochloric acid, lactic acid, lauric acid, maleic acid, malic acid, malonic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, propionic acid, salicylic acid, stearic acid, succinic acid, or tartaric acid.

[0044] The method can use the surfactant with a solvent alone or also in the presence of an acid or a buffer. The solvent used in the method can be a pure solvent, such as absolute ethanol, or a mixture of solvents such as ethanol, water, and methanol as suggested herein. The sugar, drug compound, and solvent can have the surfactant with them in a vessel and the pH can then be adjusted until a homogeneous solution is formed. Preferably the homogeneous solution remains stable for at least 30 minutes, more preferably at least 2 hours, more preferably at least about 24 hours. An exemplary surfactant is a nonionic surfactant.

[0045] The method of making the water-soluble complex can admix a molar ratio of about 1 to about 12 moles of the non-nutritive sugar for each mole of the drug compound. The sugar can be any of the DTGs, DDGs, or other non-nutritive sugars discussed herein, for example, stevioside and rubusoside. Alternatively, the water-soluble complex made by the method can have a molar ratio of about 2 to about 10 moles of the non-nutritive sugar for each mole of the drug compound (i.e., about 1:2 to about 1:10 molar ratio drug:sugar), or from about 3 to about 5 moles of the non-nutritive sugar to each mole of drug compound (i.e., about 1:3 to about 1:5 molar ratio drug:sugar). In another embodiment, the formed water-soluble complex from the method can comprise a molar ratio of about 3 moles of the sugar for each mole of the drug compound (about 1:3 molar ratio drug:sugar), as well as any 0.1 amount between 1:1.0 and 1:12.0.

[0046] These and other embodiments will be apparent to those of skill in the art upon reading the specification.

BRIEF DESCRIPTION OF THE FIGURES

[0047] FIG. 1 depicts the NMR result for the water-soluble complex formed by stevioside (sugar) and insulin lispro (drug compound).

[0048] FIG. 2 depicts the NMR result for the water-soluble complex formed by stevioside (sugar) and semaglutide (drug compound).

DETAILED DESCRIPTION

[0049] Creating new means of enhancing the formation of water-soluble complexes of blood glucose and/or A1C regulating compounds, i.e., compounds that reduce the blood glucose and/or A1C levels in subjects having elevated glucose and/or A1C levels. The A1C/glucose regulating compounds can include insulin as well as glucagon-like peptide-1 (GLP-1) agonists and glucose-dependent insulintropic polypeptide (GIP) agonists. The

compounds can have poor or insufficient water solubility or, for example, be inadequate for oral delivery due to unacceptable taste or consistency. The ability to make complexes comprising A1C/glucose regulating compounds has significant ramifications in many fields including pharmacology and animal care. The complexes formed using the methods herein can assist compounding pharmacies in formulating subject-specific amounts of an active compound as well as formulating the active compound(s) into palatable formulations for pediatric or elderly patients.

[0050] In complexes of a sugar and an A1C regulating compound, the complex and/or complex formed from the sugar compound increases the compound's solubility in water over the compound alone (not in a complex). The complex also imparts a sweeter taste, instead of a bitter or acrid taste imparted by many salts; however, the addition of the sugar to form the complex is not as a sweetener, but rather to form a complex with idebenone to enhance water-solubility when in the form of a complex. The sweeter taste will be of benefit when administering pharmaceuticals to young children as well as to geriatric patients, but is not the purpose of the non-nutritive sugar used to form the complex.

[0051] While the complexed non-nutritive sugar and drug (i.e., A1C regulating compound) may be more palatable as a complex, it must be understood that the formation of the complex is not merely to mask a drug's taste. Improving the palatability of a drug is a side benefit. The formation of the water-soluble complex by the methods described herein results in improved characteristics of the drug in the form of a complex such as improved water solubility. Additionally, improved characteristics can include improved pharmacokinetic attributes, improved stability at a pH and/or storage, and high temperatures or other conditions. Pharmacokinetic attributes include absorption into a system, its distribution in the system, the system's metabolism of the complex, and its elimination. Moreover, given the data and description herein, it should be understood that the water-soluble complex is formed by the methods described herein but is not to be considered as a mixture. The method of solubilizing a listed non-nutritive sugar with the PSD (drug compound) in a listed solvent or solvent combination can optionally be in the presence of an acid/base/surfactant (e.g., a nonionic surfactant), followed by drying using the methods described herein. The dried complex is then dissolved in water (Step 2), and optionally filtering the solution and/or drying the complex to remove the water. The final water-soluble complex yields a new more water-soluble drug in the form of a complex.

[0052] The water-soluble complex can then be further mixed with other pharmaceutical excipients, stabilizers, fillers, flavorings, sweeteners, and the like as mentioned here. After adding one or more of these other components, only then would the composition be in the form of a mixture. Not to be bound by theory, the complex formed by the described methods for forming a complex with a non-nutritive sugar and an A1C regulating compound disclosed herein optionally with a surfactant in the complex as discussed herein may involve host-guest chemistry that is not obtained when forming a mixture of different components. The solubility of the complex is not dependent on the addition of other pharmaceutical excipients, stabilizers, fillers, flavorings, sweeteners, and the like. Contemplated compositions may further comprise a salt such as NaCl, KCl, or citric acid for stabilization purposes among other pharmaceutically acceptable ingredients.

[0053] Another benefit achieved by the method and products produced by the method is a decreased amount of an active drug agent because with greater solubility there will be greater bioavailability. Another benefit obtained by the methods to produce the claimed compositions is the cost-benefit of having to utilize fewer resources for less of an active compound but still achieving the desired patient outcome.

[0054] Complexation of the drug with the DTG, DDG, or other non-nutritive sugar can be construed as a donor (sugar) receptor (drug) interaction, such as host-guest chemistry between the drug and the one or more sugars. In effect, the complexation intertwines the poorly soluble drug with the soluble non-nutritive sugar, which essentially allows the drug to capture the water solubility of the non-nutritive sugar. *See*, for example, “Absorption and distribution of steviol glycosides in animal and human models.” *Stevia Technology*. Retrieved July 31, 2023, from: <https://www.steviashantanu.com/single-post/2015/11/18/absorption-and-distribution-of-steviol-glycosides-in-animal-and-human-models>. Without being limited to any theory, enzymatic cleavage of the glucose groups results in disaggregation (e.g., decomplexation) of the complex, which releases the poorly soluble drug. This process is sufficiently slow that substantial portions of an amount of the drug released at any given time can be absorbed.

[0055] However, while the complexed sugar and drug may be more palatable as a complex, it must be understood that the formation of the complex is not merely to mask a drug’s taste. Improving the palatability of a drug is a side benefit. The formation of the water-soluble complex by the methods described herein results in improved characteristics of the

drug in the form of a complex such as improved water solubility, a pharmacokinetic attribute is improved for the drug when in the form of a complex, and/or the stability at a pH or under certain conditions is improved. Pharmacokinetic attributes include absorption into a system, its distribution in the system, the system's metabolism of the complex, and its elimination. Moreover, given the data and description herein, it should be understood that the water-soluble complex formed by the methods described herein. The method of solubilizing a listed sugar with a listed drug in a listed solvent or solvent combination optionally in the presence of an acid/base/surfactant (and/or poloxamer) surfactant, followed by drying using the methods described herein, dissolving the dried form in water, and optionally filtering and/or drying all lead to the formation of a new more water-soluble drug in the form of a complex. The water-soluble complex can then be further mixed with other pharmaceutical excipients, stabilizers, fillers, flavorants, sweeteners, and the like as mentioned here.

[0056] Without being limited to any theory, the proposed water-soluble complexes may be created by hydrogen bonding or by host-guest chemistry forming a complex, wherein two compounds are in a complex and one chemical compound has a cavity into which a "guest" compound can be accommodated. Surfactant-drug-non-nutritive sugar complexes may also involve hydrogen bonding. A water-soluble complex may also be formed by a surfactant and a drug compound. The interaction between the host and guest in an inclusion complex involves purely van der Waals bonding. In the sugar-compound form, the aggregate and/or water-soluble complex formed from non-nutritive sugar and/or surfactant (e.g., wherein the water-soluble complex can be a surfactant and drug, a surfactant and sugar, or a surfactant, sugar and drug) with the drug compound increases the compound's solubility in water over the compound alone. The complex also imparts a sweeter taste, instead of a bitter or acrid taste imparted by many salts. The sweeter taste will be of benefit when administering pharmaceuticals to young children as well as to geriatric patients by contributing the sweeter and more palatable taste.

[0057] The contemplated water-soluble complex also may improve the amount of drug compound delivered (C_{max}). The water-soluble complex also seems to be protected from harsh stomach acids. For some complexed drugs and without being bound to theory, the dose amount of the drug in the complex form may need to be decreased relative to the drug that is not in the complexed form.

[0058] The complexation of the drug compound with the non-nutritive sugar and/or surfactant (e.g., wherein the water-soluble complex can be a surfactant and drug, a surfactant and sugar, or a surfactant, sugar, and drug) can be construed as a donor (e.g., sugar or surfactant

or both) receptor (drug) interaction, such as host-guest chemistry between the drug-compound and a non-nutritive sugar and/or surfactant (e.g., wherein the complex can be a surfactant and drug, a surfactant and sugar, or a surfactant, sugar, and drug) as listed herein. In effect, the complexation is the intertwining of the drug compound with the soluble sugar, which essentially allows the drug compound to capture the water solubility of the sugar. Moreover, this captured solubility may be retained in the upper portion of the gastrointestinal tract (GI) after ingestion.

Definitions

[0059] The following definitions provide guidance on term interpretation unless otherwise indicated by the context in which the term appears elsewhere in the specification.

[0060] As used herein, the term “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur and that the description includes instances where the event or circumstance occurs and instances where it does not.

[0061] As used herein, the term “about” when used before a numerical designation, e.g., temperature, time, amount, concentration, and such other, including a range, indicates approximations that may vary by (+) or (-) 15%, 10%, 5%, 1%, or any subrange and/or value therebetween. The term “about” when used concerning a dose amount means that the dose may vary by +/- 10%. The term “about”, when modifying the quantity (e.g., kg, L, or equivalents) of a substance or composition, the value of a physical property, or the value of a parameter characterizing a process step (e.g., the temperature at which a process step is conducted), or the like refers to variation in the numerical quantity that can occur, for example, through typical measuring, handling and sampling procedures involved in the preparation, characterization and/or use of the substance or composition; through an inadvertent error in these procedures; through differences in the manufacture, source, or purity of the ingredients employed to make or use the compositions or carry out the procedures; and the like. In certain embodiments, “about” can mean a variation of ± 0.1 , 0.2, 0.3, 0.4, 0.5, 1.0, 2.0, 3.0, 4.0, or 5.0 of the appropriate unit. In certain embodiments, “about” can mean a variation of $\pm 1\%$, 2%, 3%, 4%, 5%, 10%, or 20%.

[0062] As used herein, the term “comprising” or “comprises” is intended to mean that the compositions or methods include the recited elements, but do not exclude others.

[0063] As used herein, the term “consisting essentially of” when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination for the stated purpose of improving the solubility of insulin or analog thereof

or a GIP or GLP-1 agonist. Thus, a composition consisting essentially of the elements as defined herein, or a method consisting essentially of the steps as defined herein, would not exclude other materials that do not materially affect the basic and novel characteristic(s) of the claimed subject matter.

[0064] As used herein, the term “consisting of” shall mean excluding more than trace elements of other ingredients or substantial method steps. Embodiments defined by each of these transition terms are within the scope of this disclosure.

[0065] The “molar ratio” of a “sugar to a drug compound” (wherein the “drug compound” or “compound” is intended to mean insulin, an insulin homolog, a GLP-1 agonist, and a GIP agonist) in a formulation may range from about 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, and 9:1 to about 10:1 and any 0.1 value between. Alternatively, the sugar-to-drug compound ratio can be about 1.00:1.00 to about 5.00:1.00, and any 0.01 value within that range. In one embodiment, an about 2.0 to about 1.0 molar ratio of sugar to drug compound is used.

[0066] The term “pharmaceutically acceptable salt” refers to a salt (including an inner salt such as a zwitterion) that possesses effectiveness similar to the parent compound and which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). The term “salt(s)”, as employed herein, denotes any of the following: acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. However, the compositions/compounds described herein are in a sugar form (sugar complexes) with the drug compound or drug compounds. The drug compound to be complexed with a non-nutritive sugar can be in the salt form of a drug or compound or the free form of the compound. A drug compound salt form can allow for the salt component to occupy a binding site for a non-nutritive sugar, so if a compound lacks adequate bonding sites, it can be important to use a salt or a free form to form the water-soluble complex. A pharmaceutically acceptable salt is a salt used in a medicine that is approved by the U.S. FDA or the European Medicines Agency (EMA). The use of a pharmaceutically acceptable salt as used in the methods described herein is to improve the water solubility of the sugar and water insoluble drug or drug of limited solubility. Pharmaceutically acceptable acids include 1-hydroxy-2-naphthoic acid; 2,2-dichloroacetic acid; 2-hydroxyethanesulfonic acid; 2-oxoglutaric acid; 4-acetamidobenzoic acid; 4-aminosalicylic acid; acetic acid; adipic acid; ascorbic acid (L); aspartic acid (L); benzenesulfonic acid; benzoic acid; camphoric acid (+); camphor-10-sulfonic acid (+); capric acid (decanoic acid); caproic acid (hexanoic acid); caprylic acid (octanoic acid); carbonic acid; cinnamic acid; tartaric acid; citric acid; cyclamic

acid; dodecylsulfuric acid; ethane-1,2-disulfonic acid; ethanesulfonic acid; formic acid; fumaric acid; galactaric acid; gentisic acid; glucoheptonic acid (D); gluconic acid (D); glucuronic acid (D); glutamic acid; glutaric acid; glycerophosphoric acid; glycolic acid; hippuric acid; hydrobromic acid; hydrochloric acid; isobutyric acid; lactic acid (DL); lactobionic acid; lauric acid; maleic acid; malic acid (- L); malonic acid; mandelic acid (DL); methanesulfonic acid; naphthalene-1,5-disulfonic acid; naphthalene-2-sulfonic acid; nicotinic acid; nitric acid; oleic acid; oxalic acid; palmitic acid; pamoic acid; phosphoric acid; propionic acid; pyroglutamic acid (- L); salicylic acid; sebacic acid; stearic acid; succinic acid; sulfuric acid; tartaric acid (+ L); thiocyanic acid; toluenesulfonic acid (p); and undecylenic acid. *See e.g., P. H. Stahl and C. G. Wermuth, editors, HANDBOOK OF PHARMACEUTICAL SALTS Weinheim/Zürich Wiley-VCH/VHCA, 2002.*

[0067] Examples of “bases” including “pharmaceutically acceptable bases” include sodium hydroxide, zinc hydroxide, calcium carbonate, potassium hydroxide, lithium hydroxide, rubidium hydroxide, magnesium hydroxide, barium hydroxide, calcium hydroxide, strontium hydroxide, and potassium oxide. Other bases include trimethylamine, methylamine, aniline, and pyridine. Buffers can also be used instead of an acid or base to solubilize the compound and sugar. Exemplary buffers include a bicarbonate solution, a carbonate solution, and sodium phosphate (pKa 2.1, 7.2, and 12.3).

[0068] By a “compound”, “drug-compound” and “drug” are meant “an A1C regulating compound” such as insulin, insulin analogs (e.g., insulin lispro, insulin aspart, insulin glulisine, insulin glargine, insulin detemir, insulin degludec), GIP agonists, GLP-1 agonists (e.g., peptidomimetics of GLP-1), and dual GIP/GLP-1 agonists. Such compounds are expected to also lower blood glucose levels in the subject. The compound may or may not be a poorly water-soluble compound. Exemplary compounds can be insulin, insulin analogs as listed herein, GLP-1 agonists such as semaglutide, dulaglutide, and liraglutide, as well as others. In some instances, the drug compound may be referred to as a “poorly soluble drug” or “poorly soluble compound” or “insufficiently soluble.” The drug compound can be the free form of the compound or its pharmaceutically acceptable salt. A “drug”, “compound”, or “drug compound” is meant to include those that are both water-soluble and poorly water-soluble. The compound can be an A1C and/or glucose-regulating compound that may not be considered water-soluble compromising its commercial utility. The drug compounds for complexation include “glucose regulating compounds and/or a compound for the treatment of diabetes type 1 (TD1) or diabetes type 2 (TD2), obesity (weight loss reduction), MASH (metabolic

dysfunction-associated steatohepatitis), glycemic control, prediabetes, a condition characterized by impaired fasting glucose or impaired glucose tolerance (e.g., insulin resistance), an alpha- and beta cell dysfunction, a condition having a suboptimal incretin effect.

[0069] The compromised commercial utility for poorly or insufficiently soluble drugs includes art recognized as deficient in water solubility as evidenced by attempts to improve solubility including without limitation use of nanotechnology, the use of prodrugs, the use of a non-aqueous solvent delivery, and the like. The term “insoluble” is often applied in the art to poorly or very poorly soluble compounds (*see e.g.*, Savjani et al. “Drug Solubility: Importance and Enhancement Techniques,” *ISRN Pharm.* 2012, doi: 10.5402/2012/195727). Generally, a poorly soluble compound is considered “poorly soluble” in water at 20 °C when less than about 1 mg/mL of the compound is made soluble over the physiological pH range (*see e.g.*, C. Moreton, “Poor Solubility – Where do we stand 25 years after the ‘Rule of Five’?” *Amer. Pharm. Rev.* (2021)). A drug may also be insufficiently soluble for commercial purposes; by “insufficiently soluble” it meant a drug with limited water solubility that has at least one improved pharmacokinetic attribute (e.g., C_{max} , time to C_{max} , stability, duration, and the like) as a result of forming a water-soluble complex, such as those described herein. While not being bound by theory, the drug compound preferably has available hydrogen bonding sites to form such bonds with a sugar and/or surfactant (e.g., wherein the complex can be a surfactant and drug, a surfactant and sugar, or a surfactant, sugar and drug) and/or for the compound and the sugar to form a complex. Water insolubility (and limited solubility) of a drug compound can be addressed through the methods of complexation described herein. The oral bioavailability of compounds depends on several factors including aqueous solubility, drug-compound permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability. Solubility also plays a major role in other dosage forms like parenteral formulations. Solubility is one of the important parameters to achieve the desired concentration of a drug compound in systemic circulation for achieving a required pharmacological response. Poorly water-soluble drugs often require high doses to reach therapeutic plasma concentrations after oral administration. Water is the solvent of choice for liquid pharmaceutical formulations. Unfortunately, many drugs are either weakly acidic or weakly basic and thus have poor aqueous solubility. More than 40% of the NCEs (new chemical entities) developed by the pharmaceutical industry are practically insoluble in water. These poorly water-soluble drugs will have slow drug-compound absorption which

leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs, solubility is the most important rate-limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response (Savjani et al., 2012).

[0070] By “non-ionic surfactant” is meant to include a pharmaceutically acceptable poloxamer surfactant or polysorbate surfactant, as mentioned herein. The “Drug” to non-ionic surfactant ratio can be 1:10, 1:5, and 1:0.5, and any 0.1 value for the surfactant between about 0.5 and 10.0.

[0071] Solubility can vary among the drug compounds discussed herein. Some drugs may only be soluble in DMSO or DMF or have limited solubility in ethanol, methanol, or acetonitrile. Solubility of certain compounds can be found for example at: tokutech.com/solubility-data-resource/. Soluble to very soluble is characterized as from no more than 30 parts solvent per part of solute to less than one part solvent per part of solute. Poorly soluble and having limited solubility include “sparingly soluble”, “slightly soluble”, “very slightly soluble” and “practically insoluble” ranges as follows (Savjani et al., 2012):

<u>Descriptive term</u>	<u>Part of solvent required per part of solute</u>
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

[0072] By “compound, “drug compound” and “drug” is meant to include “a GLP-1 agonist”, a “GIP agonist”, an incretin mimetic, a dual GLP-1/GIP agonist, an amylin agonist/analog, dual amylin/calcitonin receptor agonist, dual GLP-1/amylin agonist, and a GLP-1+GIP+Glucagon agonist (tri-agonist). Exemplary compounds are listed below.

TABLE 1

Drug	Brand Name	Characteristics
Albiglutide	Tanzeum®	97% sequence identity to GLP-1 amino acid sequence 30 mg and 50 mg dosing. Weekly injection.
AZD6234	No marketing approval	An amylin agonist of AstraZeneca that is in clinical study for obesity treatment.
Beinaglutide or benaglutide	No marketing approval	It received marketing approval in China in 2015 and is administered 3x daily given its 1-2 minute half-life. It is a GLP-1 agonist (also referred to as a GLP-1 receptor

Drug	Brand Name	Characteristics
		agonist, or GLP-1RA) having 100% sequence identity to GLP-1(7-36). It was approved for marketing by the China Food and Drug Administration (CFDA).
Cagrilintide	CagriSema®	This is a dual amylin and calcitonin receptor agonist that is combined with semaglutide for treating obesity and type 2 diabetes (T2D). It is formulated for a s.c. injection.
CagriSema	No marketing approval	A dual GLP-1 and amylin agonist of NN that is in clinical study for obesity treatment. Amylin is a 37-amino acid peptide with certain amino acid substitutions. Kruse et al., "Development of Cagrilintide, a Long-Acting Amylin Analogue," <i>J. Med. Chem.</i> 64(15): 11183-94 (2021).
CT388	No marketing approval	An amylin agonist is under study by Carmot Therapeutics and has not been approved yet.
CT996	No marketing approval	A GLP-1 oral drug by Carmot Therapeutics undergoing study and has not been approved yet.
Danuglipron	No marketing approval	GLP-1 agonist (small molecule) oral drug undergoing study and has not been approved yet.
Dulaglutide	Trulicity®	Subcutaneous injection to improve glycemic control. Comprises two identical GLP-1 analog peptide chains which are approximately 90% identical to native human GLP-1, which is linked to an immunoglobulin (Ig) G4 heavy chain. It has amino acid substitutions and an Fc fusion. The modification is believed to protect against DPP-4 degradation. Administered in 0.75 and 1.5 mg dosages. It has a 90-hour half-life and is administered once weekly. FDA approved 2014.
Efinopegdutide	No marketing approval	A GLP-1 + Glucagon agonist under study for weight loss by Hanmi Pharmaceutical.
Exenatide	Byetta® Bydureon®	Having amino acid substitutions; 2.4 hr half-life and administered as a twice-daily injection. FDA approved Byetta® in 2005 and Bydureon® in 2012, with the latter for weight management. There is also a sustained release form that is given as a once-weekly injection, which was FDA-approved in 2012.
HM15211	No marketing approval	A GLP-1+GIP+Glucagon agonist (tri-agonist) under clinical study by Hanmi Pharmaceutical company for weight loss.
Liraglutide	Victoza® and Saxenda®	Fatty acid side chain modification of the GLP-1 receptor agonist. Has a 13-hour half-life and is injected once daily. Victoza® was approved in 2010 and Saxenda® was approved for weight management in 2014.
Lixisenatide	Adlyxin® Lyxumia®	A GLP-1 receptor agonist for treating type 2 diabetes manufactured by Sanofi. Lixisenatide is designed as a C-terminal modification with 6 lysine residues and

Drug	Brand Name	Characteristics
		deletion of 1 proline, allowing it to withstand physiologic degradation by DPP-4. Dosages delivered s.c. are 5-mcg, 10-mcg, and 20-mcg doses. Lyxumia® was FDA-approved in 2016 and has amino acid substitution and an Fc fusion giving it a 3-4 hr half-life and requiring a once-daily injection.
Long-acting amylin agonist	No marketing approval	An amylin agonist of Eli Lilly is in clinical study for obesity treatment.
Mazdutide	No marketing approval	A GLP-1 + Glucagon dual agonist under study for weight loss by Eli Lilly. It is an analog of oxyntomodulin.
Oral amycretin	No marketing approval	A dual GLP-1 and amylin agonist of NN that is in clinical study for obesity treatment.
Orforglipron	No marketing approval	It is a non-peptide GLP-1 receptor agonist developed for weight loss by Eli Lilly. It is in clinical study awaiting FDA approval.
PEG-loxenate (PEX168)	Fu Laimei®	Has an 80-hour half-life and was approved for marketing in China in 2019. It has amino acid substitutions and is modified with a PEG group. It is formulated as a once-weekly injection. It is a GLP-1 agonist using the structure of exenatide that has been modified. Salamah et al., "Efficacy and safety of polyethylene glycol (PEG) loxenate in type 2 diabetic patients: a systematic review and meta-analysis of randomized controlled trials," <i>Sci. Rep.</i> Article No. 19041 (2023)
Pemvidutide ALT-801	No marketing approval	A GLP-1 + Glucagon dual agonist under study for weight loss and treatment of metabolic dysfunction-associated steatohepatitis (MASH) by Boehringer Ingelheim.
Retatrutide	No marketing approval	The drug is a GIP, GLP-1, and glucagon agonist (triple agonist). Not FDA approved and under study by Eli Lilly. Rosenstock et al., "Retatrutide, a GIP, GLP-1, and Glucagon receptor agonist, for people with type 2 diabetes: a randomized, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA," <i>The Lancet</i> available at DOI: doi.org/10.1016/S0140-6736(23)01053-X; Jastreboff et al., "Triple-Hormone-Receptor Agonist Retatrutide for Obesity – A Phase 2 Trial, <i>N. Engl. J. Med.</i> 389: 514-26 (2023).
SCO-094	No marketing approval	A GLP-1 + GIP agonist is under study by Scohia Pharm and has not been FDA approved yet.
Semaglutide	Ozempic® Wegovy®	Can be administered orally and subcutaneously, but was approved first subcutaneously. The weekly subcutaneous formulation of semaglutide had a significant HbA _{1c} reduction of 0.7% with the 0.5-mg dose, and 1% with the 1-mg dose, compared with the placebo. Patients in the 0.5-mg group had a weight loss

Drug	Brand Name	Characteristics
		of 2.9 kg, and the 1-mg group had a 4.3-kg weight loss. It has a 160 hr half-life. It has amino acid substitutions and a fatty acid side chain modification. Ozempic® was approved in 2017. Rybelsus® (<i>see below</i>) was approved in 2019, and Wegovy® was approved in 2021.
Semaglutide	Rybelsus®	Has a 7-day half-life and is administered once daily orally. It also has amino acid substitutions and a fatty acid side chain modification.
Survodutide	No marketing approval	A GLP-1 + Glucagon agonist under study for weight loss by Boehringer Ingelheim.
Tirzepatide	Mounjaro® Zepbound®	Once weekly injection of 5 mg, 10 mg, or 15 mg s.c. It is a dual GLP-1 / GIP agonist. FDA approved 2022 for Mounjaro® and 2023 for Zepbound®.
WK2735	No marketing approval	A GLP + GIP dual agonist formulated for oral and subcutaneous administration is under study by Viking Therapeutics and has not been approved yet.
ZP6590	No marketing approval	A GIP agonist of Zealand Pharma is in a clinical study for obesity treatment.
ZP8396	No marketing approval	An amylin agonist of Zealand Pharma that is in a clinical study for obesity treatment.

See for additional information, Tran et al., “Overview of Glucagon-Like Peptide-1 Receptor Agonists for the Treatment of Patients with Type 2 Diabetes,” *Am. Health Drug Benefits* 10(4): 178—188 (2017) and “Long Acting GLP-1 Receptor Agonist Drugs Lists and Overview” available at www.biochempeg.com/article/226.html and “Exploring FDA-approved GLP-1 receptor agonists,” available at pharmanewsintel.com/features/exploring-fda-approved-glp-1-receptor-agonists.

[0073] For embodiments of the method described herein to solubilize a drug compound and sugar, the pH of the compound, sugar, and solute can be brought to about 2.0 to about 12.0 as needed for solubilization. The pH can be adjusted to any 0.1 value between 2.0 to 12.0 as needed for solubilization.

[0074] For embodiments of the method described herein to solubilize a compound or sugar, the temperature of the compound, sugar, and solute can range from about 15 °C. to about 60 °C., generally and preferably about 5 °C. to about 10 °C. from room temperature. An exemplary temperature range is between about 20 °C. and about 30 °C.

[0075] By a “pharmaceutically acceptable composition” is meant a composition comprising a hydrogen-bonded and/or sugar-A1C regulating compound complex and one or more of a carrier, excipient (e.g., gelatin, cellulose, cellulose derivatives, polyvinylpyrrolidone, a starch, sucrose, and PEG), stabilizer (e.g., glycine, vitamin E, carboxymethylcellulose,

sodium lauryl sulfate), a thickener, a flavor, a colorant, and a further sweetener that form a mixture with the water-soluble complex formed by the methods described herein but are not essential as to the solubility of the drug compound. The composition can be a solid or a liquid form. The pharmaceutical composition may also comprise an A1C-regulating compound with a surfactant or an A1C-regulating compound with a surfactant and a non-nutritive sugar. Such excipients, carriers, stabilizers thickeners, flavorants, and/or colorants should be compatible with the complex. Other suitable pharmaceutically acceptable excipients include water, saline, dextrose, glycerol, and ethanol, or combinations thereof. Intravenous vehicles for use in delivering the water-soluble complex include fluid and nutrient replenishers, electrolyte replenishers, such as those based on Ringer's dextrose, and the like. Aqueous carriers for use in a liquid formulation containing the water-soluble complex include water, alcoholic/aqueous solutions, emulsions, or suspensions, including saline or buffered media. A pharmaceutically acceptable carrier for parenteral administration includes sterile, aqueous, or non-aqueous solutions, suspensions, and emulsions. Aqueous parenteral vehicles for delivering the water-soluble complex include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils.

[0076] For the drug compounds that are water soluble, the methods described herein of complexing such water-soluble drugs with a non-nutritive sugar is to create a drug compound-sugar complex that can have sustained release when given orally in the gastrointestinal tract of a subject administered the complex.

[0077] The term a “compound,” “drug compound,” or “poorly soluble drug” also includes insulin, an insulin variant, or an insulin analog, wherein the insulin, insulin variant, or insulin analog may or may not be poorly soluble or insoluble (e.g., a poorly soluble drug, PSD). The terms “compound,” “drug compound,” or “poorly soluble drug” are also meant to include a GLP-1 agonist, an amylin agonist, a glucagon agonist, a GIP agonist, and a drug compounding having more than one of these agonist activities. While not being bound by theory, the drug compound preferably has available hydrogen bonding sites to form such bonds with a non-nutritive sugar and/or surfactant (e.g., wherein the complex can be a surfactant and drug, a surfactant and sugar, or a surfactant, sugar and drug), and the drug compound forms the complex. For the compounds and methods described herein, the drug compound is insulin or an insulin analog such as insulin lispro (Humalog®). A drug compound is a compound that can dissolve at no more than about 100 mg per milliliter, and likely less than 50 mg per milliliter of the compound. As used herein, a “water-soluble complex” includes a complex having a

non-nutritive sugar and a drug compound, a surfactant and a drug compound, and a surfactant/non-nutritive sugar/drug compound. The terms “sugar-compound”, “sugar-drug compound”, and “sugar-drug” are equivalent terms to describe a complex between a non-nutritive sugar and a drug compound. The water-soluble complex formed can be used to treat the conditions described herein, or can regulate one or more of GIP, GLP-1, amylin, glucagon, an A1C level in a subject, the glucose level of a subject in a subject. Such a drug compound may or may not be a poorly soluble drug/compound when not complexed with a non-nutritive sugar such as that used herein; the drug compound has available hydrogen bonding sites to form such bonds with a non-nutritive sugar and/or surfactant (e.g., wherein the complex can be a surfactant and drug, a surfactant and sugar, or a surfactant, sugar, and drug) to form a water-soluble complex. The term “complex” as used herein is used interchangeably with “aggregate” and “inclusion complex” and is intended to be equivalent to include descriptions provided herein as well as in the priority application(s) to which this application claims the benefit, including, without limitation, the terms “an inclusion complex”, “aggregate” and “complex”. Each of these terms refers to a stable product formed as described herein between a sugar and a compound. The compound can be a drug compound or any other chemical compound in need of improved water solubility that is an A1C regulating compound. In the formulas provided herein “a DTG” refers to diterpene glycosides, which includes DDGs, and the other non-nutritive sugars described herein, and the drug compound as “Drug” as indicated in the following formula:

(Formula I): $[DTG]_p Drug$.

[0078] A water-soluble complex is a water-soluble complex of Formula (I) prepared by the methods described herein that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow the use of the compound for the purposes described herein (e.g., therapeutic administration to a subject) sufficient to allow the use of the drug compound in the water-soluble complex for the purposes described herein (e.g., therapeutic administration to a subject). Another characteristic that may be imparted by the method of improving a compound's water solubility is that the storage stability of the water-soluble complexes can be increased over the drug compound's storage when not in the form of a complex. By way of example, only, water-soluble complexes of any of the aforementioned complexes are deemed stable if the complex remains intact in water at pH 8.5 for at least 2 hours and/or if it remains intact in water at pH 4 for at least 2 hours. Alternatively, or additionally, the water-soluble

complex is deemed stable if it remains intact at 30 °C for at least 90 days when dried to a powder. Accordingly, in a preferred embodiment, when a complex as described herein meets any or all of these stability tests, that complex is deemed to be a stable complex. Additionally, or alternatively, the water-soluble complex formed by the described methods forms a dried complex that does not require refrigeration and is stable at room temperature for at least 24 hours. Additionally, or alternatively, the water-soluble complex formed by the methods described herein is sought to have at least a two (2), three (3), four (4), or (5) fold increase in the water solubility of the water-soluble complex at 20° C as compared to the water solubility of the drug compound when not complexed with the sugar and/or surfactant (e.g., wherein the complex can be a surfactant and drug, a surfactant and sugar, or a surfactant, sugar and drug). Additionally, or alternatively, the water-soluble complex provides a maximum amount of the sugar in a daily unit dose of the water-soluble sugar-A1C regulating compound complex is no more than about 280 mg. Additionally, or alternatively, a drug with limited water solubility may when in a water-soluble complex have at least one improved pharmacokinetic attribute (e.g., C_{max} , time to C_{max} , stability, duration, and the like). A “stable” water-soluble complex (i.e., $[DTG]_p Drug$) can be prepared by the methods described herein that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow the use of the compound for the purposes described herein (e.g., therapeutic administration to a subject).

[0079] By “insulin” or “an insulin” is meant to include a drug compound that is an insulin, a naturally occurring insulin variant, or an insulin analog. Insulin analogs are recombinant proteins that are based on the amino acid sequence and structure of insulin, for instance, human insulin, but have undergone selected amino acid substitutions, deletions, or additions. Insulin analogs achieve glucose control but have altered pharmacokinetics, e.g., altered timing and duration of the effect of insulin. A non-limiting example of an insulin analog is insulin lispro; this insulin analog has two mutations in the B-chain: amino acid proline at position B28 is replaced by lysine and the lysine in position B29 is replaced by proline. Insulin lispro has a more rapid hypoglycemic effect than native insulin. As used herein, an insulin/insulin analog includes but is not limited to, rapid-acting insulin, short-acting insulin, intermediate-acting insulin, long-acting insulin, ultra-long-acting insulin, and premixed insulin. Insulins vary in onset, peak time, and duration of effect. Onset refers to how quickly insulin lowers the blood glucose of a subject. Peak time refers to when insulin is at maximum strength. Duration refers to how long insulin works to lower the blood sugar. The following

is a summary of the different types of insulin (data from www.cdc.gov/diabetes/basics/type-1-types-of-insulin.html). Human insulin is sold under a variety of brand names including Actraphane, Actrapid, Humulin, Humulin N, Humulin R, Insulatard, Entuzity, Novolin, Novolin N, Novolin R, Insuman, and Myxredlin. Human insulin is available in two forms, regular or short-acting form or an intermediate-acting form called neutral protamine Hagedorn (NPH) insulin. The Table below lists both human insulin forms and insulin analogs. Insulin and insulin analogs can be approved for type I and/or II diabetes.

TABLE 2

Insulin Type	Onset	Peak Time	Duration	Example
Rapid-acting insulin analog	15 minutes	1 hour	2 to 4 hours	Insulin lispro (e.g., Humalog®; Pro ^{B28} ->Lys); Insulin aspart (e.g., NovoLog®; Pro ^{B28} →Asp); insulin glulisine (e.g., Apidra®; Asn ^{B3} →Lys having decreased zinc-free self-association) and Lyumjev® (insulin lispro-aabc)
Admelog, Insulin analog				Lys ^{B29} ->Pro substitution. Not currently approved as interchangeable with Humalog®.
Short-acting human insulin	30 minutes	2 to 3 hours	3 to 6 hours	Regular insulin (e.g., Novolin® R; Humulin® R Vesolulin® BR)
Technosphere insulin, Afrezza®				Monomeric human insulin adsorbed into Technosphere microparticle having a Lys ^{B29} →Glu substitution and approved for T2D and T1D manufactured by Sanofi.
Intermediate-acting human insulin	2 to 4 hours	4 to 12 hours	12 to 18 hours	NPH (neutral protamine Hagedorn) insulin; Insulin isophane (e.g., Novolin® N; Iletin® II)
Long-acting insulin analog	2 hours	Does not peak	Up to 24 hours	Insulin glargine (e.g., Lantus®); Insulin detemir (Levemir®), Lantus®, Semglee®, and Toujeo Solostar®
Ultra-long-acting insulin analog	6 hours	Does not peak	36 hours or longer	Insulin degludec (e.g., Tresiba®) manufactured by Novo Nordisk having acylation of Lys ^{B29} by γ -glu-C16-diacid
Premixed human insulin and insulin analog	5 to 60 minutes	Peaks vary (based on the mix)	10 to 16 hours.	Humalog® Mix 50/50; Humulin® 70/30

[0080] Exemplary insulins and insulin analogs include but are not limited to, Insulin Lispro (e.g., Humalog®), Insulin aspart (e.g., NovoLog™), Insulin Beef, Insulin Degludec (e.g., Tresiba®), Insulin detemir (e.g., Levemir® having *des*-B30), Insulin Glargine (e.g.,

Lantus™), Insulin glulisine (e.g., ApidraA®), Insulin Pork (e.g., Iletin® II), Insulin Regular (e.g., Humulin® R), Insulin, porcine (e.g., vetsulin), and Insulin isophane (e.g., Novolin® N). Further examples of commercial products include HUMALOG™, HUMALOG 50/50™, HUMALOG 75/25™, HUMULIN 50/50™, HUMALIN 75/25™, HUMALIN L™, HUMALIN N™, HUMALIN®, HUMALIN R U-500™, HUMALIN U™, ILETIN II LENTE™, ILETIN II NPH™, ILETIN II REGULAR™ LANTUS™, NOVOLIN 70/30™, NOVILIN N™, NOVILIN R™, NOVOLOG™, VELOSULIN BR™, and EXUBERA™. See e.g., Jarosinski et al., “New Horizons: Next-Generation Insulin Analogues: Structural Principles and Clinical Goals,” *J. Clin. Endocrin. & Metab.* 107(4): 909-28 (2022). Also contemplated are insulin analogs that a premixed after complexation with a sugar. A “pre-mixed insulin” combines two types of insulin to control blood glucose levels throughout the day. For instance, it can include a rapid-acting insulin and a longer-acting insulin. The insulin may also be suitable for cats and dogs suffering from elevated glucose levels.

[0081] The method of preparing the water-soluble complex comprising a drug compound involves dissolving a compound in ethanol in the presence of a DTG or other non-nutritive sugar, followed by drying (e.g., freeze-drying or lyophilizing) the liquid from the composition. Optionally, the dissolving step may further involve the use of one or more pharmaceutically acceptable acids. Lyophilizing may require pre-freezing of the complex, followed by primary and secondary drying steps leaving a dried water-soluble complex generally in a powder form. The dried form of the first solubilization step then must undergo resolubilization in water. After which, the water-solubilized complex can be dried and formulated as desired. For example, the water-soluble complex formed by the method can then be formulated into a solid form for oral, sublingual, and/or buccal administration, such as a pill, capsule, a caplet, a chewable (e.g., a gummy), tablet, a lozenge, and/or a soft gel. The water-soluble A1C-regulating complex (e.g., hydrogen-bonded and/or inclusion complexed sugar-drug) can also, or alternatively, be formulated for topical administration such as in a suppository, lotion, gel, and/or ointment. The water-soluble A1C-regulating complex (hydrogen-bonded and/or inclusion complexed non-nutritive sugar and drug compound and optionally a non-ionic surfactant) can also be formulated as an inhalable powder. For example, insulin and insulin analogs can be administered through a syringe, an insulin pen, an insulin pump, or an inhaler. In another aspect, the water-soluble complex can be formulated into an injectable liquid for injection into a subject subcutaneously (SC), intravenously (IV), intraperitoneal (IP), and intramuscularly (IM). Alternatively, the lyophilized water-soluble

complex can be formulated into a liquid formulation for administration such as for use as an inhaled mist or nebulized by a patient. For example, insulin and insulin analogs can be administered through a syringe, an insulin pen, an insulin pump, or via an inhaler (Mohanty et al., "Inhaled Insulin – Current Direction of Insulin Research," *J. Clin. Diagn. Res.* 11(4): doi: 10.7860/JCDR/2017/23626.9732, 2017. Other peptides may be also administered in such formulations or using such devices. In the case of non-human subjects, a lyophilized water-soluble complex can be administered to a non-human subject as a powder or in a liquid formulation. Additionally, or alternatively, a lyophilized water-soluble complex can be formulated as a food additive or as an additive into an animal feed for use in treating a diabetic animal. Suitable insulin analogs for dogs and cats, for example, can be used as the drug compound. The drug compound can be one that can be solubilized fully or partially in either 95% ethanol, an aqueous ethanol solution of 50% ethanol or greater (e.g., 50%, 55%, 60%, 70%, 80%, 85% 90%, 91%, 92%, 93%, 94%, and 95% spectrophotometric grade ethanol) or in a combination of ethanol and another solvent in the presence of a non-nutritive sugar. Preferably, the drug compound and sugar optionally having the pharmaceutically acceptable acid is solubilized in at least about 85% ethanol. Optionally, the water-soluble complex remains soluble without the formation of a precipitate for at least 24 hours after formation.

[0071] If desired, a polyethylene glycol (PEG) can be optionally added to the liquid and powdered formulations to further improve bioavailability. Typically, this is between 2,000 and 6,000 Daltons, between 3,000 and 4,500, or between 3,200 and 3,700 as well as other pharmaceutically acceptable molecular weights utilized when formulating PEG with a chemical compound. Popular commercially available PEG forms have a molecular weight of 3350, 4000, and 6000 Daltons. The preparation of PEG may be polydisperse or monodisperse, for example. If polydisperse, then the molecular weight describes the weighted average molecular weight of the preparation. According to the formulations in powder or liquid form, the weight ratio of PEG to a compound may range between and including 5:1, 6:1, 7:1, 8:1, 9:1, and 10:1. In one embodiment, the weight ratio is about 8:1. However, the PEG does not assist in rendering the drug compound water-soluble.

[0082] For administration, the powdered form may be reconstituted in a liquid vehicle, either at the point of manufacture, at the dispensing pharmacy, or by the patient. The liquid vehicle may be water, a buffered aqueous solution, a syrup, or an aqueous beverage, such as an energy drink or an electrolyte-rich drink. For example, the water-soluble complex having improved solubility for the drug compound can be reformulated into sterile saline, or another

sterile liquid carrier for administration to a subject via subcutaneous (s.c.), intraperitoneal (i.p.), intramuscular (i.m.), intravenous (i.v.), topical, or oral routes (oral to enter the gastrointestinal tract or for buccal or sublingual administration). The water-soluble complex can also be formulated to be delivered by subcutaneous or intramuscular injection.

[0083] Suitable ingredients for formulating a tablet or pill or another solid oral form of the water-soluble complex may include any or all of, for example, corn starch, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, polyethylene glycol, titanium dioxide, and hypromellose. Additional compositions incorporating the described hydrogen-bonded and/or inclusion complexed A1C-regulating compounds can include formers, oral stool softeners, oral stimulants, and/or rectal suppositories in the form of a mixture.

[0084] While the dissolution of the water-soluble complex is slow enough to allow for the drug compound to move into the small intestine without precipitating in the stomach, additional means of extending the drug compound's release are known, such as enteric-coated tablets, additionally coating the complexes with a slowly dissolving polymer wherein the polymer can be selected by a desired length and/or thickness that can vary the drug compound release rate, placing the water-soluble complex in a gelative capsule, placing the water-soluble complex into an insoluble matrix (e.g., Slow-K or Imdur Durules), placing the water-soluble complex into an eroding matrix (e.g., MST Continus, Phyllocontin Continus), and/or enclosing the water-soluble complex in a semi-permeable membrane. *See, e.g.,* June 2011 "Pharmaceutical Issues when Crushing, Opening or Splitting Oral Dosage Forms," by the Royal Pharmaceutical Society. Additional modified-release oral dosage forms include: "extended-release drug products" wherein a dosage form of the water-soluble complex allows at least a twofold reduction in dosage frequency as compared to that water-soluble complex being presented without the extended-release format. Examples of extended-release dosage forms include controlled-release, sustained-release, and/or long-acting drug products. Another modified-release oral dosage is a delayed-release drug product. In the delayed release form, the water-soluble complex dosage form releases a discrete portion or discrete portions of the water-soluble complex at a given time other than promptly after administration. Enteric-coated dosage forms are common delayed-release products (e.g., enteric-coated aspirin and other NSAID products). Another modified-release oral form of the water-soluble complex contemplated is a targeted-release drug product. A water-soluble complex dosage form that releases the water-soluble complex at and/or near the intended physiologic site of action.

Another modified-release oral dosage of the water-soluble complex is orally disintegrating tablets (ODTs) or equivalent. ODTs have been developed to disintegrate rapidly in the saliva after oral administration. An ODT form of the water-soluble complex may be used without the addition of water. The water-soluble complex is dispersed in saliva and swallowed with little or no water.

[0085] By “delayed release” is meant that the water-soluble complex does not immediately release, but rather is released slowly or at a later time point after administration, such as 1 hour to 8 hours later. Improvement of a delayed release can be obtained by using such methods as enteric-coated capsules and the like. Alternatively, the release can be via subcutaneous injection into the subject. The water-soluble complexes described herein may be further formulated to form a targeted release form of the water-soluble complex.

[0086] By using a powdered or liquid formulation, dispensing proper A1C regulating compound dosages is easier, reducing errors, variations, and waste based on variations in the pill-splitting technique. Another benefit achieved by the method and products produced by the method is a decreased amount of an active A1C regulating compound because with greater solubility there will be greater bioavailability. The method provides a cost-benefit of having to utilize fewer resources for less of an active compound but still achieving the desired patient outcome.

[0087] Any of the components can be packaged in a kit, either separately in individual vessels, or in admixtures with each other. The end user may reconstitute the components with an included diluent or with a diluent of her choosing. The kit, in addition to the components, either separately or in mixtures, may contain instructions for use, tools for mixing and/or administering, storage vessels, etc. The kit can also be in the form of a prepared injectable, either for single use or multi-use with or without instructions or a means such as a QR code to obtain instructions. Kits can be in the form of a single or multiple-use injectable pen.

[0088] By “a pharmaceutically acceptable composition” is meant a composition comprising the water-soluble complex and one or more of a carrier, excipient (e.g., gelatin, cellulose, cellulose derivatives, polyvinylpyrrolidone, a starch, sucrose, and PEG), stabilizer (e.g., glycine, vitamin E, carboxymethylcellulose, sodium lauryl sulfate), a thickener, and a further sweetener. The composition can be a solid or a liquid form.

[0089] By “improved solubility” of a compound is meant an improvement of a compound’s solubility in water that is absent without the complexation with the sugar obtained by the methods described herein. Solutes used to solubilize the compound and sugar can be

methanol at 80% methanol, 95% (ACS grade), absolute methanol, or greater, as well as combinations of methanol and ethanol or methanol and water. Combinations can also be used or contain hexane. After solubilizing the sugar and the compound in ethanol or aqueous ethanol, the ethanol is evaporated for example under a high rotary vacuum. The solubilized sugar and compound can be solubilized in any of the described solvents, and then dried as described herein. The powder resulting from the evaporation step can be then resolubilized (dissolved) in water. As above, improvements in water solubility of the drug compound now in the form of the complex are measured at about 20 °C. in water and compared to the drug compound not in the form of the complex.

[0090] By the terms “water-soluble complex” and “water-soluble sugar-drug complex” are meant to include a sugar (e.g., rubusoside, stevia, dulcoside B, stevioside, n-dodecyl- β -D-maltoside, or rebaudioside A or other indicated sugar herein) and a drug compound such as an insulin or insulin analog or other A1C regulating compound as discussed herein that through dissolution with 95% ethanol, optionally with a pharmaceutically acceptable acid or base, forms water-soluble complexes, optionally further having been solubilized in the presence of a pharmaceutically acceptable acid. The water-soluble complex can further comprise a surfactant or a surfactant can be used instead of the non-nutritive sugar. An exemplary surfactant is a nonionic surfactant. The term “complex” as used herein is meant to include complexation, wherein complexation can further include multiple complexes.

[0091] The term “animal” or “subject” can include humans as well as domesticated animals (e.g., cats and dogs) having elevated A1C levels or glucose levels. The subject may be one to treat obesity (weight loss reduction), diabetes type 2, MASH, glycemic control, prediabetes, a condition characterized by impaired fasting glucose or impaired glucose tolerance (e.g., insulin resistance), an alpha- and beta cell dysfunction, and/or a condition having a suboptimal incretin effect. The subject can be a subject that suffers from Type 2 diabetes. Prediabetes in a human subject are values falling within 5.7 to about 6.4%. Thus, A1C levels in subjects should be lowered generally to less than 7% (King et al., “Glucagon-Like Peptide 1 Receptor Agonists Have the Potential to Revolutionize the Attainment of Target A1C Levels in Type 2 Diabetes – So Why is Their Uptake So Low?” *Clin. Diabetes* 41(2): 226-38 (2023)). The incretin effect describes the phenomenon whereby oral glucose elicits higher insulin secretory responses than does intravenous glucose (see e.g., Nauck et al., “The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions,” *Lancet Diabetes Endocrinol.*

4(6): 525-36 (2016). Cats and dogs also frequently suffer from diabetes and can be assisted with the use of animal-appropriate forms of insulin and other drugs.

[0092] The term “treating” or “treatment” is meant to include the treatment of a subject having an elevated A1C level and/ or glucose level by administering one or more compositions comprising a complex created by the methods described herein. The compositions described herein can also be used to treat obesity (weight loss reduction), type 1 diabetes (T1D), type 2 diabetes (T2D), MASH, glycemic control, prediabetes, a condition characterized by impaired fasting glucose or impaired glucose tolerance (e.g., insulin resistance), an alpha- and beta cell dysfunction, suboptimal incretin effect. The subject can be a human or a domesticated animal such as a dog or a cat having one or more similar conditions.

[0093] The use of a mole ratio of a drug compound to a sugar is used herein. A range of moles of drug compound to moles of sugar is 1:1 to 1:12, or 1:1 to 1:10, or 1:1 to 1:5. The “mole ratio” of a sugar to a drug compound listed herein can range from 1.0 to 0.001 or 10.00 to 0.1 and any 0.01 value between those two ranges. The “molar ratio” of a “sugar to a drug compound” in a formulation may range from about 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, or to about 10:1 and up to about 20:1 and any 0.1 value between of sugar to an A1C regulating compound. Alternatively, the sugar-to-drug compound ratio can be about 1.00:1.00 to about 5.00:1.00, and any 0.01 value within that range. In one embodiment, a about 2.0 to about 1.0 molar ratio of sugar to an A1C regulating compound is used.

[0094] By “daily unit dose” is meant the total amount of a drug compound given daily to a subject, whether in one administration or over multiple administrations, and, when one administration is used, whether one or multiple pills, capsules, tablets, or other formulations are used. A dosage of a formulation comprising the compound (e.g., as the water-soluble complex) would contain no more than a Generally Recognized as Safe (GRAS) amount of any constituent of the formulation. For example, in the case of a steviol sugar used as the DTG, a dosage would provide no more than about 10 mg/kg of the steviol sugar, because more than that for an average male of 70 kg, would result in a dosage of 700 mg of the sugar administered in one dosage. In another embodiment, the dosage would provide no more than 5.0 mg/kg of the steviol sugar to the subject. Also contemplated are 2.0 mg/kg, 3.0 mg/kg, 4.0 mg/kg, and 6.0 mg/kg amount of steviol sugar per dosage.

[0095] The methods described herein comprise dissolving a drug compound in ethanol (or another listed solvent or solvent combination) in the presence of an indicated sugar, followed by drying or evaporating (e.g., freeze-drying or lyophilizing or other means of

evaporating the ethanol or other solvent from the mixture) the solvent from the composition (step 1). Evaporation can use various steps including pre-freezing of the complex followed by primary and secondary drying steps. If lyophilization is employed, conventional lyophilization aids can be used in combination with the complex in solution. For step 2, the dried complex is then solubilized in water and can be evaporated again if necessary. The complex when dissolved in water in step 2 can further be filtered to remove any particulates. The water-soluble complex can be dried after being solubilized in water and can also be formulated into a pill or in any of the other forms described herein.

[0096] The water-soluble complex produced by the disclosed methods can be admixed with a pharmaceutically acceptable carrier preparation. A “pharmaceutically acceptable carrier” for parenteral administration includes sterile, aqueous, or non-aqueous solutions, suspensions, and emulsions. Aqueous carriers for use in a liquid formulation containing the water-soluble complex include water, alcoholic/aqueous solutions, emulsions, or suspensions, including saline or buffered media. Parenteral vehicles for delivering the water-soluble complex include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils.

[0097] The water-soluble complex may be mixed with other pharmaceutically acceptable excipients that are pharmaceutically acceptable and are compatible with the active ingredient in the drug. Suitable “pharmaceutically acceptable excipients” include water, saline, dextrose, glycerol, and ethanol, or combinations thereof. Intravenous vehicles for use in delivering the water-soluble complex include fluid and nutrient replenishers, electrolyte replenishers, such as those based on Ringer's dextrose, and the like.

[0098] The water-soluble complex can optionally include a preservative and/or an additive. Preservatives and additives contemplated for use with the water-soluble complex can include antimicrobials, anti-oxidants, chelating agents, inert gases, and the like. The preservative and/or additive is admixed (e.g., stirred) with the water-soluble complex after the formation of the complex.

[0099] The water-soluble complexes can be formulated into a solid form for oral, sublingual, or buccal administration such as a pill, capsule, caplet, chewable, tablet, lozenge, or soft gel. The water-soluble complex can be formulated as a powder, an orally disintegrating tablet, a sublingual drop, a sugar-free lollipop, a sugar-free chewing gum, a tincture, a capsule, a thin film, a sugar-free lozenge, a chewable pill or gummy, paste, or an effervescent powder or tablet. Alternatively, the water-soluble complex can be a formulation prepared for parenteral

administration and can be administered intradermally, subcutaneously, intramuscularly, intraperitoneally, topically, or intravenously.

[0100] An oral formulation of the complex can be further modified depending on the animal to which the formulation is to be administered. When solubility is increased, generally a reduction of the dose can be achieved for the animal being treated with the complex. Additional modifications to the final formulation containing the complex can include flavorants. The amounts of the water-soluble complex to be administered would be in an amount equivalent to the active drug compound if administered in a non-complexed form or less. Amounts administered are to be based on mg/kg of the weight of the subject receiving the active drug compound based on previously approved amounts of the drug compound in its non-complexed form or amounts less than the uncomplexed form of the drug compound. For example, for subjects, orally administered medications for carnivores can be meat flavored while for vegetarian subjects and vegans, the composition can be fruit (e.g., apple or pear) or grass flavored.

[0101] The complexes discussed herein can be prepared and formulated into single or multi-use syringes or pens. The dosing syringes and pens can be preloaded. The pre-loaded syringes and pens can be dispensed as kits with new needles and set dosing amounts; such pre-loaded syringes and pens can have multiple doses in one pre-loaded syringe.

[0102] Also contemplated are kits with preloaded syringes, pens, or devices to administer the complexes to a subject. A kit can include the water-soluble complex, a means for mixing the water-soluble complex into a delivery agent (e.g., saline, water, a lotion, gel, etc.), and a delivery device. Amounts that can be mixed of the water-soluble complex are done on a mg/kg level for the subject in need thereof. Instructions for use can also be included with the kit.

[0103] The dissolving method for the first solvent step or the water step (second step) can optionally include one or more acids or bases to further improve the solubility and/or stability of the water-soluble complex formed by the method. Preferably, the acid or base is a pharmaceutically acceptable acid or base when used with a drug. The acid or base can be added until solubility is achieved for the drug compound and the sugar.

[0104] For the first step, the drug compound can be solubilized fully or partially in either 95% ethanol, absolute ethanol, an aqueous ethanol solution of 50% ethanol or greater (e.g., 50%, 55%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, and 95% spectrophotometric grade ethanol as well absolute ethanol) in the presence of a sugar. Drugs

and chemicals contemplated include those drugs that are insoluble, have limited solubility, and are soluble in water. The compound or drug compound can be any free form of a compound or its salt, hydrate, solvate, hydrate polymorph, cocrystal, or salt of the indicated free form of the drug compound. The drug compound and sugar are solubilized in at least about 85% ethanol, and optionally in the presence of an acid or a base. In another embodiment, methanol can be added to the ethanol, drug compound, sugar, and optionally acid/base to further solubilize and form the complex. When using a listed sugar to form a complex, it may be more useful to use a non-salt form of the compound, which may offer more hydrogen pairing sites for the sugar to bind to. Optionally, the water-soluble complex remains soluble without the formation of a precipitate for at least 24 hours after formation. Alternatively, the solvent may be a co-solvent such as a binary or ternary (or higher) mixture of solvents. For example, the co-solvent can be about 50% ethanol with a buffer or water in the remainder, or, alternatively, a different or further solvent can be used in combination with water or an aqueous buffered solution. Frequently, a ratio of as little as about 1:0.00005 of ethanol to methanol (e.g., 95% or greater methanol) can improve solubility over ethanol alone. Therefore, a range of 1:1 ethanol to methanol to 1:0.00001 (and all 0.00001 values within that range) is contemplated. In some embodiments, methanol can be used in place of ethanol such that the ratios of methanol to ethanol are reversed to those cited above (e.g., 1:1 methanol to ethanol to 1:0.00001 methanol to ethanol with all values therebetween included). It can also be a combination of ethanol, methanol, and isopropanol.

[0105] Other pharmaceutically acceptable solvents that can be used alone or in combination to form the water-soluble complex include acetone, acetonitrile, anisole (methoxybenzene), benzene, 1-butanol, 2-butanol, butylacetate, *tert*-butylmethylether, carbon tetrachloride (tetrachloromethane), cumene, cyclohexane, 1,2-dichloroethane, 1,1-dichloroethene, dichloromethane, 1,2-dimethoxyethane, N,N-dimethylacetamide (DMA), N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), 1,4-dioxane, ethanol, 2-ethoxyethanol, ethylacetate, 2-ethoxyethanol, ethylacetate, ethyleneglycol, ethylether, ethylformate, formamide, formic acid, heptane, hexane, isobutyl acetate, isopropyl acetate, methanol, 2-methoxyethanol, methyl acetate, 3-methyl-1-butanol (isoamylalcohol), methylbutyl ketone, methylcyclohexane, methylethyl ketone, methylisobutyl ketone, 2-methyl-1-propanol, N-methylpyrrolidone, nitromethane, pentane, 1-pentanol, 2-propanol, propyl acetate, pyridine, sulfolane, tetrahydrofuran, tetralin, toluene, 1,1,1-trichloroethane, 1,1,2-thichloroethene, triethylamine, and xylene. In another embodiment, the solvent, or

solvent combination, may be water, ethanol, DMSO, DMF, methanol, acetone, ethyl acetate, hexane, heptane, dichloromethane, tetrahydrofuran, acetonitrile, or toluene. Organic solvents contemplated alone or in combination for step 1 include hexane, p-xylene, toluene, ether, methyl t-butyl ether (MTBE), diethylamine, dioxane, chlorobenzene, tetrahydrofuran, orthodichlorobenzene (ODCB), ethyl acetate, dimethoxyethane, pyridine, methylene chloride, HMPT, 1,2-di-chloroethane, DMPU, acetone, dimethylformamide, t-butyl alcohol, sulfolane, dimethylsulfoxide, acetonitrile, nitromethane, 2-propanol, benzyl alcohol, ethanol, methanol, ethylene glycol, trifluoroethanol, hexafluoroisopropanol, and water. Water is preferably deionized water or distilled water or deionized and distilled water. The non-nutritive sugar and the PSD (drug compound) should dissolve in the solvent or solvent combination for the method. Preferable solvents include ethanol, methanol, chloroform, hexane, and aqueous forms of the same. FDA-approved solvents are provided in the *Q3C – Tables and List Guidance for Industry* from June 2017. An FDA approved solvent can be one or more of acetonitrile, chlorobenzene, cyclohexane, cumene, 1,2-dichloroethene, dichloromethane, 1,2-dimethoxyethane, N,N-dimethylacetamide, N,N-dimethylformamide, 1,4-dioxane, 2-ethoxyethanol, formamide, hexane, methanol, 2-methoxyethanol, methylbutylketone, methylcyclohexane, methylisobutylketone, N-methyl pyrrolidone, nitromethane, pyridine, sulfolane, tetrahydrofuran, tetralin, toluene, 1,1,2-trichloroethene, and xylene within the FDA limits of what can be present. Another list of FDA solvents for use in step 1 includes one or more of acetone, anisole, 1-butanol, 2-butanol, butylacetate, *tert*-butylmethylether, dimethylsulfoxide, ethanol, ethylacetate, ethyl ether, ethyl formate, heptane, isobutylacetate, isopropyl acetate, methylacetate, 3-methyl-1-butanol, methylethylketone, 2-methyl-1-propanol, pentane, 1-pentanol, 1-propanol, 2-propanol, propyl acetate, and triethylamine.

[0106] The methods of making the water-soluble complex may in some instances further include a surfactant in either the solvent step (step 1) or the water step (step 2) of the methods described herein. Preferably the surfactant is used in Step 1. A surfactant can be a non-ionic surfactant. The surfactant can also be used in combination with an acid or base in the solution. The non-ionic surfactant can be a polysorbate surfactant (PSS) and/or a poloxamer surfactant (“PXS”). PXS are poloxamer surfactants, which are a class of synthetic nonionic amphiphilic triblock linear copolymers composed of a central hydrophobic chain of non-polar blocks of poly(propylene oxide) (PPO) blocks flanked by two hydrophilic chains of polar blocks of poly(ethylene oxide) (PEO). Poloxamer surfactants are available in different molecular weights and PPO/PEO ratios. PXS surfactants are commercially available as, for

instance, Kolliphor® P (BASF, Florham Park, NJ), Pluronic® (BASF, Florham Park, NJ), Lutrol® (BASF SE, Ludwigshafen, Germany) and Synperonic™ PE (CRODA International PLC, East Yorkshire, United Kingdom). PXS surfactants are available in liquid, flake, and paste physical forms. In an embodiment, the PXS is flake solid. Polysorbate surfactants (“PSS”) derived from ethoxylated sorbitan esterified with fatty acids and are commercially available as, for instance, Tween® (Croda International LLC, Wilmington DE) and Kolliphor® PS (BASF SE, Ludwigshafen, Germany). Polysorbate surfactants (PS) include Polysorbate 20 (e.g., Tween® 20), Polysorbate 40 (e.g., Tween® 40), Polysorbate 60 (e.g., Tween® 60), Polysorbate 65 (e.g., Tween® 65), and Polysorbate 80 (e.g., Tween® 80). The number following “polysorbate” relates to the major fatty acid associated with the molecule. For instance, “20” indicates monolaurate, and “80” indicates monooleate. Tween® 80 may also be referred to herein as T80 and similarly for the other types of Tween®.

[0107] The method further can comprise drying the water-soluble complex to form a solid. The dried solid can be re-dissolved into a suitable liquid.

[0108] The use of a mole ratio (or molar ratio) of a drug compound to a non-nutritive sugar to PSS surfactant (i.e., drug:sugar:PSS) is contemplated herein. A range of drug compound to non-nutritive sugar to PSS is 1:1:1 to 1:12:12, or 1:1:1 to 1:10:10, or 1:1:1 to 1:5:5, or any 0.1 amount between 1:1.0:1.0 and 1:12.0:12.0 (moles of drug compound) to moles of non-nutritive sugar to moles of PSS; i.e., drug:sugar:PSS.

[0109] The use of a mole ratio of a drug compound to a sugar to PXS surfactant (drug:sugar:PXS) is contemplated herein. A range of drug compound to sugar to PXS is from about 1:1:0.5 to 1:12:12, or 1:1:1 to 1:12:12, or 1:1:1 to 1:10:10, or 1:1:1 to 1:5:5, or any 0.1 amount between from about 1:1.0:0.5 and about 1:12.0:12.0 (moles of drug compound to moles of sugar to moles of PXS; i.e., drug: sugar:PXS).

[0110] The method can use the surfactant with one or more solvents or also in the presence of an acid or a buffer. The solvent used in the method can be a pure solvent, such as absolute ethanol, or a mixture of solvents such as ethanol, water, and methanol as suggested herein. The sugar, drug compound, and solvent can have the surfactant with them in a vessel and the pH can then be adjusted until a homogeneous solution is formed. Preferably the homogeneous solution remains stable for at least 30 minutes, more preferably at least 2 hours, more preferably at least about 24 hours.

[0111] For administration, the powdered form may be reconstituted in a liquid vehicle, either at the point of manufacture, at the dispensing pharmacy, or by the patient. The liquid

vehicle may be water, a buffered aqueous solution, a syrup, or an aqueous beverage, such as an energy drink or an electrolyte-rich drink. For example, the water-soluble complex having improved water solubility can be reformulated, for example, into sterile saline, or another sterile liquid carrier for administration to a subject via subcutaneous (s.c.), intraperitoneal (i.p.), intramuscular (i.m.), intravenous (i.v.), or oral routes (oral to enter the gastrointestinal tract or for buccal or sublingual administration). The water-soluble complex can also be formulated into a subcutaneous or intramuscular injection.

[0112] Suitable ingredients for formulating a tablet or pill or another solid oral form of the water-soluble complex may further include any or all of, for example, corn starch, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, polyethylene glycol, titanium dioxide, and hypromellose. Additional compositions incorporating the described hydrogen-bonded and/or water-soluble complexes can include or be in the form of oral stool softeners, perfumes, colors, oral stimulants, and/or rectal suppositories.

[0113] The use of the terms “sugar” and “non-nutritive sugar” means that the sugar is a non-nutritive sweetener. A non-nutritive sugar has a sweetness of at least 50 times that of glucose with essentially no calories. A non-nutritive sweetener sugar or “DTG” as used herein can be rubusoside, dulcoside B (also known as rebaudioside C), stevia, rebaudioside A (also known as stevioside A3), stevioside (a type of diterpene glycoside and has a chemical formula of $C_{38}H_{60}O_{18}$), n-octyl glucose, n-dodecyl- β -D-maltoside (also known as dodecyl maltoside or lauryl maltoside), stevia (has a chemical formula of $C_{44}H_{70}O_{23}$), and a steviol glycoside such as that derived from *Stevia rebaudiana*. It can also be any of the other sugars discussed herein. While other stevia-like sugars are known, only those that are FDA GRAS-approved are contemplated for use in the water-soluble complex for administration to a human subject. Preferably, the sugar is one or more of rubusoside, stevia, dulcoside B, stevioside, n-dodecyl- β -D-maltoside, or rebaudioside A which can be used in any combination or permutation. Also contemplated is any permutation of these listed 6 sugars (2 of the sugars, 3 of the sugars, etc.). The price of the sugar can be a factor in whether a sugar is commercially a good sugar for solubilizing a poorly soluble or soluble drug compound. Exemplary sugars for making the “water-soluble complex” are rubusoside, dulcoside A, dulcoside B, sucrose, D-fructose, sucralose, rebaudioside A, rebaudioside B, rebaudioside D, stevioside, stevia n-octyl glucose, or n-dodecyl- β -D-maltoside, with the proviso that when the sugar is rubusoside the compound is not praziquantel. The exemplary non-nutritive sugars include diterpene di-glycosides (referenced herein as DDGs, which are a subset of DTGs). Not to be bound by a theory, it is

believed that when a water-soluble complex is formed between a sugar and a drug compound, a surfactant and a drug compound, or a sugar/surfactant/drug compound, a stable complex occurs, presumably by non-covalent hydrogen bonding and optionally hydrophobic-hydrophobic interactions, such as van der Waal forces. A “sugar” as used herein can be dulcoside A, sucrose, D-fructose, sucralose, a rebaudioside B, rebaudioside D, stevia, n-octyl glucose, Advantame®, neotame®, thaumatin, saccharin, Lou Han Guo, aspartame, acesulfame potassium (Ace-K), allulose, rubusoside, dulcoside B (also known as rebaudioside C), rebaudioside A (also known as stevioside A3), a stevioside (a type of DDG), n-octyl glucose, and a steviol glycoside such as that derived from *Stevia rebaudiana*. While other stevia-like sugars are known, only those that are FDA GRAS-approved or approved for use in Europe are contemplated for human use. Preferably, the sugar is one or more of rubusoside, stevia, dulcoside B, stevioside, or rebaudioside A which can be used in any combination or permutation. Also contemplated is any permutation of the listed sugars (2 of the sugars, 3 of the sugars, etc.) in forming a complex. The price of the non-nutritive sugar is also a factor in whether a sugar is commercially a good sugar for solubilizing a blood A1C and/or blood glucose regulating drug compound. Additional contemplated non-nutritive sugars that are not diterpene diglycoside sugars but can be paired with a drug compound as described herein include:

[0114] ADVANTAME® – is an aspartame analog; N-[N-[3-(3-hydroxy-4-methoxyphenyl) propyl]- α -aspartyl]-L-phenylalanine-1-methyl ester (Otabe et al., “Advantame® – An Overview of Toxicity Data,” Food and Chemical Toxicity 49(S1): S2-S7, 2011. Advantame® has a low glycemic index (GI) and zero calories but can cause a spike in insulin.

[0115] NEOTAME® – tradename is Newtame® and is a derivative of aspartame that is classified as an aspartyl-derived dipeptide. Neotame® has a low glycemic index (GI) and zero calories but can cause a spike in insulin.

[0116] Thaumatin – is also known as TALIN®, Soma sweet. It is a mixture of the sweet proteins thaumatin I and thaumatin II derived from *Thaumatococcus danielli*.

[0117] Saccharin – is also known as saccharine or benzosulfimide and in such salt forms as saccharin sodium and saccharin calcium. It is sold under the brand names Sweet and Low®, Sweet Twin®, Sweet’N Low® and Necta Sweet®. Saccharin has a low glycemic index (GI) and zero calories but can cause a spike in insulin.

[0118] Sucralose – sold under the name Splenda and is an organochlorine sweetener having the chemical name of 1,6-dichloro-1,6-dideoxy- β -D-fructofuranosyl-4-chloro-4-deoxy- α -D-galactopyranoside (Schiffman et al., “Sucralose, A Synthetic Organochlorine Sweetener: Overview of Biological Issues,” *J. Toxicol Environ. Health B. Crit. Rev.* 16(7): 399-451, 2013). Sucralose has a low glycemic index (GI) and zero calories but can cause a spike in insulin.

[0119] Lou Han Guo – also goes by the name of *Siraitia grosvenorii*, swingle fruit, monk fruit, and luohan guo from which sweeteners can be derived that have no calories. The FDA has called this Swingle Fruit Extract (SGFE). The compounds that give the sweetness are mogrosides, which have a mogrol backbone and glucose units (glycosides) attached to them. They may be sold under the brands Monk Fruit in the Raw®, Lakanto®, PureLo®, SPLENDA® Monk Fruit Sweetener, SweetLeaf®, and Whole Earth®. SGFE does not appear to raise blood sugar levels.

[0120] Aspartame – is sold under the names Nutrasweet, Equal, and Sugar Twin and does contain calories. The chemical name is L-aspartyl-L-phenylalanine methyl ester. It is a dipeptide composed of phenylalanine and aspartic acid. Aspartame has a low glycemic index (GI) and zero calories but can cause a spike in insulin.

[0121] Acesulfame potassium – is also known as Ace-K and is sold under the brand names Sweet One® and Sunett®. Ace-K has a low glycemic index (GI) and zero calories but can cause a spike in insulin.

[0122] Allulose - is a sugar that naturally occurs in figs and raisins. It is also known as D-psicose or D-allulose and has few calories. It does not impact insulin or blood sugar levels. Tani et al., “Allulose for the attenuation of postprandial blood glucose levels in healthy humans: A systematic review and meta-analysis,” *PLoS One* 18(4): e0281150, 2023.

[0123] The sweetness of a non-nutritive sugar is compared to table sugar (sucrose) and is summarized in the following table obtained from the US FDA:

Sugar	Times Sweeter than Sucrose
ADVANTAME®	20,000
NEOTAME®	7,000-13,000
Thaumatococin	2,000-3,000
Saccharin	200-700
Sucralose	600

Sugar	Times Sweeter than Sucrose
Steviol Glycosides	200-400
Luo Han Guo	200-250
Aspartame	200
Acesulfame Potassium (Ace-K)	200

[0124] The complexation of the drug compound with the non-nutritive sugar can be construed as a donor (sugar) receptor (drug compound) interaction, such as host-guest chemistry between the drug compound and the sugar, which essentially allows the drug compound to capture the water solubility of the sugar.

[0125] If desired, a polyethylene glycol (PEG) can be optionally added to the liquid and powdered formulations to further improve bioavailability. Typically, this is between 2000 and 6000 Daltons, between 3000 and 4500, or between 3200 and 3700 as well as other pharmaceutically acceptable molecular weights utilized when formulating PEG with a chemical compound. Popular commercially available PEG forms have a molecular weight of 3350, 4000, and 6000 Daltons. The preparation of PEG may be polydisperse or monodisperse, for example. If polydisperse, then the molecular weight describes the weighted average molecular weight of the preparation. According to the formulations in powder or liquid form, the weight ratio of PEG to an A1C regulating compound may range between and including 5:1, 6:1, 7:1, 8:1, 9:1, and 10:1. In one embodiment, the weight ratio is about 8:1.

[0126] For administration, the powdered form may be reconstituted in a liquid vehicle, either at the point of manufacture, at the dispensing pharmacy, or by the patient. The liquid vehicle may be water, a buffered aqueous solution, a syrup, or an aqueous beverage, such as an energy drink or an electrolyte-rich drink. For example, the water-soluble complex having improved water solubility can be reformulated into sterile saline, or another sterile liquid carrier for administration to a subject via subcutaneous (s.c.), intraperitoneal (i.p.), intramuscular (i.m.), intravenous (i.v.), topical, or oral routes (oral to enter the gastrointestinal tract or for buccal or sublingual administration).

[0127] Suitable ingredients for formulating a tablet or pill or another solid oral form of the hydrogen-bonded and/or water-soluble complex may include any or all of, for example, corn starch, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, polyethylene glycol (PEG), titanium dioxide, and hypromellose. Additional compositions

incorporating the described hydrogen-bonded and/or water-soluble complex can include formers, oral stool softeners, oral stimulants, and/or rectal suppositories.

[0128] Additional means of extending drug release are known, such as enteric coated tablets, additionally coating the complexes with a slowly dissolving polymer wherein the polymer can be selected by a desired length and/or thickness that can vary the drug release rate, placing the complex in a gelative capsule, placing the complex into an insoluble matrix (e.g., Slow-K or Imdur Durules), placing the complex into an eroding matrix (e.g., MST Continus, Phyllocontin Continus), and/or enclosing the complex in a semi-permeable membrane. *See*, e.g., June 2011 “Pharmaceutical Issues when Crushing, Opening or Splitting Oral Dosage Forms,” by the Royal Pharmaceutical Society. Additional modified-release oral dosage forms include: “extended-release drug products” wherein a dosage form of the complex allows at least a twofold reduction in dosage frequency as compared to that water-soluble complex being presented without the extended-release format. Examples of extended-release dosage forms include controlled-release, sustained-release, and/or long-acting drug products. Another modified-release oral dosage is a delayed-release drug product. In the delayed release form, the complex’s dosage form releases a discrete portion or discrete portions of the compound or the drug from the complex at a given time other than promptly after administration. Enteric-coated dosage forms are common delayed-release products (e.g., enteric-coated aspirin and other NSAID (non-steroidal anti-inflammatory drug) products are examples of coated drugs). Another modified-release oral form of the complex contemplated is a targeted-release drug product. A dosage form that releases the drug complex at and/or near the intended physiologic site of action. Another modified-release oral dosage of the water-soluble complex is orally disintegrating tablets (ODT) or equivalent. ODT has been developed to disintegrate rapidly in the saliva after oral administration. An ODT form of the sugar-A1C regulating compound complex may be used without the addition of water. The water-soluble complex is dispersed in saliva and swallowed with little or no water.

[0129] Any of the components can be packaged in a kit, either separately in individual vessels, or in admixtures with each other. The end user may reconstitute the components with an included diluent or with a diluent of her choosing. The kit, in addition to the components, either separately or in mixtures, may contain instructions for use, tools for mixing and/or administering to a subject, storage vessels, etc. Any of the components can be packaged in a kit, either separately in individual vessels, or in admixtures with each other.

[0130] Another characteristic that may be imparted by the method of improving a drug/compound's solubility is that the storage stability of the water-soluble complex can be increased as described herein.

[0131] In all the following examples, the same conditions were used unless otherwise noted. The water used is deionized, distilled water. Unless indicated otherwise, 95% ethanol (ACS spectrophotometric grade, unless otherwise specified) was used. High vacuum drying was performed at room temperature, using, for instance, an Edwards Model RV8 high vacuum pump with an IKA model C-mag HS7 magnetic stirrer. The example below used a Heto Drywinner model #DW-1.0-60E freeze-drying machine to remove the ethanol. A rotary evaporator such as a Heidolph Basis Hei-VAP value (No. 560-00000-01-1) can alternatively be used to remove ethanol from the mixture, for instance, under reduced pressure at 35°C bath temperature to produce the solid. The reagent used was as follows: Insulin lispro was purchased from Millipore Sigma (empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$; a molecular weight of 5.807.57 kDa; CAS Number: 133107-64-9). Humalog® (registered trademark of Eli Lilly and Company) is a commercial insulin lispro.

EXAMPLE 1 – Insulin lispro and Stevioside

[0132] The following example indicates that stevioside improves the solubility of insulin lispro.

[0133] Step 1: In an oven-dried single neck RB flask equipped with magnetic stir and septa (flask cap), 5 milligrams (mg) insulin lispro (0.00086 mmol) and 6.93 mg stevioside (0.0086 mmol) (molar ratio of 1:10 insulin lispro to stevioside) were weighed into the RB flask and dissolved in 2.0 mL absolute ethanol (spectrophotometric grade, 95%) at ambient temperature. The reaction mixture was vigorously stirred at room temperature for up to 30 min. The resulting solution was hazy. The solution was dried over a high vacuum being kept below 30 °C. for an hour to remove the ethanol completely. This was followed by a freeze/dry process. Freeze/dry process: at around -30 °C., the flask was placed in a cold bath and was rotated around in the water until the walls were like thick ice. Then freeze drying over freeze dryer under vacuum. The temperature is kept below 0 °C. until the ice evaporates, thereby obtaining a white solid (complex of stevioside and insulin).

[0134] Step 2: 2.5 mg of the obtained white solid (1:0:10.0 molar ratio insulin:stevioside complex) was then dissolved in 0.3 mL distilled water (DI) at room temperature in an RB flask with a magnetic stir bar. The reaction mixture was stirred at ambient temperature for 30 min. The resulting solution (pH~5.0) was clear and homogenous by eye.

[0135] The resulting white solid was dissolved in deionized water. The water-soluble complex was analyzed by NMR. *See* FIG. 1. The NMR analysis confirmed the solubility of the 1:0:10.0 molar ratio insulin:stevioside complex given the multiple insulin peaks seen. These data indicate that insulin is soluble in water in the presence of stevioside.

EXAMPLE 2 – Stevioside and Semaglutide

[0136] In this example, semaglutide free base (Astatech Cat. AT35750, CAS#: 910463-68-2, Lot#: P180-01178, 0.005 g 99% purity) and stevioside were combined as follows to see if a complex could be formed. This example used 3.0 mg semaglutide and 100 mg of stevioside which were placed in a round bottom flask to which 2.0 ml 85% ethanol was added and then stirred with a magnetic stir bar for 30 minutes at room temperature and initially observed to form a clear solution at room temperature. After 30 minutes, solid particles were observed to form and after 15 more minutes, the solution was white and turbid with solid particles. To this solution was added 2.0 mL absolute methanol (99.8%) and the solution was stirred for 15 more minutes. The solution remained white and turbid. A rotary evaporator, as in Example 1, was used to remove the ethanol and methanol. The material was dried until no further change of weight was observed.

[0137] To the dried material from the ethanol/methanol step above (Step 1) was added 2.0 mL deionized water and stirred for 30 minutes at room temperature. A clear homogenous solution was observed to immediately form. The sample was again dried using a rotary evaporator, but now a 30 °C. water bath also was used. The sample was dried until no further change in weight was observed. When tested by NMR, it was clear that the semaglutide and stevioside formed a soluble complex. *See* FIG. 2. Semaglutide sodium is considered insoluble in water and DMSO at 25 °C.; it is soluble at 8 mg/mL in 4-methylpyridine. Semaglutide free base has a molecular weight of 4113.58. The complex remained soluble in water solution for at least about 8 days.

EMBODIMENTS

[0138] The following are exemplary embodiments with additional embodiments being described throughout the specification.

[0139] Embodiment 1. A water-soluble complex comprising a sugar and a poorly water-soluble drug (PSD also referred to as a drug compound), which complex comprises: a molar ratio of up to about 12 moles of the sugar for each mole of the poorly water-soluble drug, wherein the sugar is one or more of rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A, provided that the water-soluble complex has at least a two (2),

three (3), four (4) or five (5) fold increase in the water solubility of the poorly soluble drug at 20 °C. as compared to the water solubility of the drug not in the water-soluble complex; and further provided that a maximum amount of the sugar in a daily unit dose of the complex is no more than about 10 mg/kg, and wherein the PSD is an insulin.

[0140] Embodiment 2. The water-soluble complex of Embodiment 1, wherein the PSD is insulin or an insulin analog.

[0141] Embodiment 3. The water-soluble complex of Embodiment 1 or 2, wherein the PSD is a rapid-acting insulin, a short-acting insulin, an intermediate-acting insulin, a long-acting insulin, or an ultra-long-acting insulin.

[0142] Embodiment 4. The water-soluble complex of any of Embodiments 1-3, wherein the sugar is rubusoside, rebaudioside A, dodecyl- β -D-maltoside, dulcoside B, or stevioside.

[0143] Embodiment 5. The water-soluble complex of Embodiment 4, wherein the sugar is rubusoside or stevioside.

[0144] Embodiment 6. The water-soluble complex of any of Embodiments 1-5, wherein the amount of the sugar in the daily unit dose is no more than 5 mg/kg.

[0145] Embodiment 7. The water-soluble complex of any of Embodiments 1-5, wherein the amount of the sugar in the daily unit dose is no more than about 280 mg.

[0146] Embodiment 8. The water-soluble complex of any of Embodiments 1-5, wherein the water-soluble complex comprises a molar ratio of the PSD to mole of sugar of about 1:1 to about 1:10 moles.

[0147] Embodiment 9. The water-soluble complex of any of Embodiments 1-5, wherein the water-soluble complex comprises a molar ratio of about 2 to about 10 moles of the sugar for each mole of the PSD.

[0148] Embodiment 10. The water-soluble complex of Embodiment 9, wherein the water-soluble complex comprises a molar ratio of about 3 moles of the sugar for each mole of the PSD.

[0149] Embodiment 11. The water-soluble complex of any of Embodiments 1-5, wherein the water-soluble complex is stable in water at pH 8.5 for at least 2 hours.

[0150] Embodiment 12. The water-soluble complex of any of Embodiments 1-5, wherein the water-soluble complex is stable in water at pH 4 for at least 2 hours.

[0151] Embodiment 13. A dried form of the water-soluble complex of any of Embodiments 1-12, wherein the dried form is stable at 30 °C. for at least 90 days.

[0152] Embodiment 14. The water-soluble complex of any of Embodiments 1 to 13, wherein the water-soluble complex is in the form of a powder, a tablet, an orally disintegrating tablet, a capsule, a liquid, a gel, a thin film, a lozenge, an effervescent powder or tablet, an emulsion, or formulated for parenteral administration.

[0153] Embodiment 15. The water-soluble complex of Embodiment 14, wherein the formulation for parenteral administration is to be administered intradermally, subcutaneously, intramuscularly, intraperitoneally, intrathecally, intravenously, topically, or as a transdermal patch.

[0154] Embodiment 16. The water-soluble complex of any of Embodiments 1 to 13, wherein the water-soluble complex is in the form of a thin film, an effervescent powder or tablet, a syrup, a solution, an elixir, an emulsion, a chewing gum, a lollipop, a sublingual drop, a soft gel, or a tincture.

[0155] Embodiment 17. A water-soluble complex comprising a sugar and a poorly soluble drug (PSD), wherein the water-soluble complex comprises: a molar ratio of about 1 to 12 moles of the sugar for each mole of the PSD, wherein the sugar is one or more of rubusoside, rebaudioside A, dulcoside B, dodecyl- β -D-maltoside (DDM), or stevioside; wherein the water-soluble complex is stable in water at pH 8.5 and at pH 4.0 for at least 2 hours each; provided that the water-soluble complex has at least a two (2), three (3), four (4) or five (5) fold increase in the water solubility of the PSD, at 20 °C. as compared to the water solubility of the PSD that is not in the water-soluble complex; and further provided that a maximum amount of the sugar in a daily unit dose of the water-soluble complex is no more than about 280 mg, wherein the PSD is an insulin.

[0156] Embodiment 18. A method of making a water-soluble complex comprising a sugar and a poorly water-soluble drug(PSD), the method comprising the steps of

admixing, in at least 85% ethanol, the sugar with the PSD in a molar ratio of from about 1 to about 12 moles of the sugar for each mole of the PSD until solubilized thereby forming the water-soluble complex, wherein formation of the water-soluble complex can be determined by nuclear magnetic resonance spectroscopy, and wherein the sugar is one or more of rubusoside, rebaudioside A, dulcoside B, dodecyl- β -D-maltoside (DDM), or stevioside; and wherein the admixing step is optionally performed with a pharmaceutically acceptable acid; and

optionally drying the water-soluble complex, wherein the PSD is an insulin.

[0157] Embodiment 19. The method of Embodiment 18, wherein the sugar is rubusoside or stevioside.

[0158] Embodiment 20. The method of any of Embodiment 18 or 19, wherein the PSD is a short-acting insulin, an intermediate-acting insulin, or a long-acting insulin.

[0159] Embodiment 21. The method of Embodiment 18, wherein the method further comprises drying the water-soluble aggregate.

[0160] Embodiment 22. The method of Embodiment 21, wherein the dried water-soluble aggregate is resolubilized in a liquid.

[0161] Embodiment 23. The method of Embodiment 18, wherein the admixing step is in the presence of a sufficient amount of a pharmaceutically acceptable acid to solubilize and render the reaction mixture homogeneous and clear.

[0162] Embodiment 24. The method of Embodiment 23, wherein the pharmaceutically acceptable acid is acetic acid, ascorbic acid, aspartic acid, citric acid, formic acid, fumaric acid, gluconic acid, glutamic acid, glutaric acid, glycolic acid, hydrochloric acid, lactic acid, lauric acid, maleic acid, malic acid, malonic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, propionic acid, salicylic acid, stearic acid, succinic acid, or tartaric acid.

[0163] Embodiment 25. The method of Embodiment 18, wherein the formed water-soluble complex comprises a molar ratio of about 1 to about 10 moles of the sugar for each mole of the PSD.

[0164] Embodiment 26. The method of Embodiment 25, wherein the sugar is rubusoside or stevioside.

[0165] Embodiment 27. The method of Embodiment 25, wherein the formed water-soluble complex comprises a molar ratio of about 2 to about 5 moles of the sugar for each mole of the PSD.

[0166] Embodiment 28. The method of Embodiment 27, wherein the sugar is rubusoside or stevioside.

[0167] Embodiment 29. The method of Embodiment 25, wherein the formed water-soluble complex comprises a molar ratio of about 2 to about 4.5 moles of the sugar for each mole of the PSD.

[0168] Embodiment 30. The method of Embodiment 29, wherein the sugar is rubusoside or stevioside.

[0169] Embodiment 31. The method of Embodiment 25, wherein the formed water-soluble complex comprises a molar ratio of about 8 moles of the sugar for each mole of the PSD.

[0170] Embodiment 32. The method of Embodiment 31, wherein the sugar is rubusoside or stevioside.

[0171] Embodiment 33. The method of Embodiment 18, wherein the formed water-soluble complex is stable in water at pH 8.5 for at least 2 hours.

[0172] Embodiment 34. The method of Embodiment 18, wherein the formed water-soluble complex is stable in water at pH 4 for at least 2 hours.

[0173] Embodiment 35. The method of Embodiment 21, wherein the method further comprises drying the water-soluble complex by freeze-drying or lyophilizing.

[0174] Embodiment 36. The method of Embodiment 35, wherein the dried water-soluble complex is formulated into a pill or a pharmaceutically acceptable liquid.

[0175] Embodiment 1A. A water-soluble complex comprising a non-nutritive sugar and a drug compound, which complex comprises:

a molar ratio of up to about 12 moles of the non-nutritive sugar for each mole of the drug compound, wherein the non-nutritive sugar is one or more of ADVANTAME®, NEOTAME®, thaumatin, saccharin, sucralose, Lou Han Guo, aspartame, acesulfame potassium, allulose, rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A,

provided that the water-soluble complex has at least a two (2) fold increase in the water solubility of the drug compound at 20 °C as compared to the water solubility of the drug compound not in the water-soluble complex and/or has at least one improved pharmacokinetic attribute (e.g., C_{max} , time to C_{max} , stability, duration and the like); and

further, provided that a maximum amount of the sugar in a daily unit dose of the water-soluble complex is no more than about 10 mg/kg, wherein the drug compound is peptide or small compound for reducing blood glucose in a subject and/or blood A1C, and the drug compound is insulin, an insulin analog, a natural insulin variant, a GLP-1 receptor agonist, an incretin mimetic, a GIP agonist, an amylin agonist, a glucagon agonist, or a salt thereof.

[0176] Embodiment 2A. The water-soluble complex of Embodiment 1A, wherein the drug compound is an insulin analog, insulin, or a natural insulin variant.

- [0177] Embodiment 3A. The water-soluble complex of Embodiment 2A, wherein the insulin analog is insulin lispro, insulin aspart, insulin glulisine, admelog insulin, NPH insulin, insulin isophane, insulin glargine, insulin detemir, or insulin degludec.
- [0178] Embodiment 4A. The water-soluble complex of Embodiment 1A, wherein the drug compound is a rapid-acting insulin, short-acting insulin, intermediate-acting insulin, long-acting insulin, or an ultra-long-acting insulin.
- [0179] Embodiment 5A. The water-soluble complex of Embodiment 1A, wherein the drug compound is a GLP-1 receptor agonist.
- [0180] Embodiment 6A. The water-soluble complex of Embodiment 5A, wherein the GLP-1 receptor agonist is semaglutide, tirzepatide, amycretin, orforglipron, albiglutide, beinaglutide, cagrilintide, CagriSema, CT996, danuglipron, efinopegdutide, HM15211, lixisenatide, pemvidutide, retratrutide, SCO-094, survodutide, WK2735, mazdutide, PEG-loxenatide (PEX168), liraglutide, dulaglutide, exenatide, or a salt thereof.
- [0181] Embodiment 7A. The water-soluble complex of Embodiment 1A, wherein the drug compound is a GIP agonist.
- [0182] Embodiment 8A. The water-soluble complex of Embodiment 7A, wherein the GIP agonist is HM15211, retratrutide, SCO-094, tirzepatide, WK2735, or ZP6590.
- [0183] Embodiment 9A. The water-soluble complex of Embodiment 1A, wherein the drug compound is a glucagon agonist.
- [0184] Embodiment 10A. The water-soluble complex of Embodiment 9A, wherein the glucagon agonist is efinopegdutide, HM15211, mazdutide, pemvidutide, or survodutide.
- [0185] Embodiment 11A. The water-soluble complex of Embodiment 1A, wherein the drug compound is an amylin agonist.
- [0186] Embodiment 12A. The water-soluble complex of Embodiment 11A, wherein the amylin agonist is AZD6234, cagrilintide, CagriSema, CT388, a long-acting amylin agonist, amycretin, or ZP8396.
- [0187] Embodiment 13A. The water-soluble complex of any of Embodiments 1A to 12A, wherein the non-nutritive sugar is rubusoside, rebaudioside A, dodecyl- β -D-maltoside, dulcoside B, or stevioside.
- [0188] Embodiment 14A. The water-soluble complex of Embodiment 13A, wherein the non-nutritive sugar is rubusoside or stevioside.

[0189] Embodiment 15A. The water-soluble complex of any of Embodiments 1A to 14A, wherein the amount of the non-nutritive sugar in the daily unit dose is no more than 5 mg/kg of subject weight.

[0190] Embodiment 16A. The water-soluble complex of any of Embodiments 1A to 14A, wherein the amount of the non-nutritive sugar in the daily unit dose is no more than about 280 mg.

[0191] Embodiment 17A. The water-soluble complex of any of Embodiments 1A to 14A, wherein the water-soluble complex comprises a molar ratio of the drug compound to the non-nutritive sugar of about 1:1 to about 1:10 moles (drug compound:non-nutritive sugar).

[0192] Embodiment 18A. The water-soluble complex of any of Embodiments 1A to 14A, wherein the water-soluble complex comprises a molar ratio (non-nutritive sugar:drug compound) of about 2 to about 10 moles of the non-nutritive sugar for each mole of the drug compound.

[0193] Embodiment 19A. The water-soluble complex of Embodiment 18A, wherein the water-soluble complex comprises a molar ratio of about 3 moles of the non-nutritive sugar for each mole of the drug compound.

[0194] Embodiment 20A. The water-soluble complex of any of Embodiments 1A to 14A, wherein the water-soluble complex is stable in water at pH 8.5 for at least 2 hours.

[0195] Embodiment 21A. The water-soluble complex of any of Embodiments 1A to 14A, wherein the water-soluble complex is stable in water at pH 4 for at least 2 hours.

[0196] Embodiment 22A. A dried form of the water-soluble complex of any of Embodiments 1A to 19A, wherein the dried form of the water-soluble complex is stable at 30 °C. for at least 90 days.

[0197] Embodiment 23A. The water-soluble complex of any of Embodiments 1A to 19A, wherein the water-soluble complex is formulated as a powder, a tablet, an orally disintegrating tablet, a capsule, a liquid, a gel, a thin film, a lozenge, an effervescent powder or tablet, an emulsion, or formulated for parenteral administration.

[0198] Embodiment 24A. The water-soluble complex of Embodiment 23A, wherein the water-soluble complex is formulated to be administered intradermally, subcutaneously, intramuscularly, intraperitoneally, intrathecally, intravenously, topically (e.g., gel, cream, or ointment), or as a transdermal patch.

[0199] Embodiment 25A. The water-soluble complex of any of Embodiments 1A to 22A, wherein the water-soluble complex is in the form of a thin film, an effervescent powder

or tablet, a syrup, a solution, an elixir, an emulsion, a chewing gum, a lollipop, a sublingual drop, a soft gel, or a tincture.

[0200] Embodiment 26A. A water-soluble complex comprising a non-nutritive sugar and a drug compound, which water-soluble complex comprises:

a molar ratio of about 1 to 12 moles of the non-nutritive sugar for each mole of the drug compound, wherein the non-nutritive sugar is one or more of ADVANTAME®, NEOTAME®, thaumatin, saccharin, sucralose, Lou Han Guo, aspartame, acesulfame potassium, allulose, rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A;

wherein the water-soluble complex is stable in water at pH 8.5 and at pH 4.0 for at least 2 hours each;

provided that the water-soluble complex has at least a two (2) fold increase in the water solubility at 20 °C. as compared to the water solubility of the drug compound that is not in the water-soluble complex or has at least one improved pharmacokinetic attribute (e.g., C_{max} , time to C_{max} , stability, duration and the like); and

further provided that a maximum amount of the non-nutritive sugar in a daily unit dose of the water-soluble complex is no more than about 280 mg; wherein the drug compound is a peptide or small compound for reducing blood glucose and/or blood A1C in a subject, wherein the drug compound is insulin, an insulin analog, a natural insulin variant, a GLP-1 receptor agonist, an incretin mimetic, a GIP agonist, an amylin agonist, a glucagon agonist, or a salt thereof.

[0201] Embodiment 27A. A method of making a water-soluble complex comprising a non-nutritive sugar and a drug compound, the method comprising the steps of: admixing, in at least 85% ethanol, the non-nutritive sugar with the drug compound in a molar ratio of from about 1 to about 12 moles of the sugar for each mole of the drug compound until solubilized thereby forming the water-soluble complex, wherein formation of the water-soluble complex can be determined by nuclear magnetic resonance spectroscopy (NMR), and wherein the non-nutritive sugar is one or more of ADVANTAME®, NEOTAME®, thaumatin, saccharin, sucralose, Lou Han Guo, aspartame, acesulfame potassium, allulose, rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A; and wherein the admixing step is optionally performed with a pharmaceutically acceptable acid; and drying the water-soluble complex and dissolving the water-soluble complex in water, wherein the drug compound is a peptide or small compound for reducing blood glucose and/or blood A1C in a

subject, and the drug compound is insulin, an insulin analog, a natural insulin variant, a GLP-1 receptor agonist, an incretin mimetic, a GIP agonist, an amylin agonist, a glucagon agonist, or a salt thereof.

[0202] Embodiment 28A. The method of Embodiment 27A, wherein the drug compound is a rapid-acting insulin, short-acting insulin, intermediate-acting insulin, long-acting insulin, or an ultra-long-acting insulin.

[0203] Embodiment 29A. The method of Embodiment 27A, wherein the drug compound is an insulin analog, insulin, or a natural insulin variant.

[0204] Embodiment 30A. The method of Embodiment 29A, wherein the insulin analog is insulin lispro, insulin aspart, insulin glulisine, admelog insulin, NPH insulin, insulin isophane, insulin glargine, insulin detemir, or insulin degludec.

[0205] Embodiment 31A. The method of any of Embodiment 27A, wherein the drug compound is a GLP-1 receptor agonist.

[0206] Embodiment 32A. The method of Embodiment 31A, wherein the GLP-1 receptor agonist is semaglutide, tirzepatide, amycretin, orforglipron, albiglutide, beinaglutide, cagrilintide, CagriSema, CT996, danuglipron, efinopegdutide, HM15211, lixisenatide, pemvidutide, retratrutide, SCO-094, survodutide, WK2735, mazdutide, PEG-loxenatide, liraglutide, dulaglutide, exenatide, or a salt thereof.

[0207] Embodiment 33A. The method of Embodiment 27A, wherein the drug compound is a GIP agonist.

[0208] Embodiment 34A. The method of Embodiment 33A, wherein the GIP agonist is HM15211, retratrutide, SCO-094, tirzepatide, WK2735, or ZP6590.

[0209] Embodiment 35A. The method of any of Embodiment 27A, wherein the drug compound is a glucagon agonist.

[0210] Embodiment 36A. The method of Embodiment 35A, wherein the glucagon agonist is efinopegdutide, HM15211, mazdutide, pemvidutide, or survodutide.

[0211] Embodiment 37A. The method of any of Embodiment 27A, wherein the drug compound is an amylin agonist.

[0212] Embodiment 38A. The method of Embodiment 37A, wherein the amylin agonist is AZD6234, cagrilintide, CagriSema, CT388, a long-acting amylin agonist, amycretin, or ZP8396.

[0213] Embodiment 39A. The method of Embodiment 27A, wherein the method further comprises drying the water-soluble complex after it was dissolved in water.

[0214] Embodiment 40A. The method of Embodiment 39A, wherein the dried water-soluble complex is resolubilized in a liquid.

[0215] Embodiment 41A. The method of Embodiment 27A, wherein the admixing step is in the presence of a sufficient amount of a pharmaceutically acceptable acid to solubilize and render the reaction mixture homogeneous and clear.

[0216] Embodiment 42A. The method of Embodiment 41A, wherein the pharmaceutically acceptable acid is acetic acid, ascorbic acid, aspartic acid, citric acid, formic acid, fumaric acid, gluconic acid, glutamic acid, glutaric acid, glycolic acid, hydrochloric acid, lactic acid, lauric acid, maleic acid, malic acid, malonic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, propionic acid, salicylic acid, stearic acid, succinic acid, or tartaric acid.

[0217] Embodiment 43A. The method of Embodiment 27A, wherein the formed water-soluble complex comprises a molar ratio of about 1 to about 10 moles of the non-nutritive sugar for each mole of the drug compound.

[0218] Embodiment 44A. The method of Embodiment 43A, wherein the non-nutritive sugar is rubusoside or stevioside.

[0219] Embodiment 45A. The method of Embodiment 43A, wherein the formed water-soluble complex comprises a molar ratio of about 2 to about 5 moles of the non-nutritive sugar for each mole of the drug compound.

[0220] Embodiment 46A. The method of Embodiment 45A, wherein the non-nutritive sugar is rubusoside or stevioside.

[0221] Embodiment 47A. The method of Embodiment 43A, wherein the formed water-soluble complex comprises a molar ratio of about 2 to about 4.5 moles of the non-nutritive sugar for each mole of the drug compound.

[0222] Embodiment 48A. The method of Embodiment 47A, wherein the non-nutritive sugar is rubusoside or stevioside.

[0223] Embodiment 49A. The method of Embodiment 43A, wherein the formed water-soluble complex comprises a molar ratio of about 8 moles of the non-nutritive sugar for each mole of the drug compound.

[0224] Embodiment 50A. The method of Embodiment 49A, wherein the non-nutritive sugar is rubusoside or stevioside.

[0225] Embodiment 51A. The method of Embodiment 27A, wherein the formed water-soluble complex is stable in water at pH 8.5 for at least 2 hours.

[0226] Embodiment 52A. The method of Embodiment 27A, wherein the formed water-soluble complex is stable in water at pH 4 for at least 2 hours.

[0227] Embodiment 53A. The method of Embodiment 39A, wherein drying the water-soluble complex comprises freeze-drying or lyophilizing.

[0228] Embodiment 54A. The method of Embodiment 53A, wherein the dried water-soluble complex is formulated into a pill or a pharmaceutically acceptable liquid.

[0229] Embodiment 55A. A method of treating a subject having diabetes type 1 (TD1), diabetes type 2 (TD2), obesity (weight loss reduction), MASH, glycemic control, prediabetes, a condition characterized by impaired fasting glucose or impaired glucose tolerance, an alpha- and beta-cell dysfunction, and/or a condition producing a suboptimal incretin effect the method comprising administering a water-soluble complex of any of Embodiments 1A to 21A to the subject in a therapeutically effective amount.

[0230] Embodiment 56A. Use of the water-soluble complex of any of Embodiments 1A to 21A for the manufacture of a medicament for treating diabetes type 1 (TD1), diabetes type 2 (TD2), obesity (weight loss reduction), MASH, glycemic control, prediabetes, a condition characterized by impaired fasting glucose or impaired glucose tolerance, an alpha- and beta-cell dysfunction, and/or a condition producing a suboptimal incretin effect.

[0231] Embodiment 1B. A water-soluble complex comprising a non-nutritive sugar and a drug compound, which complex comprises: a molar ratio of up to about 12 moles of the non-nutritive sugar for each mole of the drug compound, wherein the non-nutritive sugar is one or more of ADVANTAME®, NEOTAME®, thaumatin, saccharin, sucralose, Lou Han Guo, aspartame, acesulfame potassium, allulose, rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A, provided that the water-soluble complex has at least a two (2) fold increase in the drug compound water solubility at 20 °C. as compared to the water solubility of the drug compound not in the water-soluble complex or has one improved pharmacokinetic attribute; and further, provided that a maximum amount of the non-nutritive sugar in a daily unit dose of the water-soluble complex is no more than about 10 mg/kg, wherein the drug compound is for reducing blood glucose in a subject and/or blood A1C, and the drug compound is insulin, an insulin analog, a natural insulin variant, a GLP-1 receptor agonist, an incretin mimetic, a GIP agonist, an amylin agonist, a glucagon agonist, or a salt thereof.

- [0232] Embodiment 2B. The water-soluble complex of Embodiment 1B further comprises a non-ionic surfactant.
- [0233] Embodiment 3B. The water-soluble complex of Embodiment 1B, wherein the drug compound is an insulin analog, insulin, or a natural insulin variant.
- [0234] Embodiment 4B. The water-soluble drug complex of Embodiment 3B, wherein the insulin analog is insulin lispro, insulin aspart, insulin glulisine, admelog, NPH insulin, insulin isophane, insulin glargine, insulin detemir, or insulin degludec.
- [0235] Embodiment 5B. The water-soluble complex of any of Embodiments 3 or 4, wherein the drug compound is a rapid-acting insulin, short-acting insulin, intermediate-acting insulin, long-acting insulin, or an ultra-long-acting insulin.
- [0236] Embodiment 6B. The water-soluble complex of Embodiment 1B, wherein the drug compound is a GLP-1 receptor agonist.
- [0237] Embodiment 7B. The water-soluble complex of Embodiment 6B, wherein the GLP-1 receptor agonist is semaglutide, tirzepatide, amycretin, orforglipron, albiglutide, beinaglutide, cagrilintide, CagriSema, CT996, danuglipron, efinopegdutide, HM15211, lixisenatide, pemvidutide, retratrutide, SCO-094, survodutide, WK2735, mazdutide, PEG-loxenatide (PEX168), liraglutide, dulaglutide, exenatide, or a salt thereof.
- [0238] Embodiment 8B. The water-soluble complex of Embodiment 1B, wherein the drug compound is a GIP agonist.
- [0239] Embodiment 9B. The water-soluble complex of Embodiment 8B, wherein the GIP agonist is HM15211, retratrutide, SCO-094, tirzepatide, WK2735, or ZP6590.
- [0240] Embodiment 10B. The water-soluble complex of Embodiment 1B, wherein the drug compound is a glucagon agonist.
- [0241] Embodiment 11B. The water-soluble complex of Embodiment 10B, wherein the glucagon agonist is efinopegdutide, HM15211, mazdutide, pemvidutide, or survodutide.
- [0242] Embodiment 12B. The water-soluble complex of Embodiment 1B, wherein the drug compound is an amylin agonist.
- [0243] Embodiment 13B. The water-soluble complex of Embodiment 12B, wherein the amylin agonist is AZD6234, cagrilintide, CagriSema, CT388, a long-acting amylin agonist, amycretin, or ZP8396.

[0244] Embodiment 14B. The water-soluble complex of any of Embodiments 1B-13B, wherein the non-nutritive sugar is rubusoside, rebaudioside A, dodecyl- β -D-maltoside, dulcoside B, or stevioside.

[0245] Embodiment 15B. The water-soluble complex of Embodiment 14B, wherein the non-nutritive sugar is rubusoside or stevioside.

[0246] Embodiment 16B. The water-soluble complex of any of Embodiments 1B-15B, wherein the non-nutritive sugar in the daily unit dose is no more than 5 mg/kg of subject weight.

[0247] Embodiment 17B. The water-soluble complex of any of Embodiment 1B to 15B, wherein the non-nutritive sugar in the daily unit dose is no more than about 280 mg.

[0248] Embodiment 18B. The water-soluble complex of any of Embodiments 1B to 15B, wherein the water-soluble complex comprises a molar ratio of the drug compound to mole of sugar of about 1:1 to about 1:10 (drug compound:sugar).

[0249] Embodiment 19B. The water-soluble complex of any of Embodiments 1B to 15B, wherein the water-soluble complex comprises a molar ratio of about 2 to about 10 moles of the drug compound to sugar.

[0250] Embodiment 20B. The water-soluble complex of Claim 19B, wherein the water-soluble complex comprises a molar ratio of about 3 moles of the non-nutritive sugar for each mole of the drug compound.

[0251] Embodiment 21B. The water-soluble complex of any of Embodiments 1B to 15B, wherein the water-soluble complex is stable in water at pH 8.5 for at least 2 hours.

[0252] Embodiment 22B. The water-soluble complex of any of Embodiments 1B to 15B, wherein the water-soluble complex is stable in water at pH 4 for at least 2 hours.

[0253] Embodiment 23B. A dried form of the water-soluble complex of any of Embodiments 1B to 20B, wherein the water-soluble complex when dried is stable at 30 °C. for at least 90 days.

[0254] Embodiment 24B. The water-soluble complex of any of Embodiments 1B to 20B, wherein the water-soluble complex is formulated as a powder, a tablet, an orally disintegrating tablet, a capsule, a liquid, a gel, a thin film, a lozenge, an effervescent powder or tablet, an emulsion, or for parenteral administration.

[0255] Embodiment 25B. The water-soluble complex of Embodiment 24B, wherein the water-soluble complex is formulated to be administered intradermally,

subcutaneously, intramuscularly, intraperitoneally, intrathecally, intravenously, topically (e.g., a gel, lotion, spray or inhaled form), or as a transdermal patch.

[0256] Embodiment 26B. The water-soluble complex of any of Embodiments 1B to 25B, wherein the water-soluble complex is in the form of a thin film, an effervescent powder or tablet, a syrup, a solution, an elixir, an emulsion, a chewing gum, a lollipop, a sublingual drop, a soft gel, or a tincture.

[0257] Embodiment 27B. A water-soluble complex comprising a non-nutritive sugar and a drug compound, which water-soluble complex comprises: a molar ratio of about 1 to 12 moles non-nutritive sugar to mole of drug compound, wherein the non-nutritive sugar is one or more of ADVANTAME®, NEOTAME®, thaumatin, saccharin, sucralose, Lou Han Guo, aspartame, acesulfame potassium, allulose, rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A; wherein the water-soluble complex is stable in water at pH 8.5 and/or at pH 4.0 for at least 2 hours each; provided that the water-soluble complex has at least a two (2) fold increase in the water solubility at 20 °C. as compared to the drug compound water solubility not in the water-soluble complex, and/or at least one improved pharmacokinetic attribute; and further provided the non-nutritive sugar in a daily unit dose of the water-soluble complex is no more than about 280 mg, wherein the drug compound is for reducing blood glucose and/or blood A1C in a subject, and the drug compound is insulin, an insulin analog, a natural insulin variant, a GLP-1 receptor agonist, an incretin mimetic, a GIP agonist, an amylin agonist, a glucagon agonist, or a salt thereof.

[0258] Embodiment 28B. A method of making a water-soluble complex comprising a non-nutritive sugar and a drug compound, the method comprising the steps of: a) admixing, one or more solvents, the non-nutritive sugar, and the drug compound in a molar ratio of from about 1 to about 12 moles of the the non-nutritive sugar to mole of the drug compound, wherein formation of the water-soluble complex can be determined by nuclear magnetic resonance spectroscopy (NMR), and wherein the non-nutritive sugar is one or more of ADVANTAME®, NEOTAME®, thaumatin, saccharin, sucralose, Lou Han Guo, aspartame, acesulfame potassium, allulose, rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A; and wherein the admixing step is optionally performed with a pharmaceutically acceptable acid and/or a non-ionic surfactant; and b) drying the water-soluble complex and dissolving the water-soluble complex in water, and wherein the drug compound is a peptide or small compound for reducing blood glucose and/or blood A1C in a subject, wherein the drug compound is for reducing blood glucose and/or blood A1C in a

subject, and is insulin, an insulin analog, a natural insulin variant, a GLP-1 receptor agonist, an incretin mimetic, a GIP agonist, an amylin agonist, a glucagon agonist, or a salt thereof.

[0259] Embodiment 29B. The method of Embodiment 28B, wherein the method further comprises adding a non-ionic surfactant to the solvent of step a).

[0260] Embodiment 30B. The method of Embodiment 28B, wherein the drug compound is a rapid-acting insulin, short-acting insulin, intermediate-acting insulin, long-acting insulin, or ultra-long-acting insulin.

[0261] Embodiment 31B. The method of Embodiment 28B, wherein the drug compound is an insulin analog, natural insulin, or an insulin variant.

[0262] Embodiment 32B. The method of Embodiment 31B, wherein the insulin analog is insulin lispro, insulin aspart, insulin glulisine, admelog insulin, NPH insulin, insulin isophane, insulin glargine, insulin detemir, or insulin degludec.

[0263] Embodiment 33B. The method of Embodiment 28B, wherein the drug compound is a GLP-1 receptor agonist.

[0264] Embodiment 34B. The method of Embodiment 33B, wherein the GLP-1 receptor agonist is semaglutide, tirzepatide, amycretin, orforglipron, albiglutide, beinaglutide, cagrilintide, CagriSema, CT996, danuglipron, efinopegdutide, HM15211, lixisenatide, pemvidutide, retratrutide, SCO-094, survodutide, WK2735, mazdutide, PEG-loxenatide, liraglutide, dulaglutide, exenatide, or a salt thereof.

[0265] Embodiment 35B. The method of Claim 28B, wherein the drug compound is a GIP agonist.

[0266] Embodiment 36B. The method of Embodiment 35B, wherein the GIP agonist is HM15211, retratrutide, SCO-094, tirzepatide, WK2735, or ZP6590.

[0267] Embodiment 37B. The method of Embodiment 28B, wherein the drug compound is a glucagon agonist.

[0268] Embodiment 38B. The method of Embodiment 37B, wherein the glucagon agonist is efinopegdutide, HM15211, mazdutide, pemvidutide, or survodutide.

[0269] Embodiment 39B. The method of Embodiment 28B, wherein the drug compound is an amylin agonist.

[0270] Embodiment 40B. The method of Embodiment 39B, wherein the amylin agonist is AZD6234, cagrilintide, CagriSema, CT388, a long-acting amylin agonist, amycretin, or ZP8396.

- [0271] Embodiment 41B. The method of Embodiment 28B, wherein the method further comprises drying the dissolved water-soluble complex of step b).
- [0272] Embodiment 42B. The method of Embodiment 41B, wherein the dried water-soluble complex is resolubilized in a liquid.
- [0273] Embodiment 43B. The method of Embodiment 28B, wherein step a) comprises a sufficient amount of a pharmaceutically acceptable acid to solubilize and render the reaction mixture homogeneous and clear.
- [0274] Embodiment 44B. The method of Embodiment 43B, wherein the pharmaceutically acceptable acid is acetic acid, ascorbic acid, aspartic acid, citric acid, formic acid, fumaric acid, gluconic acid, glutamic acid, glutaric acid, glycolic acid, hydrochloric acid, lactic acid, lauric acid, maleic acid, malic acid, malonic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, propionic acid, salicylic acid, stearic acid, succinic acid, or tartaric acid.
- [0275] Embodiment 45B. The method of Embodiment 28B, wherein the water-soluble complex comprises a molar ratio of about 1 to about 10 moles of the non-nutritive sugar to each mole of the drug compound.
- [0276] Embodiment 46B. The method of Embodiment 45B, wherein the non-nutritive sugar is rubusoside or stevioside.
- [0277] Embodiment 47B. The method of Embodiment 45B, wherein the water-soluble complex comprises a molar ratio of about 2 to about 5 moles of the non-nutritive sugar for each mole of the drug compound.
- [0278] Embodiment 48B. The method of Embodiment 47B, wherein the non-nutritive sugar is rubusoside or stevioside.
- [0279] Embodiment 49B. The method of Embodiment 45B, wherein the water-soluble complex comprises a molar ratio of about 2 to about 4.5 moles of the non-nutritive sugar for each mole of the drug compound.
- [0280] Embodiment 50B. The method of Embodiment 49B, wherein the non-nutritive sugar is rubusoside or stevioside.
- [0281] Embodiment 51B. The method of Embodiment 45B, wherein the water-soluble complex comprises a molar ratio of about 8 moles of the non-nutritive sugar for each mole of the drug compound.
- [0282] Embodiment 52B. The method of Embodiment 51B, wherein the non-nutritive sugar is rubusoside or stevioside.

[0283] Embodiment 53B. The method of Embodiment 28B, wherein the water-soluble complex is stable in water at pH 8.5 for at least 2 hours.

[0284] Embodiment 54B. The method of Embodiment 28B, wherein the water-soluble complex is stable in water at pH 4 for at least 2 hours.

[0285] Embodiment 55B. The method of Embodiment 41B, wherein the method further comprises drying the water-soluble complex by freeze-drying or lyophilizing.

[0286] Embodiment 56B. The method of Embodiment 55B, wherein the dried water-soluble complex is formulated into a pill or a pharmaceutically acceptable liquid.

[0287] Embodiment 57B. A method of treating a subject having diabetes type 1 (TD1), diabetes type 2 (TD2), obesity (weight loss reduction), MASH, glycemic control, prediabetes, a condition characterized by impaired fasting glucose or impaired glucose tolerance, an alpha- and beta-cell dysfunction, and/or a condition having a suboptimal incretin effect the method comprising administering the water-soluble complex of any of Embodiments 1B to 27B to the subject in a therapeutically effective amount.

[0288] Embodiment 58B. Use of the water-soluble complex of any of Embodiments 1B to 27B for the manufacture of a medicament for treating diabetes type 1 (TD1), diabetes type 2 (TD2), obesity (weight loss reduction), MASH, glycemic control, prediabetes, a condition characterized by impaired fasting glucose or impaired glucose tolerance, an alpha- and beta-cell dysfunction, and/or a condition having a suboptimal incretin effect.

CLAIMS

1. A water-soluble complex comprising a non-nutritive sugar and a drug compound, which complex comprises:

a molar ratio of up to about 12 moles of the non-nutritive sugar for each mole of the drug compound, wherein the non-nutritive sugar is one or more of ADVANTAME®, NEOTAME®, thaumatin, saccharin, sucralose, Lou Han Guo, aspartame, acesulfame potassium, allulose, rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A,

provided that the water-soluble complex has at least a two (2) fold increase in the drug compound water solubility at 20 °C. as compared to the water solubility of the drug compound not in the water-soluble complex or has one improved pharmacokinetic attribute; and

further, provided that a maximum amount of the non-nutritive sugar in a daily unit dose of the water-soluble complex is no more than about 10 mg/kg, wherein the drug compound is for reducing blood glucose in a subject and/or blood A1C, and the drug compound is insulin, an insulin analog, a natural insulin variant, a GLP-1 receptor agonist, an incretin mimetic, a GIP agonist, an amylin agonist, a glucagon agonist, or a salt thereof.

2. The water-soluble complex of claim 1 further comprising a non-ionic surfactant.

3. The water-soluble complex of claim 1, wherein the drug compound is an insulin analog, insulin, or a natural insulin variant.

4. The water-soluble drug complex of claim 3, wherein the insulin analog is insulin lispro, insulin aspart, insulin glulisine, admelog, NPH insulin, insulin isophane, insulin glargine, insulin detemir, or insulin degludec.

5. The water-soluble complex of any of claims 3 or 4, wherein the drug compound is a rapid-acting insulin, short-acting insulin, intermediate-acting insulin, long-acting insulin, or an ultra-long-acting insulin.

6. The water-soluble complex of claim 1, wherein the drug compound is a GLP-1 receptor agonist.

7. The water-soluble complex of claim 6, wherein the GLP-1 receptor agonist is semaglutide, tirzepatide, amycretin, orforglipron, albiglutide, beinaglutide, cagrilintide, CagriSema, CT996, danuglipron, efinopegdutide, HM15211, lixisenatide, pemvidutide, retratrutide, SCO-094, survodutide, WK2735, mazdutide, PEG-loxenatide (PEX168), liraglutide, dulaglutide, exenatide, or a salt thereof.

8. The water-soluble complex of claim 1, wherein the drug compound is a GIP agonist.

9. The water-soluble complex of claim 8, wherein the GIP agonist is HM15211, retratrutide, SCO-094, tirzepatide, WK2735, or ZP6590.

10. The water-soluble complex of claim 1, wherein the drug compound is a glucagon agonist.

11. The water-soluble complex of claim 10, wherein the glucagon agonist is efinopegdutide, HM15211, mazdutide, pemvidutide, or survodutide.

12. The water-soluble complex of claim 1, wherein the drug compound is an amylin agonist.

13. The water-soluble complex of claim 12, wherein the amylin agonist is AZD6234, cagrilintide, CagriSema, CT388, a long-acting amylin agonist, amycretin, or ZP8396.

14. The water-soluble complex of any one of claims 1-13, wherein the non-nutritive sugar is rubusoside, rebaudioside A, dodecyl- β -D-maltoside, dulcoside B, or stevioside.

15. The water-soluble complex of claim 14, wherein the non-nutritive sugar is rubusoside or stevioside.

16. The water-soluble complex of any one of claims 1 to 15, wherein the non-nutritive sugar in the daily unit dose is no more than 5 mg/kg of subject weight.

17. The water-soluble complex of any one of claims 1 to 15, wherein the non-nutritive sugar in the daily unit dose is no more than about 280 mg.

18. The water-soluble complex of any one of claims 1 to 15, wherein the water-soluble complex comprises a molar ratio of the drug compound to the non-nutritive sugar of about 1:1 to about 1:10 (drug compound: non-nutritive sugar).

19. The water-soluble complex of any one of claims 1 to 15, wherein the water-soluble complex comprises a molar ratio of about 2 to about 10 moles of the non-nutritive sugar for each mole of the drug compound.

20. The water-soluble complex of claim 19, wherein the water-soluble complex comprises a molar ratio of about 3 moles of the non-nutritive sugar for each mole of the drug compound.

21. The water-soluble complex of any one of claims 1 to 15, wherein the water-soluble complex is stable in water at pH 8.5 for at least 2 hours.

22. The water-soluble complex of any one of claims 1 to 15, wherein the water-soluble complex is stable in water at pH 4 for at least 2 hours.

23. A dried form of the water-soluble complex of any one of claims 1 to 20, wherein the water-soluble complex when dried is stable at 30 °C. for at least 90 days.

24. The water-soluble complex of any one of claims 1 to 20, wherein the water-soluble complex is formulated as a powder, a tablet, an orally disintegrating tablet, a capsule, a liquid, a gel, a thin film, a lozenge, an effervescent powder or tablet, an emulsion, or for parenteral administration.

25. The water-soluble complex of claim 24, wherein the water-soluble complex is formulated to be administered intradermally, subcutaneously, intramuscularly, intraperitoneally, intrathecally, intravenously, topically (e.g., a gel, lotion, spray or inhaled form), or as a transdermal patch.

26. The water-soluble complex of any one of claims 1 to 22 and 24 to 25, wherein the water-soluble complex is in the form of a thin film, an effervescent powder or tablet, a syrup, a solution, an elixir, an emulsion, a chewing gum, a lollipop, a sublingual drop, a soft gel, or a tincture.

27. A water-soluble complex comprising a non-nutritive sugar and a drug compound, which water-soluble complex comprises:

a molar ratio of about 1 to 12 moles of the non-nutritive sugar for each mole of the drug compound, wherein the non-nutritive sugar is one or more of ADVANTAME®, NEOTAME®, thaumatin, saccharin, sucralose, Lou Han Guo, aspartame, acesulfame potassium, allulose, rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A;

wherein the water-soluble complex is stable in water at pH 8.5 and/or at pH 4.0 for at least 2 hours each;

provided that the water-soluble complex has at least a two (2) fold increase in the water solubility at 20 °C. as compared to the drug compound water solubility not in the water-soluble complex, and/or at least one improved pharmacokinetic attribute; and

further provided the non-nutritive sugar in a daily unit dose of the water-soluble complex is no more than about 280 mg,

wherein the drug compound is for reducing blood glucose and/or blood A1C in a subject, and is insulin, an insulin analog, a natural insulin variant, a GLP-1 receptor agonist, an incretin mimetic, a GIP agonist, an amylin agonist, a glucagon agonist, or a salt thereof.

28. A method of making a water-soluble complex comprising a non-nutritive sugar and a drug compound, the method comprising the steps of:

a) admixing, one or more solvents, the non-nutritive sugar, and the drug compound in a molar ratio of from about 1 to about 12 moles of the non-nutritive sugar for each mole of the drug compound, wherein formation of the water-soluble complex can be

determined by nuclear magnetic resonance spectroscopy (NMR), and wherein the non-nutritive sugar is one or more of ADVANTAME®, NEOTAME®, thaumatin, saccharin, sucralose, Lou Han Guo, aspartame, acesulfame potassium, allulose, rubusoside, dulcoside B, dodecyl- β -D-maltoside, stevioside, or rebaudioside A; and wherein the admixing step is optionally performed with a pharmaceutically acceptable acid and/or a non-ionic surfactant; and

b) drying the water-soluble complex and dissolving the water-soluble complex in water, and

wherein the drug compound is for reducing blood glucose and/or blood A1C in a subject, and is insulin, an insulin analog, a natural insulin variant, a GLP-1 receptor agonist, an incretin mimetic, a GIP agonist, an amylin agonist, a glucagon agonist, or a salt thereof.

29. The method of claim 28, wherein the method further comprises adding a non-ionic surfactant to the solvent of step a).

30. The method of claim 28, wherein the drug compound is a rapid-acting insulin, short-acting insulin, intermediate-acting insulin, long-acting insulin, or ultra-long-acting insulin.

31. The method of claim 28, wherein the drug compound is an insulin analog, natural insulin, or an insulin variant.

32. The method of claim 31, wherein the insulin analog is insulin lispro, insulin aspart, insulin glulisine, admelog insulin, NPH insulin, insulin isophane, insulin glargine, insulin detemir, or insulin degludec.

33. The method of claim 28, wherein the drug compound is a GLP-1 receptor agonist.

34. The method of claim 33, wherein the GLP-1 receptor agonist is semaglutide, tirzepatide, amycretin, orforglipron, albiglutide, beinaglutide, cagrilintide, CagriSema, CT996, danuglipron, efinopegdutide, HM15211, lixisenatide, pemvidutide, retratrutide, SCO-

094, survodutide, WK2735, mazdutide, PEG-loxenate, liraglutide, dulaglutide, exenatide, or a salt thereof.

35. The method of claim 28, wherein the drug compound is a GIP agonist.

36. The method of claim 35, wherein the GIP agonist is HM15211, retatrutide, SCO-094, tirzepatide, WK2735, or ZP6590.

37. The method of claim 28, wherein the drug compound is a glucagon agonist.

38. The method of claim 37, wherein the glucagon agonist is efinopegdutide, HM15211, mazdutide, pemvidutide, or survodutide.

39. The method of claim 28, wherein the drug compound is an amylin agonist.

40. The method of claim 39, wherein the amylin agonist is AZD6234, cagrilintide, CagriSema, CT388, a long-acting amylin agonist, amycretin, or ZP8396.

41. The method of claim 28, wherein the method further comprises drying the dissolved water-soluble complex of step b).

42. The method of claim 41, wherein the dried water-soluble complex is resolubilized in a liquid.

43. The method of claim 28, wherein step a) comprises a sufficient amount of a pharmaceutically acceptable acid to solubilize and render the reaction mixture homogeneous and clear.

44. The method of claim 43, wherein the pharmaceutically acceptable acid is acetic acid, ascorbic acid, aspartic acid, citric acid, formic acid, fumaric acid, gluconic acid, glutamic acid, glutaric acid, glycolic acid, hydrochloric acid, lactic acid, lauric acid, maleic acid, malic acid, malonic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, propionic acid, salicylic acid, stearic acid, succinic acid, or tartaric acid.

45. The method of claim 28, wherein the water-soluble complex comprises a molar ratio of about 1 to about 10 moles of the non-nutritive sugar for each mole of the drug compound.

46. The method of claim 45, wherein the non-nutritive sugar is rubusoside or stevioside.

47. The method of claim 45, wherein the water-soluble complex comprises a molar ratio of about 2 to about 5 moles of the non-nutritive sugar for each mole of the drug compound.

48. The method of claim 47, wherein the non-nutritive sugar is rubusoside or stevioside.

49. The method of claim 45, wherein the water-soluble complex comprises a molar ratio of about 2 to about 4.5 moles of the non-nutritive sugar for each mole of the drug compound.

50. The method of claim 49, wherein the non-nutritive sugar is rubusoside or stevioside.

51. The method of claim 45, wherein the water-soluble complex comprises a molar ratio of about 8 moles of the non-nutritive sugar for each mole of the drug compound.

52. The method of claim 51, wherein the non-nutritive sugar is rubusoside or stevioside.

53. The method of claim 28, wherein the water-soluble complex is stable in water at pH 8.5 for at least 2 hours.

54. The method of claim 28, wherein the water-soluble complex is stable in water at pH 4 for at least 2 hours.

55. The method of claim 28, further comprising drying the water-soluble complex comprises freeze-drying or lyophilizing.

56. The method of claim 55, wherein the dried water-soluble complex is formulated into a pill or a pharmaceutically acceptable liquid.

57. A method of treating a subject having diabetes type 1 (TD1), diabetes type 2 (TD2), obesity (weight loss reduction), MASH (metabolic dysfunction-associated steatohepatitis), glycemic control, prediabetes, a condition characterized by impaired fasting glucose or impaired glucose tolerance, alpha- and beta-cell dysfunction, and/or suboptimal incretin effect the method comprising administering the water-soluble complex of any of Claims 1 to 27 to the subject in a therapeutically effective amount.

58. Use of the water-soluble complex of any one of claims 1 to 27 for the manufacture of a medicament for treating diabetes type 1 (TD1), diabetes type 2 (TD2), obesity (weight loss reduction), MASH (metabolic dysfunction-associated steatohepatitis), glycemic control, prediabetes, a condition characterized by impaired fasting glucose or impaired glucose tolerance, an alpha- and beta-cell dysfunction, and/or a condition having a suboptimal incretin effect.